Human biomonitoring initiative (HBM4EU) - Strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment

Petra Apel, Christophe Rousselle, Rosa Lange, Fatoumata Sissoko, Marike Kolossa-Gehring, Eva Ougier

International Journal of Hygiene and Environmental Health 230 (2020) 113622

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Human biomonitoring initiative (HBM4EU) - Strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment

Petra Apel [a,*], Christophe Rousselle [b], Rosa Lange [a], Fatoumata Sissoko [b], Marike Kolossa-Gehring [a], Eva Ougier [b]

[a] German Environment Agency (UBA), Corrensplatz 1, 14195, Berlin, Germany
[b] French Agency for Food, Environmental and Occupational Health & Safety (ANSES), France

ARTICLE INFO

Keywords:
Human biomonitoring
Internal exposure
Body burden
Biomarker
Risk assessment
Health-based guidance values
Human biomonitoring guidance values
HBM-GV
HBM4EU

ABSTRACT

The European Joint Program "HBM4EU" is a joint effort of 30 countries and the European Environment Agency, co-funded under the European Commission's Horizon 2020 program, for advancing and implementing human biomonitoring (HBM) on a European scale and for providing scientific evidence for chemical policy making. One important outcome will be a Europe-wide improvement and harmonization of health risk assessment following the coordinated derivation or update of health-related guidance values referring to the internal body burden. These guidance values - named HBM guidance values or HBM-GVs - can directly be compared with HBM data. They are derived within HBM4EU for priority substances identified by the HBM4EU chemicals prioritization strategy based on existing needs to answer policy relevant questions as raised by national and EU policy makers. HBM-GVs refer to both the general population and occupationally exposed adults. Reports including the detailed reasoning for the values' proposals are subjected to a consultation process within all partner countries of the consortium to reach a broad scientific consensus on the derivation approach and on the derived values. The final HBM-GVs should be applied first within the HBM4EU project, but may also be useful for regulators and risk assessors outside this project. The subsequent adoption of derived HBM-GVs at EU-level needs to be discussed and decided within the responsible EU bodies. Nevertheless, the establishment of HBM-GVs as part of HBM4EU is already a step forward in strengthening HBM-based policy efforts for public and occupational health.

The strategy for deriving HBM-GVs which is based on already existing approaches from the German HBM Commission, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) as well as from the US-based scientific consultant Summit Toxicology, the allocation of a level of confidence to the derived values, and the consultation process within the project are comprehensively described to enlighten the work accomplished under the HBM4EU initiative.

1. Introduction

The main objectives of HBM studies are at first the identification and quantification of chemicals and/or their metabolites in human biological matrices and then the interpretation of the measurements to identify if chemicals' management measures or regulation is necessary. Assessments can be driven by comparing the measured HBM levels of a selected substance with either a reference value characterizing the general population's background body burden or, preferably, with an internal benchmark level based on epidemiological and/or toxicological data. The interpretation in terms of health risk of measured aggregated exposure levels (i.e. HBM data) can be useful to guide public policies relating to chemical substances (Choi et al., 2015). To this end, health-related assessment values are derived for comparison with general population HBM data by the German HBM Commission (HBM values) and by the team from the Summit Toxicology consulting firm as well as Health Canada (Biomonitoring Equivalents - BEs) (HBM Commission, 2007; Hays et al., 2007, 2008; Angerer et al., 2011; Aylward et al., 2013; St-Amand et al., 2014; Health Canada, 2016a, 2016b; Apel et al., 2017; Faure et al., 2020, Murawski et al., 2020; Duffek et al., 2020 inter alia).

In the field of occupational health, Biological Limit Values (BLVs) set by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) as well as by the former Scientific Committee on

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

https://doi.org/10.1016/j.ijheh.2020.113622
Received 9 March 2020; Received in revised form 25 August 2020; Accepted 1 September 2020
Available online 9 October 2020

Occupational Exposure Limits (SCOEL), Biomonitoring Action Levels (BALs) set by the Finnish Institute of Occupational Health (FIOH), or Biological Tolerance Values at the Workplace (BAT values) set by the German Research Foundation (DFG, 2005) are examples of values derived to help assessing occupational exposure.

Given this diversity of values, the use of common approaches could provide added value to risk assessors by increasing confidence in the derived values. This point has been picked up by the HBM4EU initiative and a harmonized, systematic and generally accepted strategy for the derivation of HBM-GVs at the European level has been developed under task 5.2, based on the current practices for setting health-related assessment values for internal exposure. Exemplary HBM-GVs have been established, which will be used for health-related risk assessments within the HBM4EU project, thereby supplementing already existing risk assessment approaches which only relate to external concentrations of environmental chemicals.

The HBM-GVs already derived refer to selected phthalates and DINCH (Lange et al., submitted), Bisphenol A (Ougier et al., submitted) and cadmium (Lamkarkach et al., submitted). These newly derived or updated (according to the present knowledge) values were shared with all countries involved in the project, together with the information underlying their derivation. A consultation period allowed national experts to provide comments on the values' derivation. The general procedure of this consultation is detailed in section 4 of this article. Further HBM-GVs are planned for the Bisphenols S and F, NMP (1-methyl-2-pyrrolidone) and NEP (1-ethylpyrrolidin-2-one), TDI (Toluene diisocyanate), mercury and chromium, for active ingredients of plant protection products (deltamethrin and cyfluthrin) and the mycotoxin deoxynivalenol (DON), if the toxicological and epidemiological data allow it.

For substances for which assessment values for the internal exposure already exist (HBM values or BEs), these values are taken into account in HBM4EU activities. It is assessed if there is new data justifying an update or if the available values are still valid. In any case, similarities or differences in derivation are highlighted.

This will ensure that comparable and up-to-date interpretations of HBM data are carried out within the framework of HBM4EU.

1.1. HBM-GV definition and application

Health-based HBM-GVs can be used directly for the interpretation of HBM data and thus for the conduction of an improved health risk assessment when compared to a risk assessment performed solely on the basis of estimations of external intakes. They are an easy-to-use tool to assess whether the exposure of the population to environmental chemicals is below the accepted HBM-GV, or to identify the fraction of a population that has biomonitoring levels exceeding this HBM-GV. Thus, these values can facilitate the communication of potential risks to public health and help policy makers to set priorities in the regulation of chemicals. A careful assessment of the extent to which these values can be used to interpret biomonitoring information related to human health is required, and the limitations of the interpretation must also be disclosed (La Kind et al., 2008). In some countries, like Germany, the health-related HBM-I and HBM-II values for the general population are also used to give the study participants and sample donors an approximate orientation with regard to the health relevance of their measurements. The HBM-I value represents hereby the concentration of a substance in human biological material at and below which – according to the knowledge and judgement of the HBM Commission – there is no risk for adverse health effects and, consequently, no need for action. The HBM-II value represents the concentration of a substance in human biological material at and above which – according to the knowledge and judgement of the HBM Commission – there is an increased risk for adverse health effects and, consequently, an immediate need for exposure reduction measures (HBM Commission, 1996; Apel et al., 2017). The uncertainties underlying the derivation of these values as well as the limited interpretability of the measurement results with regard to multiple individual and health-associated factors (lifestyle, age, genetic disposition) are addressed in the information provided to sample donors.

1.2. HBM-GVs derived for the general population

The HBM-GVs derived for the general population (HBM-GV_{GenPop}) represent the concentration of a substance or its specific metabolite(s) in human biological media (e.g. urine, blood, hair) at and below which, according to current knowledge, there is no risk of health impairment anticipated, and consequently no need for action. They are equivalent to the HBM-I values from the German Human Biomonitoring Commission (Angerer et al., 2011; Apel et al., 2017). When they are estimates of chemicals' concentrations in biological matrices consistent with existing external exposure guidance values (toxicity reference values or TRVs), they correspond in this case to BEs (Hays et al., 2007, 2008). This concept for deriving health-related assessment values was adopted by Health Canada for rapid screening health risk assessment (Health Canada, 2016a; Faure et al., 2020).

Specific HBM-GVs may also be derived for particularly vulnerable population groups and/or for certain phases of life by considering differences in physiology (e.g. women of child-bearing age, children, elderly), and these can then be published along with specific recommendations for action. A lifelong exposure is usually assumed for the derivation of an HBM-GV_{GenPop}. For reprotoxic substances however, the exposure during the critical time window is taken into consideration. In case of bioaccumulating substances, HBM-GV_{GenPop} can also be given according to age ranges.

If HBM results of the population for a substance exceed the derived HBM-GV_{GenPop}, this is a strong signal for monitoring the health status of the population, the identification of possible sources of exposure and the assessment of whether and how exposure can be reduced by risk management measures. This signal of a potential public health problem and the potential need for a reduction of exposure should be brought to the attention of decision makers.

