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COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COC).

Development of Human Biomonitoring Guidance Values in the HBM4EU project

1. This paper outlines the methodology for the derivation of human biomonitoring guidance values by the European Human Biomonitoring Initiative referred to as HBM4EU which is a project designed to develop a harmonised and systematic strategy for the derivation of HBM-GVs. Information is provided concerning other types of human biomonitoring guidance values to allow comparison with established methods, and the potential application of HBM4EU strategy and values and relevance to the UK discussed. An overview of human biomonitoring (HBM) is provided, for information, in Annex A. A description of schemes that gather HBM data is provided in Annex B. Four illustrative case studies on BBzP, DINCH, BPA and Cadmium, conducted by the HBM4EU partners, are included for discussion in Annex C.

Background

2. HBM has been defined as “a scientifically-developed approach for assessing human exposures to natural and synthetic compounds from the environment, occupation, and lifestyle” (Choi et al., 2015). The approach uses single or repeated, controlled measurement of chemical or biochemical markers (biomarkers) in biological samples taken from subjects exposed to the substance of interest occupationally and/or through the general environment (Ladeira and Viegas, 2016).

3. Biomarkers are used as an integrated method of measurement of exposure to a given agent (i.e., internal dose), resulting from multiple pathways of human exposure and also incorporates toxicokinetic information and individual characteristics such as genetically-based susceptibility. More information is available in Annex A.

Human biomonitoring guidance values

4. HBM programmes can provide essential information for identifying chemicals and population exposures to those chemicals that can be assessed against a number of different kinds of derived guidance values (GVs) with regard to potential health risks in specific population subgroups or areas. These can both be important complements to the conventional sources of information for regulatory chemical risk assessments and for supporting public and occupational health protection policies.

5. There is currently a diversity in the derivation of health-based guidance values for both the general population and for occupational exposure. The HBM4EU

initiative aims to increase confidence in HBM-GVs derived using a harmonised, systematic and generally accepted strategy for the derivation of HBM-GVs at the European level.

6. HBM4EU is a joint effort of 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. The initiative is a novel collaboration between scientists and chemical risk assessors and risk managers and has established 'bridges' between the researchers and policy makers to try and deliver benefits to society in terms of enhanced chemical safety.

7. HBM4EU uses HBM to assess existing human exposure to chemicals in Europe, to better understand the associated health impacts and to improve chemical risk assessment. In addition, the findings of the project will inform the safe management of chemicals and so better protect human health in Europe. It is noted that the UK does not have a national HBM programme for comparison of background exposures with those of other countries. The UK has been involved in the project with Public Health England leading the UK input. Further information about the initiative is detailed at: https://www.hbm4eu.eu/

How are HBM4EU-GVs derived?

8. Importantly, the HBM4EU strategy is based on current practices for deriving health-based assessment values based on internal exposure which will supplement those already derived relating to external measurements (Apel et al., 2020). The key schemes on which the HBM-GV derivation methodology is based are those already existing from the German Human Biomonitoring Commission (Shultz et al., 2007; Angerer et al., 2011; Apel et al., 2017), Summit Toxicology (Hays et al., 2007, 2008; Aylward et al., 2013) and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES, 2014).

- The German Human biomonitoring (HBM) values are derived on the basis of toxicological and epidemiological studies. Two levels are defined: HBM-I and HBM-II. The HBM-I-value represents the concentration of a substance in human biological material below which – 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-I-value should therefore be regarded as a verification or control value. The HBM-II-value represents the concentration of a substance in a human biological material above which – according to the knowledge and judgement of the HBM Commission – there is an increased risk for adverse health effects and, consequently, an acute need for exposure reduction measures and the provision of biomedical advice. The HBM-II-value should therefore be regarded as an intervention or action level.

- Summit Toxicology has established methodology for the derivation of biological equivalents (BE) which are a calculated concentration of a biomarker (e.g. chemical in blood or urine) consistent with a health protective guidance value for the general population (e.g. tolerable daily intakes, chronic reference doses). BE development is contingent on the

availability of an appropriate exposure guidance value; a relevant target analyte (biomarker); and pharmacokinetic data. Methods for deriving BE include the urinary mass balance approach (less data informed), the steady-state blood concentrations approach and the internal dose-based extrapolation approach (most data informed).

