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New human biomonitoring methods for chemicals of concern—the German approach to enhance relevance

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ABSTRACT

In Germany strong efforts have been made within the last years to develop new methods for human biomonitoring (HBM). The German Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (BMUB) and the German Chemical Industry Association e. V. (VCI) cooperate since 2010 to increase the knowledge on the internal exposure of the general population to chemicals. The projects aim is to promote human biomonitoring by developing new analytical methods Key partner of the cooperation is the German Environment Agency (UBA) which has been entrusted with the scientific coordination. Another key partner is the "HBM Expert Panel" which each year puts together a list of chemicals of interest to the project from which the Steering Committee of the project choses up to five substances for which method development will be started. Emphasis is placed on substances with either a potential health relevance or on substances to which the general population is potentially exposed to a considerable extent.

The HBM Expert Panel also advises on method development. Once a method is developed, it is usually first applied to about 40 non-occupationally exposed individuals. A next step is applying the methods to different samples. Either, if the time trend is of major interest, to samples from the German Environmental Specimen Bank, or, in case exposure sources and distribution of exposure levels in the general population are the focus, the new methods are applied to samples from children and adolescents from the population representative 5th German Environmental Survey (GerES V). Results are expected in late 2018.

This article describes the challenges faced during method development and solutions found. An overview presents the 34 selected substances, the 14 methods developed and the 7 HBM-I values derived in the period from 2010 to mid 2016.

Abbreviations: ASE/ASEP, Mesamoll®, C10-C20 Alkylsulfonic acid phenylester; BAuA, Federal Institute for Occupational Safety and Health; BfR, Federal Institute of Risk Assessment; BHT, Butylated Hydroxy Toluene, 2,6-Di-*tert*-butyl-*p*-cresol; BMUB, German Ministry for the Environment, Nature Conservation, Building and Nuclear safety; CIT/MIT (3:1), 5-Chloro-2-methyl-4-isothiazolin-3-one/2-Methylisothiazol-3(2H)-one; CMR, carcinogenic, mutagenic, reprotoxic; DEHTP, Di(2-ethylhexyl) terephthalate; DINCH, 1,2-Cyclohexane dicarboxylic acid diisononyl ester; DPHP, Di(2-propylheptyl) phthalate or Bis(2-propylheptyl) benzene-1,2-dicarboxylate; ESB, German Environmental Specimen Bank; GerES, German Environmental Survey; HBM, human biomonitoring; HBCDD, Hexabromocyclododecane; Hexamoll® DINCH®, 1, 2-Cyclohexane dicarboxylic acid diisononyl ester or Diisononyl cyclohexane-1, 2-dicarboxylate; LOD, Limit of detection; LOQ, limit of quantification; 4-MBC, 3-(4-Methylbenzylidene) camphor; 2-MBT, 2-Mercaptobenzothiazole; MDI, Methylenediphenyl-diisocyanate; NEP, *N*-ethyl-2-pyrrolidone; NMP, *N*-methyl-2-pyrrolidone; RKI, Robert Koch-Institute; TDCP, Tris(2-chlor-1-(chlormethyl)ethyl)phosphat; UBA, German Environment Agency; VCI, German Chemical Industry Association.

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1. Introduction and background

The exposure of the German population to chemicals is substantially related to the use and production of chemicals, to products and consumer goods, to the contamination of food as well as todayís living conditions. Their safety for human beings and the environment has to be safeguarded by producers and the government. One important tool for identifying exposure levels and sources, informing policy decisions and evaluating the success of risk reduction strategies is human biomonitoring (HBM) (Angerer, 2012; Kolossa-Gehring et al., 2012). HBM is the most appropriate scientific technique for assessing human exposure to environmental pollutants based usually on sampling and analysis of blood or urine. By linking the biomonitoring results with environmental and health data or by a toxicologically/epidemiologically based assessment of the exposure levels HBM can build bridges between exposure to pollutants and health effects and can give indication for appropriate public health measures. Time trends of exposure and different exposure levels of sub-groups of the population can also be detected (Schulz et al., 2007a,b).

Exposures of concern, such as to heavy metals like lead, to persistent organic pollutants like PCB and DDT, to PAHs taken up from outdoor air pollution and to phthalates used e. g. as plasticizers have been efficiently reduced by the introduction of risk reduction measures like restriction in use or complete bans of chemicals. However, banned or restricted chemicals are often substituted by substances for which no data on internal exposure and/or no toxicologically derived guidance values for an assessment of their health relevance are available. Without data it is not possible to distinguish between recommendable and problematic substitutes or to give advice to the general population on how to efficiently reduce an impact on health from the exposure to chemicals (Zota et al., 2014; Schütze et al., 2014; Göen et al., 2011). HBM should thus also be used to investigate substitutes.