When the body of scientific evidence is sufficient to quantify an effect threshold with certainty for a substance (e.g. proteinuria as a renal effect due to cadmium exposure), an HBM-GV_{GenPop} can be derived (provided also the availability of epidemiological, toxicodynamic and toxicokinetic data). For the time being, if no effect threshold can be identified, e.g. for genotoxic carcinogens, HBM-GV_{GenPop} are not proposed for the general population.

1.3. HBM-GVs derived for occupationally exposed adults

The HBM-GVs derived for occupationally exposed adults (HBM-GV_{Worker}) represent a concentration of a substance or its relevant metabolite(s) in human biological media aiming to protect workers exposed to the respective substance regularly (each work day), and over the course of a working life from the adverse effects related to medium- and long-term exposure (DFG, 2002 et seq.; Bolt and Thier, 2006; ANSES, 2014).

The legal background for ensuring the protection of the health and safety of workers from the risks related to chemical agents at work in the EU is framed by the Council Directive 98/24/EC on chemical agents (the Chemical Agents Directive (CAD)) and the Carcinogens and Mutagens (CMD) Directive 2004/37/EC (SCOEL, 2013). These Directives, amended by Directive 2014/27/EU in order to align them to the Classification, Labelling and Packaging (CLP) EU Regulation, set indicative and binding Occupational Exposure Levels (OELs) and Biological Limit Values (BLVs), these last being similar in the definition as the HBM-GV_{Worker}. To date, the only binding BLV concerns lead and its ionic compounds. The process of establishing binding limits includes an assessment of the technical feasibility and socio-economic factors of applying the limit at the workplace.

In case a quantitative risk assessment has to be performed for occupational exposures to non-threshold carcinogenic substances, HBM-

GV_{Worker} can be expressed as a scale of concentrations corresponding to additional lifetime risks 10^{-4}, 10^{-5} and 10^{-6}, provided enough quantitative data allows for it (ANSES, 2014). In this particular case, it has to be acknowledged and clearly specified that the estimated values are "risk-based guidance values" and not "health-based guidance values". The methodology detailed hereafter will however not describe the approach for deriving HBM-GV_{Worker} for non-threshold substances. The approach for deriving risk-based HBM-GV_{Worker} corresponding to additional lifetime risks will be discussed and evaluated in the work frame of the HBM4EU project.

HBM-GV_{Worker} can be considered as guidance values for the limitation of occupational exposures based on health risk assessment. Air monitoring and biological monitoring are two complementary methodologies allowing for the protection of the health of workers exposed to chemicals. Biomonitoring is particularly worthwhile compared to air monitoring for assessing exposure to substances causing systemic effects and having multiple uptake routes (such as or including the dermal route), and/or are bioaccumulating, and/or when the working conditions, the personal protection equipment, inter-individual differences in respiratory ventilation, etc. determine large differences in the internal doses between individuals (ANSES, 2014). Indeed, due to uptake, distribution and elimination kinetics, and biological variability, it is possible for an individual's single measurement to exceed the HBM-GV_{Worker} without that individual incurring an increased health risk. However, exceedance of the HBM-GV_{Worker} observed from a worker sample should motivate an enhanced surveillance. In case measurements in samples obtained from a worker on several occasions persistently exceed the HBM-GV_{Worker} or if the majority of measurements of samples obtained from a group of workers at the same workplace exceed the HBM-GV_{Worker}, the cause of the excessive values must be investigated and proper action taken by risk managers to reduce occupational exposure.

2. Methodology for deriving HBM-GVs for the general population and for occupationally exposed adults

The starting points for drafting the following methodology for HBM-GVs' derivation are the already existing derivation schemes as elaborated and used by the German Human Biomonitoring Commission (HBM Commission, 2007, 2014; Angerer et al., 2011; Apel et al., 2017), by Summit Toxicology, a US-based scientific consultant (Hays et al., 2007, 2008; Aylward et al., 2013) and by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES, 2014).

2.1. Data collection

The data to be collected in order to derive HBM-GVs refer to the following:

- Toxicological data on the substance, i.e. toxicokinetic and toxicodynamic information on the parent compound including information on its mode of action (MOA). By definition, studies examining the toxicokinetics (TK) of a chemical substance are conducted to obtain adequate information on its absorption, distribution, biotransformation (i.e. metabolism) and excretion, to aid in relating concentration or dose to the observed toxicity (OECD, Test No. 417, 2010). The term "toxicodynamic" on the other hand, refers to the process of interaction of chemical substances with the body and the subsequent reactions leading to adverse effects (EFSA glossary).
- Information on the specificity and toxicology of the potential biomarker(s) and the factors that may affect interpretation of the HBM results of the chosen biomarker(s) (co-exposure to other substances for example): a biomarker is defined as any substance, structure or process that can be measured in the body or its products and influences or predicts the incidence of outcome or disease. Biomarkers can be classified into biomarkers of exposure, of effect and of susceptibility (WHO, 2001).

2.2. Options for deriving HBM-GVs

Be it for the derivation of HBM-GV_{GenPop} or of HBM-GV_{Worker}, three options for the HBM-GV's derivation are available. The selection of one of these options is conditioned by the availability of data, their quality and their relevance in deriving HBM-GVs. The three options are presented in the following according to the established order of preference to use them.

2.2.1. First option: HBM-GV derivation from human data based on a relationship between internal concentrations and health effects

The most informative studies for deriving HBM-GVs are well-conducted human studies adequately reporting measured internal concentration levels of a substance, sampling times, analytical methods used, along with the relationships between concentrations of a substance or its metabolites in human biological media and the occurrence of adverse effects. This way, assumptions and uncertainties underlying the extrapolation of toxicological animal data to humans are avoided. If relevant and qualitatively acceptable human studies are available, a key human study together with a Point of Departure (POD) is selected. The POD shall be chosen according to the critical effect, which is considered to be the most sensitive among all adverse effects that may arise from exposure to the substance (e.g. changes in morphology, physiology, growth, development, reproduction or life span resulting in an impairment of functional capacity, in an impairment of the capacity to offset additional stress, or in an increase in sensitivity) (WHO IPCS, 2004; ANSES, 2016). An example of the reasoned selection of a key study among numerous epidemiological studies and a POD ($NOAEC_{serum}$ related to the reduction of vaccine antibody formation) is detailed in EFSA's recent TWI (tolerable weekly intake) draft proposal for the sum of four perfluoroalkyl substances (EFSA, 2020). If necessary, a selected POD has to be corrected by assessment factors (AFs) to obtain the HBM-GV.

Several types of epidemiological studies may contribute to the assessment of a substance's toxicity in humans. For example, cross-sectional field studies may be useful to establish an exposure-effect relationship and to identify a POD. Cohort- and case-control studies may provide powerful evidence of associations between adverse effects and long-term exposure, if the exposure is well characterized and potential bias and confounding factors are well controlled. Indicators calculated in these studies, e.g. the relative risk (RR) for cohort studies as ratio between the occurrence of an event in the exposed group and in the non-exposed group, or the odds ratio (OR) for case-control studies as equivalent of the RR in case of rare diseases, can be used to derive HBM-GVs. Clinical trials and case reports may be considered as supporting evidence in a weight of evidence approach (ANSES, 2014).

Meta-analysis, which consist in a statistical analysis of data collected in separate but similar studies, lead to the estimation of the magnitude of an effect and the associated confidence interval. They are thus very useful for finding critical and quantitative answers to specific questions, hence drawing firmer conclusions than isolated studies would permit. They also improve the strength of the findings obtained (ANSES, 2014; Martin et al., 2018).

Quality assessment of available epidemiological studies is necessary, thereby taking into account e.g. the potential role of bias, confounding factors, and the effect of chance. The assessment can be performed in view of various criteria as e.g. adequate description of the study population, of the effects explored, the exposure levels, statistical methods used, and others. Different methods and systematic tools for carrying out the study evaluation exist, as e.g. the Office of Health Assessment and Translation (OHAT) approach for systematic review and evidence integration (NTP, 2015) or the Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument described by

Table 1
Examples of TRVs for threshold effects set for protecting the general population from chemical exposure.