- ANSES calculate toxicity reference values (TRV) using methodology that defines a critical dose for a toxic effect in humans or animals. Uncertainty factors are applied to the critical dose to derive TRVs for threshold chemicals and for non-threshold chemicals, linear extrapolation from the origin is carried out to determine a potency factor.

9. The HBM-GVs can be used to directly interpret HBM data as they provide a means to assess which members of a population exceed the HBM-GV, thereby facilitating communication of potential risks and identifying any policy priorities. However, it is not currently known to what extent the HBM-GVs can be used to interpret biomonitoring information related to human health at an individual level.

10. Three options are defined in the HBM4EU scheme for the derivation of HBM-GV_{GenPop} or HBM-GV_{Worker}, dependant on the availability and quality of data (Apel et al. 2020). In preference order these are: **(i)** HBM-GV derivation from human data based on a relationship between internal concentrations and health effects; **(ii)** HBM-GV derivation based on a defined external toxicity reference value or on a defined occupational exposure limit; and **(iii)** derivation based on a critical effect observed in experimental animal studies.

HBM-GVs for the general population

11. 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 or concern of health impairment anticipated, and consequently no need for action". As such they are equivalent to the HBM-I values from the German Human Biomonitoring Commission (Angerer et al., 2011; Apel et al., 2017, 2020). Where the HBM-GVs are estimates of the concentration of a chemical in a biological matrix consistent with external exposure GVs, then these may correspond to biological equivalents (BEs) (Hays et al.,2007, 2008 and Apel et al., 2020).

12. The scheme also allows for derivation of HBM-GVs for specific population groups that may be more vulnerable to exposure due to existing medical conditions or, different life stages (e.g., women of child-bearing age, children, elderly). Although a lifelong exposure is usually assumed during the derivation, for reproductive and developmental toxicants, the critical window is considered and for bioaccumulating substances, age-specific values can be given. In the case where HBM data suggest an exceedance of the HBM-GV_{GenPop} this is considered to signal a potential health problem which may require further assessment of the health status of the population, identification of the exposure source and introduction of risk management strategies.

13. At this present time, an HBM-GV_{GenPop} can only be derived for chemicals with a verified threshold effect (e.g., proteinuria as a renal effect due to cadmium exposure). For chemicals where no effect threshold has been established (e.g., for genotoxic carcinogens) HBM-GVs are not currently proposed for the general population.

HBM-GVs for occupationally exposed adults

14. 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 workday), and over the course of a working life from the adverse effects related to medium- and long-term exposure" (Bolt and Thier, 2006; ANSES, 2014). HBM-GV_{Worker} are defined as "guidance values for the limitation of occupational exposures based on health risk assessment" (Apel et al., 2020).

15. Air monitoring (or other occupational hygiene measurements) and biological monitoring are two commonly used methodologies to monitor occupational exposures and protect the health of workers exposed to chemicals. HBM in particular facilitates assessment of the exposure to chemicals where large differences in internal exposure between individuals are brought about through: inter-individual differences (e.g., in respiration rate); differences in working conditions/use of personal protective equipment; potential for multiple routes of exposure; and properties of individual chemicals (e.g., bioaccumulation). Exceedance of the HBM-GV_{Worker} in a worker is considered a signal to introduce enhanced surveillance and to consider exposure reduction. The scheme recommends that if samples from an individual persistently exceed the HBM- GV_{Worker} or if the majority of workers at the same workplace exceed the HBM- GV_{Worker} then the cause of excessive exposure should be identified, and actions taken by risk managers to reduce the exposure.

Level of confidence / classifying uncertainty

16. An important factor that is included in the HBM4EU scheme (as in many other schemes) is the overall level of confidence which is attributed to each derived HBM-GV. The option chosen to derive the HBM-GV directly influences the overall level of confidence with those derived according to option (i) having a higher level of confidence than option (ii) or (iii). In addition, the following individual aspects are given a level of confidence (low, medium or high) and then combined to derive an overall level of confidence:

- Level of confidence in the choice of the critical effect and the mode of action
- Level of confidence in the key study
- Level of confidence in the choice of the critical dose (POD)
- Level of confidence with regard to extrapolations across and within species

17. It should be noted that attributing a low level of confidence does not indicate a low level of protection as the HBM-GV derivation is based on very conservative scenarios and default assumptions. In addition, an HBM-GV can only be derived if specified minimum data requirements are met.