In the past HBM methods have primarily been developed for chemicals relevant at the workplace. Later on, a set of methods for heavy metals, persistent compounds, biocides and industrial chemicals relevant for the general population has been established. Most of the HBM studies worldwide measure a similar set of chemicals today (Kolossa-Gehring, 2012). In many cases the awareness of exposure and the subsequent development of appropriate risk reduction measures led to a reduction of exposure. Subsequent studies observed and followed up these reductions.

In Germany, a cooperation was set up in 2010 to broaden the toolbox of HBM methods and thus enhance the use of HBM for policy making. The German Ministry for the Environment, Nature Conservation, Building and Nuclear safety (BMUB) and the German Chemical Industry Association (VCI), supported by the German Environment Agency (UBA) and an “HBM Expert Panel”, identify chemicals with potential consumer exposure and potential health relevance for the general population which up to now cannot be (reliably) measured by HBM. Each year up to five chemicals are chosen for the development of new HBM methods (Kolossa-Gehring et al., 2012; Kolossa-Gehring 2012).

The VCI has taken on the responsibility of developing the new detection methods. While advised by the HBM Expert Panel, it is the task of the VCI to commission an analytical laboratory which it considers suitable for developing a valid analytical method.

Applying the methods in suitable studies and interpreting their results is the responsibility of the BMUB in close cooperation with the UBA. Thus there is a clear division of responsibilities which is a core feature of the project.

Reliable exposure data alone, however, does not allow to evaluate the health relevance of a given level of exposure. That evaluation is performed outside of the cooperation project. It is performed by the German Human Biomonitoring Commission (Schulz et al., 2007b; Angerer et al., 2011; Apel et al., 2016) which derives HBM values from toxicological data. The HBM Commission was established in 1992 and has the mandate to support the UBA by giving advice concerning HBM related issues and health-related environmental monitoring. The Commission members are appointed by the President of the UBA. They are independent scientists and experts from authorities at the Federal and Bundesländer (Federal States) level, universities, public health institutes and clinical institutes.

In the following, the operation (modus operandi) and the achievements reached so far by the BMUB/VCI cooperation are described.

2. Methods

2.1. Identification of chemicals of relevance

The HBM Expert Panel consists of experts from the Federal German scientific agencies in charge of chemicals regulation, that is the Federal Institute for Risk Assessment (BfR), the Federal Institute for Occupational Safety and Health (BAuA) and the UBA as well as of experts from chemical industry enterprises and from universities and other scientific institutions. This panel provides advice on the selection of substances and the development of methods.

A steering committee composed of representatives of the BMUB, the UBA, the VCI and VCI member companies decides each year for which substances new methods are to be developed.

The idea for the project was created in 2009 in a joint BMUB/VCI meeting on HBM. An agreement was negotiated and the project then started in 2010. To get the work of the HBM Expert Panel started, a list of chemicals of interest was put together by the BfR, the BAuA and the UBA. It was based on at that time available lists of nationally and internationally relevant substances already compiled by other experts. The first focus was laid on the REACH-Annex XIV-candidate list and the list of PBT/vPvB- substances. For the following year a list of 120 substances of interest was set up.

Table 1 gives an overview about the most relevant substance lists which were considered. Additionally the scientific Federal Agencies identified chemicals of interest from their respective fields of competence which had raised concern or were under discussion in science or in the public. Representatives from industry also proposed additional chemicals for method development.

The above mentioned list is regularly reviewed in the course of the cooperation and supplemented as needed. Any expert, or institution, participating in the HBM Expert Panel, can suggest new substances. It is, however, required that any suggestion for a new substance is accompanied by a fact sheet with i.a. toxicological information.

In that list the substances are classified in 13 groups: 1) Phthalates and substitutes; 2) Flame retardants; 3) Per-and polyfluorinated alkyl substances (PFAS); 4) Chemicals used in cosmetics; 5) (Musk) fragrances; 6) Allergenic substances; 7) (Phenol-)Benzothiazoles; 8) SVHC candidates (REACH Art. 57); 9) Aromatic amines; 10) Metals; 11) Nano particles; 12) Contaminants in food; 13) Others. Substance attribution to a group follows either its chemical constitution or use (e.g. Phthalates, including other plasticizers) or its potential health effect (Allergenic substances) depending on the main characteristics. The basic criteria for selection of substances besides their toxicology are their good or very good bioavailability (health relevance), a high likelihood of consumer exposure (consumer relevance) and non-existence or unsuitability of an existing HBM-method (for mother compound or metabolites).

Once a year, following a scientific discussion, the HBM Expert Panel releases a short list of proposed substances with sufficient data available to classify them as eligible for the cooperation

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