Country/Region	Agency	Acronym	Name	Exposure route
Europe	EFSA	ADI	Acceptable Daily Intake	Oral
		TDI	Tolerable Daily Intake	Oral
		TWI	Tolerable Weekly Intake	Oral
		TMI	Tolerable Monthly Intake	Oral
Europe	ECHA	Population-DNEL	Population-Derived No-Effect Level	Oral & inhalation & dermal
France	ANSES	TRV	Toxicity Reference Value	Oral & inhalation
		ADI	Admissible Daily Intake	Oral
		TDI	Tolerable Daily Intake	Oral
		TWI	Tolerable Weekly Intake	Oral
		TMI	Tolerable Monthly Intake	Oral
The Netherlands	RIVM (National Institute for Public Health and the Environment)	MPR	Maximum Permissible Risk level	Oral & inhalation
		ADI	Acceptable Daily Intake	Oral
		TCA	Tolerable Concentration in Air	Inhalation
		TDI	Tolerable Daily Intake	Oral
USA	OEHHA (California Office of Environmental Health Hazard Assessment)	REL	Reference Exposure Level	Oral & inhalation
	ATSDR	MRL	Minimum Risk Level	Oral & inhalation
	EPA (Environmental Protection Agency)	RfD	Reference Dose	Oral
		RfC	Reference Concentration	Inhalation
Canada	Health Canada	ADI	Admissible Daily Intake	Oral
		TDI	Tolerable Daily Intake	Oral
		CA	Admissible Concentration in Air	Inhalation
United Nations	WHO	TCA	Tolerable Concentration in Air	Inhalation
		ADI	Acceptable Daily Intake	Oral
		TDI	Tolerable Daily Intake	Oral
		TWI	Tolerable Weekly Intake	Oral

LaKind et al. (2014), which aims at evaluating the quality of research proposals and studies incorporating biomonitoring data on short-lived chemicals. With reference to workers, it has further to be considered that the exposure conditions in the key study are compatible with a scenario of occupational exposure.

2.2.2. Second option: HBM-GV derivation based on a defined external toxicity reference value or on a defined occupational exposure limit

If human data are not sufficient and/or not adequate for deriving an HBM-GV, then a toxicologically justified external exposure guidance value (toxicity reference value – TRV) proposed by a European or relevant non-European institution (e.g. TDI, OEL, see also Table 1 und 2) can be translated into a corresponding HBM-GV. This approach has been previously proposed by Hays et al. (2007, 2008) through the setting of BEs and also by the German HBM Commission with a variant for deriving HBM-I values (HBM Commission, 2007; Angerer et al., 2011) (see also Fig. 1).

The date of the value's establishment, the critical effect underlying the setting of the value, the POD and the AFs determine the TRV selection for the HBM-GV derivation. The rationale for choosing a value over others has to be substantiated in each individual case.

2.2.2.1. General population. Once a TRV is selected, after a critical assessment of the available values, a corresponding concentration of the substance of concern/its metabolite(s) in human biological media can be calculated by means of TK extrapolation (HBM Commission, 2007; Hays et al., 2007, 2008). Additional AFs might have to be applied, depending upon the construction of the selected TRV and especially the critical effect it is based on.

For the identification of an adequate biomarker, information relating to the fraction of absorption, distribution in the body, retention, blood half-life, route of elimination and elimination half-life are considered (Health Canada, 2016b). The selection of the adequate biomarker(s) also depends on the robustness of the data regarding a relationship between the biomarker's concentration and the substance's external exposure levels or between the biomarker's concentration and the internal target tissue concentrations associated with the critical effect underlying the selected TRVs (Angerer et al., 2011).

The approach discussed here relies on the assumption that a steady-state has been reached in the human body, i.e. that a balance exists between the substance's intake and the substance's/metabolite's internal concentration/excretion. Regular intake of a substance may result in such steady-state condition. Under steady-state conditions, the concentration in blood is proportional to the exposure dose per kg of body weight. Thus, steady-state blood, serum or plasma concentrations consistent with the selected TRV can be calculated either by a simple TK model or by a fully developed physiologically based toxicokinetic (PBTK) model (see also Fig. 1). For compounds mainly eliminated through urine and for which suitable urinary biomarker(s) were identified, biomarker(s)' concentrations consistent with a TRV may be calculated based on a urinary mass balance approach (see also Fig. 1). Under steady-state conditions of exposure to the substance, the urinary excretion rate of the biomarker(s) is a constant fraction of the intake rate. Thus, based on human studies exploring the absorption, metabolism and elimination characteristics of the compound, a proportional urinary excretion factor (F_{ue}) for the selected biomarker(s) can be determined, which allows to predict the daily excretion rate of these biomarker(s). The biomarker(s)' steady-state urinary concentrations corresponding to the selected TRV can then be estimated by dividing the respective daily excretion rate by an estimate of the typical daily urinary flow rate. This typical daily urinary flow rate can be appraised by measured data; however, it has to be acknowledged that the urinary flow rate is strongly subject to within- and between individual's variations. Yet, as intake levels (such as ADI or TDI values) are stated pertaining to body weight and as a relation exists between body weight and urine excretion (Ciba-Geigy, 1977), the following mass balance equations (1)–(3) can be proposed:

Situation 1: the biomarker selected is the parent compound

$$\mathrm{HBM-GV_{GenPop}} = \frac{\mathrm{TRV}\cdot\mathrm{Fue}(\mathit{Substance})}{\mathit{Daily\ urinary\ flow\ rate\ adjusted\ to\ the\ bw}} \quad (1)$$

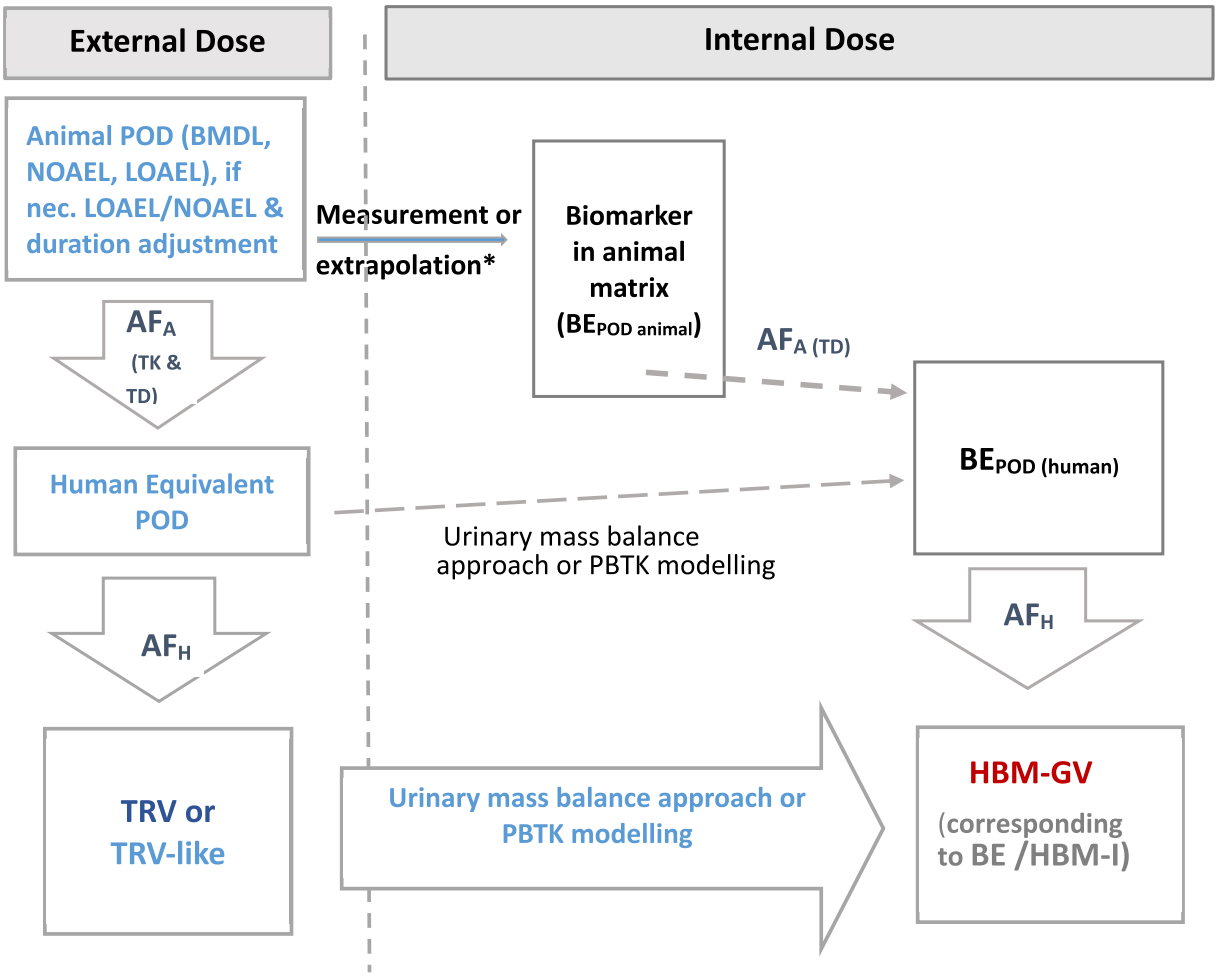

Fig. 1. Schematic illustration of different possibilities to derive the HBM-GV dependent on the availability of human and animal toxicokinetic data or models (modified according to Hays et al., 2008; Angerer et al., 2011).
*biomarker concentration relates directly to critical dose metric; POD, point of departure; $AF_{A\ (TK)}$, toxicokinetic part of the default interspecies assessment factor; $AF_{A\ (TD)}$, toxicodynamic part of the default interspecies assessment factor; AF_H, default intraspecies assessment factor

Situation 2: the biomarker selected is a relevant metabolite

$$HBM - GV_{GenPop} = \frac{TRV \cdot \frac{MW(Metabolite) \cdot Fue(Metabolite)}{MW(Substance)}}{Daily\ urinary\ flow\ rate\ adjusted\ to\ the\ bw} \quad (2)$$

Situation 3: the biomarkers selected are two relevant metabolites

$$HBM - GV_{GenPop} = \frac{TRV \cdot \left[\frac{MW(Met.1) \cdot Fue(Met.1) + MW(Met.2) \cdot Fue(Met.2)}{MW(Substance)}\right]}{Daily\ urinary\ flow\ rate\ adjusted\ to\ the\ bw} \quad (3)$$

bw = body weight [kg]; TRV = Toxicity Reference Value [mg/kg bw/d]; Daily urinary flow rate adjusted to the bw [ml/kg bw/d]; MW = Molecular Weight [g/mol]; F_{ue} = proportional urinary excretion factor.