How do HBM4EU values compare with other types of HBGVs?

18. Several programmes have been established that use HBM for a number of purposes which relate to either occupational or, general population exposures. These comprise those which simply gather HBM data so that the uptake of the substance of concern can be understood within the general population, or sub-groups of the population, in a descriptive fashion or, schemes for using this, and other data to establish different kinds of reference values, based on toxicological or percentile distribution values to be used for public health purposes. Of relevance to this paper are those that set reference values, and these are detailed below. Those schemes that gather HBM data alone are of less relevance here but are described, for completeness in Annex B.

Occupational exposure monitoring schemes and biological limits

19. The most well-developed HBM and longest established schemes are those that have been set up to support occupational health risk assessment and control. The workplace, ranging from chemical manufacturing and downstream-using industries, to agriculture and farming and their attendant workforces are cohorts who have been most heavily exposed to many potentially harmful substances. Levels are often many hundreds or even thousands of times greater that the level to which the general public might be exposed and sometimes, exposure can also be to unique chemicals (for example, process chemical intermediates and catalysts). The schemes set out to establish reference values to be used only in the context of adult workers in workplace situations and, as part of a risk reduction strategy, often alongside air monitoring or other occupational hygiene tools. They may be based on known exposure-response relationships for specific toxicological endpoints (if known) or, other more pragmatic parameters described below.

20. In general, workers are primarily exposed to these substances through inhalation in the form of dusts, fumes, gases and vapours and thus, inhalation exposure has been monitored in the short and long-term to assess acute or chronic ill-health effects respectively. Personal airborne sampling techniques (in the breathing zone) have been developed both to monitor and set occupational exposure limits (OELs) in most jurisdictions as usually the primary means of both assessing and controlling exposure to workers; both in the short and long term, as part of the means of preventing ill health.

21. However, for some substances, air monitoring and OELs alone are not sufficient for assessing and controlling total exposure, especially for those chemicals that can readily penetrate the skin such as organophosphate pesticides and substances such as 4,4'-methylenebis(2-chloroaniline), commonly used as a curing agent in polyurethane production, or those that may be rapidly taken up by the gut, such as lead. In these cases, HBM has been developed to *complement* or, in some

rare cases, to virtually replace air monitoring as a means of assessing **total** uptake with the aim of controlling exposure to certain substances. Hence, various forms of "guidelines" or "limits" of HBM occupational standards have evolved which may or may not be part of some regulatory process. Further information on the uses of occupational HBM, particularly within the context of Europe can be found at:

22. The International Commission on Occupational Health (ICOH) have defined Biological Limit Values (BLVs) as the biomarker level that can be directly associated with (the lack of) a biological effect or disease (Mano et al. 2010). There are a number of different organisations that derive occupational BLVs, and some of these are described below.

23. **In the US** the American Conference of Industrial Hygienists (ACGIH), which is the professional non-governmental body, has produced the most internationally-recognised and used OELs (in their case called Threshold Limit Values - TLVs® since the 1940's) and Biological Exposure Indices (BEIs®). These are used as guidelines to control health hazards in the workplace and are not standards. TLVs and BEIs are established following Committee review of available data from a number of disciplines (i.e. industrial hygiene, toxicology, occupational medicine, epidemiology) and represent a level of exposure that can be experienced by a typical worker without adverse health effects. TLVs represent chemical air concentrations, whereas BEIs are guidance values for assessing HBM data. Most BEIs are based on a direct correlation with the corresponding TLV for that substance, i.e., the concentration of that substance, in the blood or urine, that would be reached if that person were exposed to the TLV for a normal 8-hr working day. Some however, such as lead, are more akin to the ICOH definition where there is a good understanding on the adverse health effect(s) related to the biomarker itself.

24. **In Europe**, the best developed and most well-known occupational HBM schemes are those derived **in Germany** by the MAK Commission alongside their "OELs" (known as MAK values). The Commission establishes BAT values ("Biologische Arbeitsstoff-Toleranzwerte": biological tolerance values for occupational settings) and BLW ("Biologische Leit-Werte": Biological Guidance Values) which enable the evaluation of the risk to an individual's health which results from exposure to a substance at the workplace. The BAT value describes 'the occupational-medical and toxicological derived concentration for a substance, its metabolites or a biological effect parameter in the corresponding biological matrix (urine or blood) at which the health of an employee generally is not adversely affected, even when the person is repeatedly exposed during long periods'[1].

