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New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission

Petra Apel[a,*], Jürgen Angerer[b], Michael Wilhelm[c], Marike Kolossa-Gehring[a]

[a] German Environment Agency, Dessau-Roßlau/Berlin, Germany
[b] Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA), Germany
[c] Ruhr-University Bochum, Institute for Hygiene, Social and Environmental Medicine, Germany

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ABSTRACT

The German Human Biomonitoring Commission (HBM Commission) derives health-related guidance values (Human Biomonitoring assessment values, HBM values) according to the procedures described in the HBM Commission's position papers. Since the last adaption of the methodology in 2014, the HBM Commission has established a series of new HBM values, mainly on the basis of internationally agreed TDI/RfD values, or of toxicologically well- founded points of departure observed in animal studies. The derivation of these new HBM values for HBCDD, triclosan, 2-MBT, PFOA and PFOS as well as for the metabolites of glycol ethers, of Hexamoll® DINCH®, DPHP, DEHTP, NMP, NEP, and 4-MBC is specified, and the HBM values are presented together with already established HBM values for other substances. Furthermore, the HBM Commission has defined provisional reference values for 2-methoxyacetic acid and for several parabens in the urine of the German population. It has also updated provisional reference values for PCB in the blood of the German population. An overview of all available reference values is given.

Contents

Abbreviations: ADI/TDI, acceptable daily intake/tolerable daily intake; AF, assessment factor; BE, biomonitoring equivalent; BMD/BMDL, benchmark dose/benchmark dose lower bound or benchmark dose lower confidence limit; bw, body weight; DEHTP, di(2-ethylhexyl) terephthalate; DPHP, di(2-propylheptyl) phthalate or bis(2-propylheptyl) benzene-1,2-dicarboxylate; EFSA, European Food Safety Authority; fue, percentage of substance-specific metabolites eliminated with the urine in relation to the total dose of substance administered (molar basis); HBM, human biomonitoring; HBCDD, hexabromocyclododecane; Hexamoll® DINCH®, cyclohexane-1,2-dicarboxylic acid-diisononyl ester or diisononyl cyclohexane-1,2-dicarboxylate; LOAEL, lowest observed adverse effect level; 4-MBC, 3-(4-methylbenzylidene) camphor; 2-MBT, 2-mercaptobenzothiazole; NEP, *N*-ethyl-2-pyrrolidone; NMP, *N*-methyl-2-pyrrolidone; NOAEC, no observed adverse effect concentration; NOAEL, no observed adverse effect level; NOEL, no observed effect level; PBPK/PBTK, physiologically-based pharmacokinetic/physiologically-based toxicokinetic; PCB, polychlorinated biphenyls; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid or perfluorooctane sulfonate; POD, point of departure; PTWI, provisional tolerable weekly intake; RfD, reference dose.

* Corresponding author.
E-mail address: petra.apel@uba.de (P. Apel).

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1. Introduction

Human biomonitoring (HBM) implies the determination of human's internal exposure to chemicals and/or their metabolites by analysing human biological matrices, predominantly human body fluids (biomarkers of exposure). Additionally, HBM can be used to determine early effects of harmful substances (biomarkers of effect). It plays a decisive role in the monitoring of pollutants and the evaluation of the exposure of a population, of population sub-groups or individuals (Kommission HBM, 1996a). Based on the Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH), industry is responsible for the risk assessment of substances and their safety throughout the substance's life cycle. Monitoring to ensure compliance with legislation on chemical safety is the task to be accomplished by politics and the authorities providing scientific advice. Thus, HBM data can be used to assess if regulatory or voluntary measures to reduce exposure are needed. It is also of use to follow up the decrease of the population's exposure to harmful substances, i.e. those that have been banned or restricted for use.

With this paper a description is given of the science-based approaches for developing guidance values to interpret human biomonitoring data. Furthermore an overview of the up-to date guidance values is presented and the board responsible for the determination of the guidance values in Germany is introduced.

2. The HBM Commission

The HBM Commission was established in 1992 and has the mandate to support the German Environment Agency by giving advice concerning HBM related issues.

The HBM Commission's members are appointed every three years by the president of the German Environment Agency (at last in 2016). They are scientists, experts from authorities at the federal and Bundesländer (Federal States) level, universities, public health institutes and clinical institutes. In addition to regular members, permanent guests are invited, representing the Permanent Working Group of the Highest Health Authorities of the Federal States, the Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety, the Federal Ministry of Health, the Robert Koch-Institute and the Federal Institute for Risk Assessment. The main fields of activity of the HBM Commission include for the appointment period 2013–2016:

- the derivation of health-related guidance values (HBM I and HBM II values),
- the description of the background exposure of the population by statistically derived reference values,
- the intensified examination of physiologically-based pharmacokinetic (PBPK) models,
- the advice for the planning and realisation of HBM studies, esp. the German Environmental Survey 2014–2017, GerES V,
- the enhancement of international cooperation for reciprocal transfer of knowledge in the field of HBM and for a comparative analysis of different evaluation methods (Kommission HBM, 2015a).

3. HBM values

Usually HBM values are derived for the general population including all sub-groups and for an assumed lifelong exposure at a corresponding level. Separate HBM values and recommendations for action are derived for particularly vulnerable population groups and/or certain phases of life (e.g. women of child-bearing age, children and the elderly) if needed. The HBM I value represents the concentration of a substance in human biological material at which and below which, according to the current knowledge and assessment by the HBM Commission, there is no risk of adverse health effects, and, consequently, no need for action. The HBM II value describes the concentration of a substance in human biological material at which and above which adverse health effects are possible and, consequently, an acute need for the reduction of exposure and the provision of biomedical advice is given.

For levels between the HBM I value and the HBM II value adverse health effects cannot be excluded any more with sufficient certainty and a follow-up examination should be performed to determine whether there is a continued elevated exposure. If repeated measurements confirm the initial result a search for potential sources of exposure should be undertaken. Exposure to such sources should be minimized or eliminated when achievable with an acceptable level of effort (Kommission HBM, 1996b).

In its new position paper, the HBM Commission describes three methods for deriving HBM values (Kommission HBM, 2014a). Firstly, HBM values can be derived on the basis of experiences with humans. Epidemiological studies providing evidence of a relationship between concentrations of a substance and/or its metabolites in human body fluids and the occurrence of adverse effects are the best fundament for the value's derivation. Secondly, HBM