After review of the available literature on urinary flow rates and the analysis of age dependencies, Aylward et al. (2015) presented for children average daily urinary flow rates between 33.4 ml/kg bw/d (age of 3) to 20.5 ml/kg bw/d (adolescents, age < 15 years). The average daily urinary flow rates currently proposed by the German HBM Commission are 30 ml/kg bw/d and 20 ml/kg bw/d for children and adults respectively. Aylward et al. (2015) observed that the urinary flow rates in adults were consistent across the range of ages from 15 to 80, averaging approximately 20 ml/kg bw/d with no consistent differences between males and females. As with data for children, the coefficient of variation is high (in the order of 100% based on spot samples), indicating that inter-individual variation can be substantial. Pregnant women might have higher urinary flow rates as adults in general, thus, this population group is not specifically covered by the current default value.

According to Lermen et al. (2019), values for daily urinary flow rates of young adults (20–30 years) increased from 1997 to 2016 with a similar rate in both sexes (in males by 32%, from 1532 ml/24 h in 1997 to 2039 ml/24 h in 2016; in females by 36% from 1459 ml/24 h in 1997 to 1987 ml/24 h in 2016) with relatively constant body weights (males: 80 kg; females 60 kg). This is a hint to check the database also for other population groups and to revise the default values assumed for the daily urinary flow rate per kg body weight, where necessary.

The concentration of a substance in urine will depend on the rate of urine production, but also e.g. on the hydration status or the fluid loss via perspiration. Therefore, correction of results based on creatinine concentration or urine density (specific gravity) may be necessary to compensate for the state of dilution and for variability related to the person's age and weight (Viau et al., 2004). However, the creatinine adjustment approach does not achieve a complete compensation for different volumes of excretion per time (Barr et al., 2005; HBM Commission, 2005) and is not necessarily adequate for substances that are not following the urinary excretion pattern of creatinine.

2.2.2.2. Occupationally exposed adults. Occupational exposure limits concerning allowable concentrations of chemical compounds in the ambient air of workplaces that should not be exceeded over a determined reference period, and below which the risk of impaired health is negligible, have been established in several countries worldwide. These

OELs are typically derived based on scientific appraisal by competent national authorities or by scientific committees, as the former Scientific Committee on Occupational Exposure Limits (SCOEL) at European level, or since 2019 by ECHA's Risk Assessment Committee (see Table 2 for an overview). Exposures to chemicals in the workplace are mostly airborne and/or dermal. For substances which are taken up via the skin and enter the bloodstream, monitoring of concentrations in ambient air may not be sufficient, and biological monitoring is necessary as part of the occupational health surveillance. For this reason, SCOEL and ANSES for example set BLVs and the German DFG sets BAT values.

An HBM-GV_{Worker} can be derived by using an OEL as starting point (as listed in Table 2) provided a correlation exists between airborne concentrations of the compound and concentrations of the selected biomarker(s). Such a correlation can be determined from either field studies or volunteer studies, performing both HBM and ambient air concentration measurements. For setting the HBM-GV_{Worker} based on a correlation determined from a volunteer study, additional adjustments may be necessary in order to consider the real occupational exposure conditions, as e.g. the duration of exposure or the workload (ANSES, 2014). If adequate data are available, the translation of an OEL to a corresponding concentration of the selected biomarker(s) is also possible by using TK modelling (compartment model, PBTK model), whereby uncertainties have to be assessed in individual cases. In any case, a thorough understanding of the toxicokinetics of a chemical, for which different routes of exposure contribute to the overall exposure, is necessary to derive a reasonable HBM-GV_{Worker} (e.g. Ougier et al., 2020 submitted).

The selection of (one or more) specific, traceable biomarker(s) of exposure is a crucial step for deriving HBM-GV_{Worker} and the TK and toxicodynamic parameters of potential biomarker(s) in biological media determine the most appropriate sampling times. Urinary HBM measurements in workplaces are usually performed periodically and not over a 24-h period. End of shift sampling is appropriate for rapidly excreted substances. Substances with half-lives in the order of weeks or more may not require a specific sampling time, but steady-state conditions must have been reached after a certain period of exposure (SCOEL, 2013). Sampling times are therefore recommended considering also practical reasons (prior to shift, end of shift, beginning or end of the work-week or at any time).

2.2.3. *Third option: Derivation based on a critical effect observed in experimental animal studies*

If the database on the substance of concern does not allow the derivation of an HBM-GV based on the two previous options, a third option consists in extrapolating a critical dose (POD) identified in a key animal study into a human internal concentration of a selected biomarker, thereby applying default AFs to account for uncertainties in the extrapolation process and whenever available toxicokinetic data and models to reduce uncertainty. This approach, which includes different variants, is also part of the concepts developed by Hays et al. (2007, 2008) and by the German HBM Commission (HBM Commission, 2014; Apel et al., 2017).

The variant via a "TRV-like" value (see Fig. 1) follows acknowledged rules for toxicological data assessment, as required for example under the REACH procedure (ECHA, 2012). At first, a critical effect is determined, i.e. the first adverse effect that occurs at the lowest dose. A priori, this is a protective choice with regard to the other effects observed, if the nature of the dose-effect relationships observed in the animal species from the selected study is transposable to humans (ANSES, 2014). If available, mechanistic *in vitro* studies using preferentially human cells or tissues, as well as human studies, alone not sufficient for option 1, may serve as supporting information for the critical effect determination. The subsequent choice of the key study to characterize the critical effect should preferably be made in such a way that human relevant exposure conditions have been investigated. If two routes of exposure are identified as similarly decisive for the most sensitive adverse systemic effect for human exposure, then a comparative route specific toxicokinetic evaluation (e.g. on absorption, first-pass effect etc.) is required. Generally, differences in the toxicokinetics between routes will be taken into account when deriving HBM-GVs. Selecting a key study also requires the assessment of the study quality, which is related e.g. to the method used, the reporting of the results and the conclusions that are drawn. Elaborated tools providing comprehensive criteria and guidance for reliability evaluations of toxicological data are available, as e.g. the software-based "ToxRTool" (Toxicological data Reliability Assessment Tool) developed by the EU Reference Laboratory for alternatives to animal testing (EURL ECVAM; Schneider et al., 2009) and the Science in Risk Assessment and Policy (SciRAP) web-based platform (Beronius et al., 2018).

For the choice of the POD, the dose-effect curve, the toxicological mechanisms as well as the severity and type of effect are to be taken into account. The preferred option is to use a benchmark dose (BMD) approach. The benchmark response (BMR) is set to a level of e.g. 1%, 5% or 10% increase or decrease in response compared with the background response, according to the critical effect (biological considerations) and also the statistical power of the study (statistical considerations). According to EFSA (2017), a default BMR value of 10% (extra risk) should be used for quantal data and 5% (change in mean response) for continuous data from animal studies. The BMDL as the BMD's lower confidence bound is normally used as the POD. The 2nd option is to select a POD based on a NOAEL/LOAEL pair related to the selected critical effect. In case the available studies allow only for identifying one reference dose (either a LOAEL or a NOAEL), then a NOAEL is preferred over a LOAEL. This will thus affect the previous step of choosing a key study by favoring studies indicating a NOAEL regarding the critical effect. To obtain a "TRV-like" value, default values are used for the individual AFs, as specified in the ECHA Guidance Document R.8 (ECHA, 2012), except if there is a substantiated reason to deviate from them (e.g. if specific substance-relevant information is available). In any case, the choice and magnitude of AFs is to be explained and substantiated. The final step is to calculate from this "TRV-like" value the corresponding concentration of the substance or its biomarker(s) in the selected human biological matrix exactly as described in section 2.2.2 "HBM-GV

Table 2
Examples of occupational exposure limits established for protecting workers from chemical exposures in the ambient air of workplaces.