25. BAT values are derived by the DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area following Committee review of available studies that either show a relationship between an adverse health effect and external and systemic exposure (measured as parent chemical, metabolite or adduct) or between the systemic exposure and effect parameters and adverse health effects. Sex-related differences that may affect the overall exposure of individual workers are also considered. BLWs are specifically derived for

[1] https://onlinelibrary.wiley.com/doi/pdf/10.1002/9783527826889.oth

carcinogenic substances and, for substances without sufficient data to determine a BAT value. In addition, the MAK also sets BAR values (Biologische Arbeitsstoff-Referenzwerte; biological reference values for agents), biological reference values for occupational settings. These are used where there is insufficient data to set a BAT and are usually based on the 95th percentile of values of that substance (or its metabolite) in the non-occupationally exposed general population. This is considered to be a pragmatic way of facilitating judgement on exposure in an occupational group in the absence of sufficient data.

26. **In France**, the Agency for Food, Environmental and Occupational Health & Safety (ANSES) is responsible for setting OELs. When considered appropriate for a specific chemical, ANSES also recommends biological limit values (BLV) which are intended 'to protect workers from harmful effects related to exposure to the chemical in question, over the medium- or long-term.

27. They take into account repeated exposure throughout a worker's working life'[2]. Two types of BLV are derived, depending on the availability of data:

- where a dose-response relationship has been defined, the BLV is defined on the basis of health data (i.e., a threshold of effect or acceptable risk level for non-threshold carcinogens);

- where such data are not available, the BLV is calculated as the concentration of biomarker that is expected following exposure at the 8-h OEL. In the case of non-threshold carcinogens, a pragmatic BLV may need to be defined if there is insufficient quantitative data, which aims to limit exposure to these chemicals.

Whenever possible, biological reference values (BRV) are also recommended which correspond to 'concentrations found in a general population of adults whose characteristics are similar to those of the French population (preferentially for the biological indicators of exposure) or, by default, in a non-worker control population exposed to the substance being studied (preferentially for the biological indicators of effects)'. BRV's provide a useful reference point when BLVs cannot be determined.

Use of occupational HBM in European regulatory frameworks

28. At the European level, occupational HBM is used in two broad regulatory frameworks. These are the occupational safety and health regulations (OSH) and, in more recent years, the REACH regulations. The EU Directive on the protection of the health and safety of workers from the risks related to chemical agents at work (Directive 98/24/EC) provides the basis for setting indicative occupational exposure limit values (IOELVs) and binding occupational exposure limit values (BOELVs) for workplace air.

29. In addition, this Directive also provides for the basis for setting binding biological limit values. A binding biological limit value (BLV) is the 'limit of the

[2] https://www.anses.fr/en/content/biological-limit-values-chemicals-used-workplace

concentration in the appropriate biological medium of the relevant agent, its metabolite, or an indicator of effect'. If a BLV is established, all Member States are required to include a corresponding national binding biological limit within their own health and safety legislation. These national biological limits must be based on the EU value but may not exceed this value. Also, if a binding BLV exists then health surveillance is a compulsory requirement for individuals working with the hazardous chemical in question. However, to date only one binding BLV exists in the EU which has been set for the blood-lead levels and in the UK, this have been incorporated into the Control of Lead at Work Regulations 2002 (CLAW).

30. Exposure to carcinogens and mutagens at work is regulated under the directive on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Directive 2004/37/EC). Annex III lists the limit values for occupational exposure, but no biological limit values have, as yet been set. It is stated under Annex II of the carcinogens and mutagens directive that health surveillance of the workers exposed to carcinogens and mutagens must include, where appropriate, biological surveillance. Since only one binding biological limit value exists, there are many differences between Member States.