Country	Agency or committee	Acronym	Name	Pathway
Europe	ECHA	Worker-DNEL	Worker-Derived No-Effect Level	Inhalation
	SCOEL (Scientific Committee on Occupational Exposure Limits)	OEL-TWA	Occupational Exposure Limit - Time Weighted Average	Inhalation
	OSHA (Agency for Safety and Health at Work)	PEL-TWA	Permissible Exposure Level - Time Weighted Average	Inhalation
Germany	DFG	MAK	Maximale Arbeitsplatzkonzentration	Inhalation
France	ANSES	8-h-OEL	8-h occupational exposure limit value	Inhalation
Denmark	OEL setting committee	TWA-8-h	Time Weighted Average - 8-h	Inhalation
The Netherlands	DECOS	TWA-8-h	Time Weighted Average - 8-h	Inhalation
USA	NIOSH (National Institute for Occupational Safety and Health)	REL–TWA	Recommended Exposure Level - Time Weighted Average	Inhalation
		REL-C	Recommended Exposure Level – Ceiling	Inhalation
	ACGIH (American Conference of Governmental Industrial Hygienists)	TLV-TWA	Threshold Limit Values - Time Weighted Average	Inhalation

derivation based on a defined external toxicity reference value or on a defined occupational exposure limit".

Alternatively, the animal external dose POD might first be converted by relevant AFs to a Human Equivalent external dose POD and further to the expected concentration in human blood or urine through appropriate TK modelling. This derivation approach is equivalent to the BE_{POD} approach by Hays et al. (2007, 2008). The subsequent application of intraspecies factors is necessary in order to obtain the HBM-GV, BE or HBM-I value (Angerer et al., 2011) (Fig. 1). Another possibility, preferred if the biomarker is measured in blood, is the estimation of the biomarker's concentration in the animal blood at the external dose POD via TK modelling and then the application of the interspecies toxicodynamic AF. This approach also represents one of the BE_{POD} calculation approaches (Hays et al., 2007, 2008). Here too, the application of the intraspecies factors is necessary for the derivation of an HBM-GV (as well as a BE or HBM-I value) (Angerer et al., 2011) (Fig. 1). The appropriate application of human and animal TK data and models, the consideration of default AFs in the context of internal dose extrapolations, and the relevance of the MOA in TK modelling and identification of screening values have been discussed in detail at an Expert Panel Workshop on BE derivation. The results are comprehensively described by Hays et al. (2008) providing guidance for the most appropriate method.

3. Level of confidence attributed to the derived HBM-GVs

An overall level of confidence is attributed to each derived HBM-GV aiming to reflect the uncertainties related to its derivation. Therefore, the individual criteria described below are assessed and given a high, medium or low confidence level (or their intermediates). By equally combining the confidence levels of each individual criteria, an overall level of confidence is set and described in detail in the respective substance dossier. The option chosen for deriving the HBM-GV will directly influence the overall level of confidence attributed: as human data are considered more reliable over animal studies, HBM-GVs derived by option 1 will have higher levels of confidence than HBM-GVs derived by option 2 or 3. Even if guidance is provided here below to assess the reliability of the data and of the calculation method, levels of confidence are relying on expert judgment.

- Level of confidence in the nature and quality of the data

Epidemiological and/or toxicological studies available should cover many different effects, exposure times and exposure windows. Studies conducted in humans are preferred over animal studies. If there should be only a few animal studies or if available animal studies should be conducted only on a single species, then the level of confidence would be low or medium at best. For reproductive toxicity, a low level of confidence is attributed if only a subchronic study is available; a medium/high level of confidence is attributed if a multi-generational reproductive toxicity study and a developmental study were conducted on two different species.

- Level of confidence in the choice of the critical effect and the mode of action

The likelihood of the transferability of the critical effect (as well as the MOA) from animal species to humans will be given a level of confidence (for the duration and route of exposure considered).

- Level of confidence in the key study

The criteria from e.g. the above mentioned tools, the OHAT approach for systematic review and evidence integration (NTP, 2015) or the Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument (LaKind et al., 2014), are helpful for attributing the level of confidence for a selected key epidemiological study. For a selected key animal study following an OECD guideline at best a medium/high confidence level can be assigned to take into account uncertainties regarding the transferability of study results between species.

- Level of confidence in the choice of the critical dose (POD)

Using a BMDL is considered of higher level of confidence than the use of a NOAEL/LOAEL pair, itself leading to a higher level of confidence than the use of a single LOAEL or NOAEL. The quality of the dose-response relationship (possibly depending on the number of doses tested in the study and the difference in concentration between the doses tested) also determines the level of confidence in the choice of the critical dose.

- Level of confidence with regard to extrapolations across and within species

Using quality PBTK models to extrapolate a "TRV-like" value from a POD is considered more reliable than the use of default AFs accounting for inter- and intra-species differences.

Attributing low levels of confidence for the criteria described here above may also help to highlight the data gaps and to address them to the scientific research community. However, a low level of confidence does not necessarily mean a low level of protection, because the HBM-GV derivation is based on very conservative scenarios and default assumptions, which are addressed in detail in each substance dossier. And of course, an HBM-GV is only derived if certain minimum data requirements are met.

Transparency in the documentation of the level of confidence is also an important issue in the BE derivation (LaKind et al., 2008). In this context, two main elements for assessing the confidence in the derived BE values are highlighted:

1. Understanding of the relationship between the measured biomarker and the critical or relevant target tissue dose metric; and
2. Robustness of the available pharmacokinetic models and data.

As the World Health Organization (WHO, 2006) has already done to characterize and communicate uncertainties in exposure estimation, LaKind et al. (2008) also classify uncertainties as high, medium or low.

4. Consultation process within HBM4EU

The consultation with experts nominated by the countries participating in the European HBM initiative HBM4EU has been organized for:

1. The overall methodology for deriving HBM-GVs for the general population and the occupationally exposed adults as presented here; and
2. The derived HBM-GVs on substances prioritized in HBM4EU.

The documents prepared by the German Environment Agency (UBA) and ANSES are sent for a consultation period to all the countries participating in HBM4EU as well as to the EU Policy Board. A contact point in each country is thereby asked to send out these documents to national experts willing to freely contribute to the scientific relevancy of the work. Comments from members of the EU Policy Board are also sought. The two following forms are systematically sent together with the call for consultation:

- a "Nomination form" explaining the context of the work and requirements for an expert to contribute to the task. This form specifies that the contribution of any national expert must be provided on a

voluntary basis, which means that no remuneration is foreseen for the work provided.
- a "Declaration of Interest" form. The countries are asked to take over the responsibility for checking the Declaration of Interest of any contributing national expert, to ensure the absence of any conflict of interest.

Any expert willing to contribute is requested to fill in the Nomination form and send it along with its comments to UBA and ANSES before the deadline specified in the call for contribution. All comments received during the consultation period are gathered by UBA and ANSES, and taken as much as possible into account to revise and finalize the working document. Responses to main comments are drafted by UBA and ANSES and sent to the experts having brought in their expertise. The whole procedure is outlined in Fig. 2.

5. Results and discussion

The growing availability of European HBM data generated within the HBM4EU program according to standardized methods, allows in principle for conducting health risk assessments based on the measured aggregated internal exposures. However, for the broader use of HBM data in health risk assessment, it is regarded necessary to develop scientifically sound health-related HBM-GVs at EU and/or global level (e.g. WHO, FAO), preferably with at least some regulatory recognition (Louro et al., 2019). Such kind of health-related assessment values (BEs from Summit Toxicology and Health Canada or HBM values from the German HBM Commission) are already available for a variety of substances such as metals and trace elements, plasticizers, flame retardants or active substances in crop protection agents; they also have been used for the screening of national population data, whereby for instance chemical-specific hazard quotients and/or cancer risk estimates were constituted to support prioritization and risk management efforts (Aylward et al., 2013; St-Amand et al., 2014; Apel et al., 2017; Hays and Kirman, 2019; Poddalgoda et al., 2017, 2019; Faure et al., 2020; Murawski et al., 2020; Duffek et al., 2020). At the European level however, there is currently no harmonized method for deriving health-related assessment values. Furthermore, existing values like BEs or HBM-I values should be checked to ensure that they are still up to date. For these reasons the Europe-wide derivation of HBM-GVs for the general population and also in parallel for workers was initiated, whereby for the latter the specifics of this area must be taken into account and disclosed. The general strategy for deriving HBM-GVs agreed between the partners involved in HBM4EU and the newly derived or updated HBM-GVs agreed upon could now lead to a broader perception of this types of values and promote their wider use for health risk assessment.

As described previously, it is possible with the help of HBM-GVs to directly screen if the measurements of internal biomarkers in a broad HBM study are reaching concentrations that may lead to a health risk for the population or, on the contrary, if the HBM measurements are of no concern for health. This is a step forward not only in improving risk assessment for human health with regard to the regulation of chemicals, but also with regard to the tasks of the public health system. Up to now, HBM-GVs have been derived for the general population, and also for workers in the majority of cases, for five phthalates (Di (2-ethylhexyl)phthalate (DEHP), Di (2-propylheptyl)phthalate (DPHP), Butylbenzylphthalate (BBzP), Di-n-butylphthalate (DnBP), and Di-isobutylphthalate (DiBP)), for the alternative plasticizer Diisononylcyclohexane-1,2-dicarboxylate (Hexamoll DINCH®), for Bisphenol A (BPA) and Cadmium (publications submitted). The data basis for the derivation of the values differs quantitatively and qualitatively and the overall levels of confidence are often deemed to be medium. For example, in cases where the conversion of a TRV (or TRV-like value) to a concentration of metabolite(s) in human urine had to be performed, the factor reflecting the elimination of the selected biomarker(s) in urine was calculated only on the basis of studies involving few volunteers and few different doses administered. Thus, the range of variability occurring in the general population due to age, sex, intensity of exposure and other influencing factors is not fully mirrored and potential under- or over-estimation cannot be excluded. For reducing the uncertainties towards this but also towards the extrapolation from a selected animal POD value to the corresponding TRV (or TRV-like value), validated PBTK models for the respective substances could be helpful.

Despite the mentioned uncertainties, it can be assumed that a sufficient level of protection with regard to possible health risks is achieved if the HBM-GVs are complied with, since a precautionary approach to the derivation of the HBM-GVs was chosen (e.g. lifelong exposure assumed). Exceedances of HBM-GVs should be verified by further HBM measurements and, if confirmed, should serve as a clue for the need to reduce

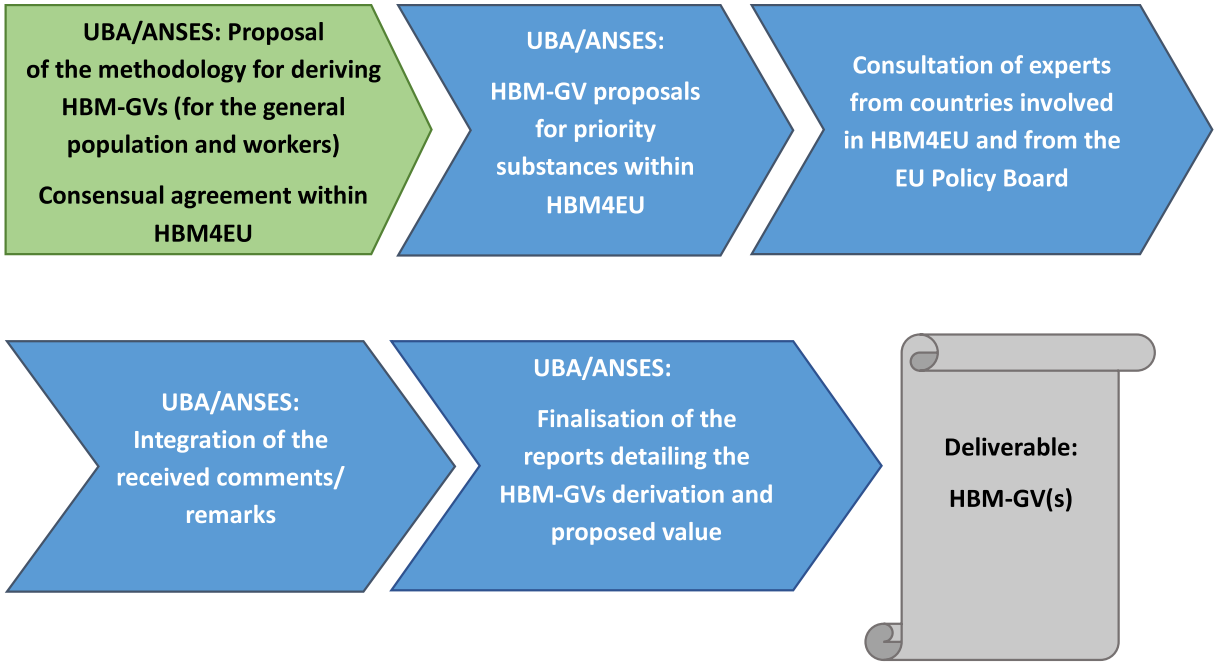

Fig. 2. Agreed strategy for deriving HBM-GVs within HBM4EU and participatory process to set HBM-GVs for specific substances.

exposure and thus to achieve risk minimization.

Differences between the values for workers and adults of the general population are attributable to different key studies that are selected according to their relevance for the different exposure scenarios. For reprotoxic substances, the key study enabling the selection of a POD for a reprotoxic effect for the HBM-GV_{Worker} derivation should not expose the animals throughout pregnancy and lactation, as working women should not be exposed to reprotoxic substances from the moment they have informed their employer of their pregnancy. Nonetheless, pregnant women are very much likely to be exposed at the workplace during the 1st trimester of their pregnancy, before knowing their pregnancy status, thus, depending on the adverse effect and of the window of susceptibility, a key study exposing animals during the gestation period corresponding to the human first pregnancy trimester may be chosen. Moreover, different AFs for intraspecies differences between workers and adults of the general population are used where appropriate. The HBM-GV_{Worker} should allow for occupational risk assessment and, where deemed necessary, implementation of risk management measures for the worker's health protection.

The derivation of HBM-GVs should be based on study results published in the scientific literature following a peer-review process. In some cases, however, studies were provided by industry as part of a regulatory process, but were not published as peer-reviewed papers. These data, although they may not be as comprehensible as desired, should nevertheless also be considered, but their quality should be carefully reviewed and assessed.

Regarding the measurement of urinary biomarker(s), more reliable evaluations of the exposures could be made based on 24-h urine collections, especially if the substance and/or its metabolite(s) has/have a short elimination half-live. However, collecting 24-h urine in large general population biomonitoring studies is often not feasible in practice. Spontaneous/early morning urine samples are more often used in practice. A recent publication by Casas et al. (2018), which quantifies the variability of biomarker measurements of many non-persistent chemicals in urine, shows that for many of these compounds several dozen samples are required to accurately determine exposure over periods of several months. On the other hand, on a population basis, spot and 24-h samples produce rather comparable results, e.g. see Christensen et al. (2012): "Overall, spot urinary concentrations of DEHP metabolites and BPA have variability roughly comparable with corresponding 24-h average concentrations obtained from a comparable population, suggesting that spot samples can be used to characterize population distributions of intakes. However, the analysis also suggests that caution should be exercised when interpreting the high end of spot sample data sets."

Due to the difficulty in correctly interpreting high concentrations of short-lived biomarkers in a distribution of HBM results (differentiation between increased acute or chronic exposure, influencing factors like choice of sampling time in relation to exposure time), Phillips et al. (2014) proposed a stochastically based Monte Carlo approach to calculate a distribution of BE values for a chemical. This approach uses a probabilistic exposure model to simulate realistic scenarios considering variability in physiology and pharmacokinetics at different exposure levels. Using this approach enables a more appropriate assessment of the central tendency and especially the upper percentiles (e.g. 95th percentile) of a population distribution of HBM data and should be taken into account in future with further refinement of this strategy.

Declaration of competing interest

None.

Acknowledgement

This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 733032 HBM4EU, and received co-funding from the author's organisations. The authors thank all other participants that contributed to this work.