31. The European Scientific Committee on Occupational Exposure Limits (SCOEL) defined: 'A Biological Limit Value (BLV) is a reference value for the evaluation of potential health risk in the practice of occupational health. [...]. Exposure concentrations equivalent to the BLV generally do not affect the health of the employee adversely, when they are attained regularly under workplace conditions (8 hrs/day, 5 days/week), except in cases of hypersensitivity.' It is presented as the concentration in the appropriate biological matrix (blood or urine) of the relevant agent, its metabolite, or biological equivalent. The SCOEL Biological Limit Values (BLV) can be either health-based or exposure-based.

32. A health-based BLV is derived directly from human studies containing data on cohorts with dose response effects or early biological effects. Although these values are preferred, the number of such biomarkers is limited. Therefore, a further option is to derive the BLV from the OEL on the basis of established correlations between air levels and biomarker level. In that case, the BLV is obtained from the corresponding OEL by matching the 'mean' level of a biological index with the corresponding OEL (concentration limit in the workplace air). This is very much the same as the derivation of most of the BEIs set by the US ACGIH. These values are calculated from studies comparing exposures (OEL) and the corresponding biological concentrations observed. For non-traditional working durations (not 8 hours/day, 5 days/week) BLVs can be derived from toxicokinetic and toxicodynamic bases.

33. When an OEL serves as protection against non-systemic effects (e.g., respiratory irritation), and also for substances with significant non-inhalatory exposure routes, the BLV is set to avoid systemic effects (e.g., early renal effects) and is not derived from the OEL. Whenever the toxicological data cannot support a health-based BLV, only a BGV may be established. This value represents the upper concentration of the substance, or a metabolite of the substance, in any appropriate

biological medium corresponding to a specified percentile (generally 90 or 95 percentile) in a defined reference population. This is the equivalent to processes used in setting the BAR values by the German MAK Commission. A value exceeding the BGV might help to identify the need for an expert consideration of the working conditions. Unlike BLVs, BGVs are not health-based and therefore do not set a limit between absence or presence of adverse health effects.

34. In 2014, SCOEL published a List of recommended health-based BLVs and BGVs for 22 substances (SCOEL, 2014). As the IOELV, BLV and BGV recommending function has now been transferred to the Risk Assessment Committee (RAC) of ECHA, further such values, if and when developed, will come from this Committee via ECHA.

35. HBM can be used for risk assessment within the framework of REACH (Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). For the registration of chemicals, a chemical safety report (CSR) is often required that documents the chemical safety assessment undertaken as part of the REACH registration process. One of the objectives of the risk assessment is to determine the Derived No-Effect Level (DNEL) which is defined as the level below which no adverse effects are expected based on the current knowledge. DNELs may be expressed also as internal exposure biomarkers (DNEL*biomarker*). In general, when both internal exposure (HBM) and external exposure monitoring data are available, and effects data corresponding to both types of exposure data are accessible, the most appropriate and/or reliable method should be used for the setting of the DNEL. Interestingly, REACH requirements do not include the need to explain the relationship between internal exposure biomarkers and effects. Therefore, the development of knowledge on the relationship between any biological effects and the internal doses of substances is not required for the REACH registration dossier.

36. **In the UK**, the Health and Safety Executive (HSE) publish detailed guidance on the use of HBM as part of the Control of Substances Hazardous to Health Regulations 1994 (COSHH). Clear criteria for interpreting the results of biological monitoring are essential to their effective use in exposure assessment. HSE have established a system of non-statutory biological monitoring guidance values (BMGVs) to provide an authoritative guide to the interpretation of biological monitoring results. There is no requirement in the COSHH Regulations for compliance with BMGVs. Their purpose is as guidance in the interpretation of biological monitoring data.

37. There are two types of guidance value: Health guidance value (HGV) and Benchmark guidance values (BGV). HGVs are set at a level at which there is no indication, from the scientific evidence available, that the substance being monitored is likely to be injurious to health. Values not greatly in excess of an HGV are unlikely to produce serious short or long-term effects on health. However, regularly exceeding the HGV does indicate that control of exposure may not be adequate. Under these circumstances, employers will need to look at current work practices to see how they can be improved to reduce exposure. BGVs are not health based but

rather, they are considered to be practicable, achievable levels set at the 90th percentile of the current available biological monitoring results collected from a representative sample of workplaces with good occupational hygiene practices. If a result is greater than a BGV it does not necessarily mean that ill health will occur, but it does indicate that control of exposure may not be adequate. Under these circumstances, employers will need to look at current work practices to see how they can be improved to reduce exposure. HSE has set 17 BMGVs and these are to be found in EH40/2005,4th Edition 2020[3].