Annex - Standardized summarizing factsheet reporting the data underlying the HBM-GVs derivation

Compound	Target population: General population or occupationally exposed adults		
Parameter	Note	Comments	Value/ descriptor
HBM-GV and Status			
HBM-GV	1	Mass/volume [µg/l]	
HBM-GV year of issue	2	Year when the HBM-GV has been issued	
General Information			
CLP-INDEX-No.	3		
EC-No.	4	EINECS – ELINCS - NLP	
CAS-No.	5	Chemical Abstracts Service number	
Harmonized CLP classification	6		
Molar mass	7	[g/mol]	
Biomarker(s)			
Identification	8		
Molar mass of biomarker(s)	9		
Half-life of selected biomarker(s)	10		
Factor for metabolic conversion (F_{ue})	11		
Derivation method, starting point and assessment factors			
Type of derivation method selected	12	Option 1, 2 or 3 as described in this document	
Key study, Author(s), Year	13	Critical study with relevant critical effect	
Species	14		
Exposure route of study	15	Inhalation, oral, dermal	
Study length	16	Days (subchronic, chronic)	
Exposure duration	17	Hrs/day, days/week	
Critical endpoint	18	Effect(s), site of	
Point of departure (POD) value	19	LOAEL, NOAEL, BMDL	

(*continued on next page*)

(*continued*)

Compound	Target population: General population or occupationally exposed adults		
Parameter	Note	Comments	Value/ descriptor
Extrapolations	20	External TRV to HBM-GV; animal POD to external TRV-like to HBM-GV; animal POD to HED_{POD} to BE_{POD} to HBM-GV; …	
PBTK model for animal-human data extrapolation or intra-species extrapolation	21	Name, author, type of PBTK model	
Assessment Factors (AFs)	22		
Rounded value of HBM-GV	23	[µg/l]	
Additional Comments			

Explanation of notes

1) **HBM guidance value (HBM-GV)**: numerical value of the HBM-GV in µg/l
2) **HBM-GV year of issue:** year when the HBM guidance value has been issued by the formal body
3) **CLP Number:** according to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. Implementing the globally harmonized system of chemical classification or GHS. http://guidance.echa.europa.eu/docs/guidance_document/clp_introductory_en.pdf
4) **EC Number:** under European Inventory of Existing Commercial chemical Substances (EINECS), ELINCS (European List of Notified Chemical Substances) in support of Directive 92/32/EEC, the 7th amendment to Directive 67/548/EEC, NLP (No-Longer Polymers)
5) **CAS Number:** collection of disclosed chemical compound information by Chemical Abstracts Service. Almost all molecule databases can be searched by CAS Registry Number
6) **Harmonized CLP classification:** CLP classification including CMR and other health relevant effects. In the case that classification is not harmonized, this should be stated. For self-classifications by industry the ECHA- CLP inventory can be searched at: http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database
7) **Molar mass:** symbol *M*, is a physical property characteristic of a given substance (chemical element or chemical compound), namely its mass per amount of substance [g/mol]
8) **Identification of the selected biomarker(s):** type of biomarker (exposure or effect biomarker(s)), specificity
9) **Molar mass of biomarker(s)**
10) **Half-life of selected biomarker(s):** excretion half-life of the biomarker(s) in the selected biological matrix, in hours or years (indication of the underlying TK study providing the data)
11) **Factor for metabolic conversion (F_{ue}):** in case of urinary biomarker(s), fraction of the biomarker(s) excreted compared to the total dose of the parent compound absorbed (indication of the underlying TK study providing the data)
12) **Derivation method selected**: either option 1 (internal dose-effect relationship from human study/studies) or option 2 (existing TRV) or option 3 (animal POD)
13) **Key study, Authors, Year:** name, authors and year of publication of selected key study/studies (for option 2: key study underlying the selected TRV derivation)
14) Species
15) **Type of study:** route of exposure (oral, dermal or inhalation study)
16) **Study length:** duration of the human or animal study
17) **Exposure duration:** exposure conditions in hours per day and days per week
18) **Critical endpoint:** selected critical adverse effect observed in the study and used for derivation of the HBM-GV ("either the adverse effect that first appears in the dose response curve, or an effect known to be a precursor of the first adverse effect")
19) **Point of departure (POD):** the dose corresponding to a given effect. Lowest concentration or dose at which the critical effect occurred or did not occur. POD will be mainly LOAEL(C), NOAEL(C), or BMDL
20) **Extrapolations of the starting point:** calculation to transpose the selected starting point (POD or TRV) into corresponding human internal biomarker(s) concentration
21) **PBTK model:** in case peer-reviewed PBTK models are available and used for deriving the HBM-GVs, they should be described
22) **Assessment Factors (AF):** numerical adjustment values used to extrapolate the selected POD to the target population. They are physiological scaling factors that account for differences between species and variability within populations. They also account for differences in study protocols, exposure conditions and other uncertainties
23) **Rounded value of the calculated HBM-GV:** numerical value of the HBM-GV and eventually recommendation for the moment of sampling (especially for the occupational field)

References

Angerer, J., Aylward, L.L., Hays, S.M., et al., 2011. Human biomonitoring assessment values: approaches and data requirements. Int. J. Hyg Environ. Health 214 (5), 348–360. http://www.sciencedirect.com/science/article/pii/S1438463911000745.

ANSES, 2014. Reference Document for the derivation and the measurement of exposure limit values for chemical agents in the workplace (OELs). French Agency for Food. Environ. Occupat. Health. Safety (ANSES). https://www.anses.fr/en/system/files/VLEP2009sa0339RaEN.pdf.

ANSES, 2016. Opinion of the French Agency for Food, Environmental and Occupational Health & Safety Regarding the Progress Report on the Assessment of the Weight of Evidence at ANSES: Critical Literature Review and Recommendations at the Hazard Identification Stage. https://www.anses.fr/en/system/files/AUTRE2015SA0089EN.pdf.

Apel, P., Angerer, J., Wilhelm, M., Kolossa-Gehring, M., 2017. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int. J. Hyg Environ. Health 220, 152–166.

Aylward, L.L., Kirman, C.R., Schoeny, R., Portier, C.J., Hays, S.M., 2013. Evaluation of biomonitoring data from the CDC National Exposure Report in a risk assessment context: perspectives across chemicals. Environ. Health Perspect. 121 (3), 287–294.

Aylward, L.L., Hays, S.M., Vezina, A., Deveau, M., St-Amand, A., Nong, A., 2015. Biomonitoring Equivalents for interpretation of urinary fluoride. Regul. Toxicol. Pharmacol. 72 (1), 158–167. https://doi.org/10.1016/j.yrtph.2015.04.005.

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113 (2), 192–200.

Beronius, A., Molander, L., Zilliacus, J., Rudén, C., Hanberg, A., 2018. Testing and refining the Science in Risk Assessment and Policy (SciRAP) web-based platform for evaluating the reliability and relevance of in vivo toxicity studies. Appl Toxicol 38, 1460–1470.

Bolt, H.M., Thier, R., 2006. Biological monitoring and biological limit values (BLV): the strategy of the European union. Mini-review. Toxicol. Lett. 162, 119–124.

Casas, M., Basagaña, X., Sakhi, A.K., Haug, L.S., Philippat, C., Granum, B., Manzano-Salgado, C.B., Brochot, C., Zeman, F., de Bont, J., Andrusaityte, S., Chatzi, L., Donaire-Gonzalez, D., Giorgis-Allemand, L., Gonzalez, J.R., Gracia-Lavedan, E., Grazuleviciene, R., Kampouri, M., Lyon-Caen, S., Pañella, P., Petraviciene, I., Robinson, O., Urquiza, J., Vafeiadi, M., Vernet, C., Waiblinger, D., Wright, J., Thomsen, C., Slama, R., Vrijheid, M., 2018. Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children. Environ. Int. 121 (Pt 1), 561–573. https://doi.org/10.1016/j.envint.2018.09.046, 2018 Oct 6.

Choi, J., Mørck, T.A., Polcher, A., Knudsen, L.E., Joas, A., 2015. Review of the State of the Art of Human Biomonitoring for Chemical Substances and its Application to Human Exposure Assessment for Food Safety. EFSA supporting publication, 2015: EN-724.

Christensen, K.L., Lorber, M., Koch, H.M., Kolossa-Gehring, M., Morgan, M.K., 2012. Population variability of phthalate metabolites and bisphenol A concentrations in spot urine samples versus 24 or 48 h collections. J. Expo. Sci. Environ. Epidemiol. 22 (6), 632–640.

Ciba-Geigy, A.G., 1977. Wissenschaftliche Tabellen Geigy. Teilband Körperflüssigkeiten. CIBA-GEIGY, Basel.

Deutsche Forschungsgemeinschaft, German Research Foundation, 2002. In: The MAK-Collection for Occupational Health and Safety. Wiley-VCH Verlag GmbH & Co. KG aA.

Deutsche Forschungsgemeinschaft, German Research Foundation, 2005. In: Concepts of Biological Limit Values (BAT Values, Eka and BLW). The MAK-Collection Part II: BAT Value Documentations, vol. 4. WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Duffek, A., Conrad, A., Kolossa-Gehring, M., Lange, R., Rucic, E., Schulte, C., Wellmitz, J., 2020. Per- and polyfluoroalkyl substances in blood plasma – results of the German Environmental Survey for children and adolescents 2014–2017 (GerES V). Int. J. Hyg Environ. Health 228, 113549.

ECHA, 2012. Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.8: Characterisation of Dose [Concentration]-response for Human Health. Version: 2.1. https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258.

EFSA. Glossary. https://www.efsa.europa.eu/en/glossary-taxonomy-terms.

EFSA Scientific Committee, 2017. Update: guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 15 (1), 4658, 41 pp.

EFSA, 2020. Public Consultation on the Draft Scientific Opinion on the Risks to Human Health Related to the Presence of Perfluoroalkyl Substances in Food. http://www.efsa.europa.eu/en/consultations/call/public-consultation-draft-scientific-opinion-risks-human-health.

Faure, S., Noisel, N., Werry, K., Karthikeyan, S., Aylward, L.L., St-Amand, A., 2020. Evaluation of human biomonitoring data in a health risk based context: an updated analysis of population level data from the Canadian Health Measures Survey. Int. J. Hyg Environ. Health 223, 267–280.

Hays, S.M., Becker, R.A., Leung, H.W., Aylward, L.L., Pyatt, D.W., 2007. Biomonitoring equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective. Regul. Toxicol. Pharmacol. 47 (1), 96–109.

Hays, S.M., Aylward, L.L., LaKind, J.S., Bartels, M.J., Barton, H.A., Boogaard, P.J., Brunk, C., DiZio, S., Dourson, M., Goldstein, D.A., Lipscomb, J., Kilpatrick, M.E., Krewski, D., Krishnan, K., Nordberg, M., Okino, M., Tan, Y.M., Viau, C., Yager, J.W., 2008. Guidelines for the derivation of biomonitoring equivalents: report from the biomonitoring equivalents expert workshop. Regul. Toxicol. Pharmacol. 51 (3 Suppl. l), 4–15.

Hays, S.M., Kirman, C.R., 2019. Biomonitoring equivalents (BEs) for tetrabromobisphenol A. Regul. Toxicol. Pharmacol. 102, 108–114. https://doi.org/10.1016/j.yrtph.2018.12.014. Epub 2018 Dec 26.

Health Canada, 2016a. Biomonitoring Equivalents as a Screening Tool for Population Level Biomonitoring Data: A Health Canada Perspective. Prepared for: Task Force on Scientific Risk Assessment (TFSRA). Prepared by: Working Group on Biomonitoring Equivalents. Pub, p. 160132.

Health Canada, 2016b. Science Approach Document for the Biomonitoring-based Approach 2 for Barium-containing Substances, Molybdenum-containing Substances, Silver-containing Substances, Thallium-containing Substances and Inorganic Tin-containing Substances. http://www.ec.gc.ca/ese-ees/D335D89F-8F01-45F5-B5E6-B72940A87C8B/SciAD-Biomonitoring-Approach-EN.pdf.

HBM Commission, HBM-Kommission des Umweltbundesamtes, 2007. Ableitung von Human-Biomonitoring-(HBM) Werten auf der Basis tolerabler Aufnahmemengen - Teil II: Grundlagen und Ableitungsweg. Bundesgesundheitsbl 50 (2), 251–254.

HBM Commission, HBM-Kommission des Umweltbundesamtes, 2014. Grundsatzpapier zur Ableitung von HBM-Werten. Bundesgesundheitsbl 57 (1), 138–147.

HBM Commisson, HBM-Kommission des Umweltbundesamtes, 2005. Normierung von Stoffgehalten im Urin – Kreatinin. Bundesgesundheitsbl 48, 616–618.

HBM Commission, HBM-Kommission des Umweltbundesamtes, 1996. Konzept der Referenz- und Human-Biomonitoring-Werte (HBM) in der Umweltmedizin. Bundesgesundheitsbl 39 (6), 221–224.

LaKind, J.S., Aylward, L.L., Brunk, C., DiZio, S., Dourson, M., Goldstein, D.A., Kilpatrick, M.E., Krewski, D., Bartels, M.J., Barton, H.A., Boogaard, P.J., Lipscomb, J., Krishnan, K., Nordberg, M., Okino, M., Tan, Y.M., Viau, C., Yager, J.W., Hays, S.M., 2008. Guidelines for the communication of Biomonitoring Equivalents: report from the biomonitoring equivalents expert workshop. Regul. Toxicol. Pharmacol. 51, S16–S26.

LaKind, J.S., Sobus, J.R., Goodman, M., Barr, D.B., Fürst, P., Albertini, R.J., Arbuckle, T. E., Schoeters, G., Tan, Y.M., Teeguarden, J., Tornero-Velez, R., Weisel, C.P., 2014. A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument. Environ. Int. 73, 195–207. https://doi.org/10.1016/j.envint.2014.07.011.

Lermen, D., Bartel-Steinbach, M., Gwinner, F., Conrad, A., Weber, T., von Briesen, H., Kolossa-Gehring, M., 2019. Trends in characteristics of 24-h urine samples and their relevance for human biomonitoring studies – 20 years of experience in the German Environmental Specimen Bank. Int. J. Hyg Environ. Health 222 (5), 831–839. https://doi.org/10.1016/j.ijheh.2019.04.009.

Louro, H., Heinälä, M., Bessems, J., Buekers, J., Vermeire, T., Woutersen, M., van Engelen, J., Borges, T., Rousselle, C., Ougier, E., Alvito, P., Martins, C., Assunção, R., Silva, M.J., Pronk, A., Schaddelee-Scholten, B., Del Carmen Gonzales, M., de Alba, M., Castaño, A., Viegas, S., Humar-Juric, T., Kononenko, L., Lampen, A., Vinggaard, A.M., Schoeters, G., Kolossa-Gehring, M., Santonen, T., 2019. Human biomonitoring in health risk assessment in Europe: current practices and recommendations for the future. Int. J. Hyg Environ. Health 222, 727–737.

Martin, P., Bladier, C., Meek, B., Bruyere, O., Feinblatt, E., Touvier, M., Watier, L., Makowski, D., 2018. Weight of evidence for hazard identification: a critical review of the literature. Environ. Health Perspect. 126 (7), 076001.

Murawski, A., Schmied-Tobies, M.I.H., Schwedler, G., Rucic, E., Gries, W., Schmidtkunz, C., Küpper, K., Leng, G., Conrad, A., Kolossa-Gehring, M., 2020. 2-Mercaptobenzothiazole in urine of children and adolescents in Germany – human biomonitoring results of the German Environmental Survey 2014–2017 (GerES V). Int. J. Hyg Environ. Health 228, 113540. https://doi.org/10.1016/j.ijheh.2020.113540.

NTP, 2015. Handbook for Conducting a Literature-Based Health Assessment Using Office of Health Assessment and Translation (OHAT) Approach for Systematic Review and Evidence Integration. Research Triangle Park. NTP: National Toxicology Program. http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf.

OECD, 2010. Test No. 417: Toxicokinetics, OECD Guidelines for the Testing of Chemicals, Section, vol. 4. OECD Publishing, Paris. http://www.oecd.org/env/test-no-417-toxicokinetics-9789264070882-en.htm.

Phillips, M.B., Sobus, J.R., George, B.J., Isaacs, K., Conolly, R., Tan, Y.M., 2014. A new method for generating distributions of biomonitoring equivalents to support exposure assessment and prioritization. Regul. Toxicol. Pharmacol. 69 (3), 434–442.

Poddalgoda, D., Macey, K., Assad, H., Krishnan, K., 2017. Development of biomonitoring equivalents for barium in urine and plasma for interpreting human biomonitoring data. Regul. Toxicol. Pharmacol. 86, 303–311.

Poddalgoda, D., Macey, K., Hancock, S., 2019. Derivation of biomonitoring equivalents (BE values) for zinc. Regul. Toxicol. Pharmacol. 106, 178–186.

SCOEL, 2013. Methodology for the Derivation of Occupational Exposure Limits. Scientific Committee on Occupational Exposure Limits (SCOEL). Key Documentation version 7.

Schneider, K., Schwarz, M., Burkholder, I., Kopp-Schneider, A., Edler, L., Kinsner-Ovaskainen, A., Hartung, T., Hoffmann, S., 2009. ToxRTool", a new tool to assess the reliability of toxicological data. Toxicol. Lett. 189 (2), 138–144. https://doi.org/10.1016/j.toxlet.2009.05.013.

St-Amand, A., Werry, K., Aylward, L.L., Hays, S.M., Nong, A., 2014. Screening of population level biomonitoring data from the Canadian Health Measures Survey in a risk-based context. Toxicol. Lett. 231, 126–134.

Viau, C., Lafontaine, M., Payan, J.P., 2004. Creatinine normalization in biological monitoring revisited: the case of 1-hydroxypyrene. Int. Arch. Occup. Environ. Health 77 (3), 177–185.

WHO IPCS (International Programme on Chemical Safety), 2001. Biomarkers in risk assessment: validity and validation. http://www.inchem.org/documents/ehc/ehc/ehc222.htm.

WHO IPCS (International Programme on Chemical Safety & Organisation for Economic Co-operation and Development), 2004. IPCS Risk Assessment Terminology. World Health Organization (WHO), Geneva. http://apps.who.int/iris/bitstream/handle/10665/42908/9241562676.pdf?sequence=1&isAllowed=y.

World Health Organization WHO, 2006. Harmonization Project DRAFT Document for Public and Peer Review, Draft Guidance Document on Characterizing and Communicating Uncertainty in Exposure Assessment. Available from: http://www.who.int/ipcs/methods/harmonization/areas/draftundertainty.pdf.