38. A summary table (Table 1) is provided below to allow comparison of biological monitoring reference values.

[3] https://www.hse.gov.uk/pubns/books/eh40.htm

Table 1 - Summary of biological monitoring reference values

Occupational biological monitoring reference values	**Jurisdiction**	**Regulatory Status**	**Health-based**	**Comment**
Biological limit value (BLV)	EU (SCOEL)	No	Yes	Reference values for evaluating potential health risks in the practice of occupational health. Exposure equivalent to the BLV generally do not affect the health adversely, when attained regularly under workplace conditions, except in cases of hypersensitivity.
Biological guidance value (BGV)	EU (SCOEL)	No	No	This value represents the upper concentration of the substance or a metabolite of the substance in any appropriate biological medium corresponding to a certain percentile (generally 90th or 95th percentile) in a defined reference population.
Biological limit value (BLV) - binding	EU (European Commission)	Yes	Yes	The EU also has the ability to set binding BLVs which it has done only in the case of lead. These values must be adopted by all Member States and incorporated into their national legislation
Biomonitoring guidance value (BMGV)	UK (Health and Safety Executive)	No	Yes or No – depending on the data available	BMGVs are either based on a relationship between biological concentrations and health effects, between biological concentrations and exposure at the level of the airborne Workplace Exposure Limit (WEL) or, on data collected from a representative sample of workplaces correctly applying the principles of good occupational hygiene practice.

Occupational biological monitoring reference values	Jurisdiction	Regulatory Status	Health-based	Comment
Biologische Arbeitsstoff-Toleranzwerte (BAT)	Germany (MAK Commission)	No	Yes	Maximum concentration of a chemical substance (as gas, vapour or particulate matter) in the workplace air which generally does not have known adverse effects on the health of the employee nor cause unreasonable annoyance (e. g. by a nauseous odour) even when the person is repeatedly exposed during long periods, usually for 8 hours daily but assuming on average a 40-hour working week
Biologischer Arbeitsstoff-Referenzwert (BAR)	Germany (MAK Commission)	No	No	Describes the background level of a substance which is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to this substance. The BAR reference values are based on the 95th percentile without regarding effects on health.
Biological limit values (BLV)	France (ANSES)	No	Yes and No – depending on the data available	The biological limit values are recommended by ANSES as biological exposure markers which are considered to be relevant in the workplace. They are intended to protect workers from harmful effects related to exposure to the chemical in question, over the medium- or long-term. They take into account repeated exposure throughout a worker's working life.
Biological Reference values (BRV)	France (ANSES)	No	No	These correspond to concentrations found in a general population of adults whose characteristics are similar to those of the French population (preferentially for the biological indicators of exposure) or, by default, in a non-worker control population exposed to the substance being studied (preferentially for the biological indicators of effects).

Occupational biological monitoring reference values	Jurisdiction	Regulatory Status	Health-based	Comment
Biological Exposure Indices (BEI©)	USA (American Conference of Governmental Hygienists - ACGIH)	No	No	Guidance values for assessing biomonitoring results, and represent levels of determinants most likely to be observed in urine or blood samples collected from healthy workers exposed to the same extent as workers with inhalation exposure at the ACGIH Threshold Limit Value (TLV©).

Use of environmental HBM in European regulatory frameworks

39. Since its establishment in 1992, the German Human Biomonitoring Commission[4] (HBM Commission) has derived health-related guidance values (Human Biomonitoring assessment values, HBM values). Using points of departure from animal investigations (NOAELS, LOAELs etc.) and the collected BM data, they have derived a large number of health-related guidance values (HBM I and HBMII values) for many environmental chemicals. 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 actions can be 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.

40. The HBM I value represents the concentration of a substance in human biological material at 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 intervention. The HBM II value describes the concentration of a substance in human biological matrix 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 some substances, background exposure of the population provides reference values (normally 95th percentile) which can be used for public health purposes (see Annex B for the German and other national general population biomonitoring schemes from which such advisory reference values can be drawn).

41. An interesting and useful development in the interpretation of HBM data has been that of Biomonitoring Equivalents (BE) (Hays and Aylward, 2012). The BE is defined as the concentration of chemical (or metabolite) in blood, urine or some other tissue, consistent with exposure guidance values for the general population such as a Tolerable Daily Intake (TDI), Reference Dose (RfD), Reference Concentration (RfC), or risk specific doses (cancer). In some ways, this approach is the equivalent of the approach described above for the setting of BEIs by the ACGIH where the BEIs are defined as the biomonitoring level consistent with exposure to the airborne TLV for that chemical substance in occupational settings.

42. The BE approach integrates available pharmacokinetic data to convert an existing guidance value into an equivalent concentration in a biological medium (Hays and Aylward, 2009). For the establishment of a BE, data needs to be available regarding the systemic toxicity (usually in rats) to establish a POD for relevant endpoints; a good knowledge of the steady-state toxicokinetics of that substance in rats and humans is also required; and a reliable biomarker of that substance (usually that substance itself or a stable metabolite) must be defined. The BE can then be used with existing HBM datasets to assess if any concerns are raised by the measured exposures that may require action. For example, Health Canada has explored the utility of BEs in interpreting HBM data obtained from results of Canadian population biomonitoring studies (Health Canada, 2016) and has

[4] https://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/german-environmental-survey-geres

contributed to BE development for a number of substances (Hays et al., 2016; Hays et al., 2018).

43. Clearly, it is easier to establish BEs for data rich substances and to date, BEs have been established for over 60 substances. Interpretation should focus on assessing priority for risk assessment follow-up, which may include exposure pathway evaluations to determine major routes and source of exposure, risk assessment evaluations. It should be noted that:

- BEs are not intended to be “bright lines” between safe and unsafe exposures.
- BEs should be used to interpret biomonitoring data at a population level and not for individuals.

Application of HBM4EU scheme and relevance to the UK

44. At this time, HBM-GVs have been derived for the general population, and in the majority of cases, also for workers for the following chemicals: phthalates (Di (2-ethylhexyl)phthalate (DEHP), Di (2-propylheptyl)phthalate (DPHP), Butylbenzyl-phthalate (BBzP), Di-n- butylphthalate (DnBP), and Di-isobutylphthalate (DiBP)); alternative plasticisers (Diisononylcyclohexane-1,2-dicarboxylate (Hexamoll DINCH®); bisphenol A (BPA); and cadmium. To date, the majority have been determined as having ‘medium’ overall levels of confidence. These chemicals have toxicological databases that range in size and quality, but none can be considered as “data poor”. The problem of establishing HBM-based guidelines for data-rich and data-poor (and those in-between) substances has been extensively discussed and some strategies proposed (Bevan et al. 2012).

45. Evaluations of the draft HBM-GVs derived for DINCH, BBzP, BPA and cadmium are provided in Annex C. These evaluations set out the data and process used in developing the HBM-GV recommended values and also provide a number of observations which are of relevance to their potential use in the UK.

46. Lessons learned from these case studies and relevance to the UK can be seen in Annex C. It is relevant to note, that in a survey (n=436) of biomarkers in the urine 15 substances (metals, pesticides, plasticizers etc.) carried out in the UK, randomly across the whole population (Bevan et al. 2013), the results were remarkably similar for those substances to far larger surveys conducted in the US (NHANES) and Germany (GerES). It is thus likely that the range of biomarker levels reported for substances within the HBM4EU may well be relevant for the UK and the HBM-GV values can be considered with this in mind.

Questions for the Committee

47. Members are asked to consider this paper and in particular:

i. Does the Committee wish to make any specific comments on aspects raised in this paper, or are there areas where further information should be included?

ii. Are there any aspects Members are aware of that are not covered by the paper?

iii. Is the strategy developed by HBM4EU robust and scientifically valid?

iv. In the future these values may be regarded as European values, does the Committee agree with the use of HBM-GVs derived by the HBM4EU in the UK?

IEH Consulting under contract supporting the PHE Secretariat
March 2021

References

Angerer J, Aylward LL, Hays SM, et al. (2011) Human biomonitoring assessment values: approaches and data requirements. Int J Hyg Environ Health. 214(5):348-60.

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). Available at: https://www.anses.fr/en/system /files/VLEP2009sa0339RaEN.pdf [accessed February 2021].

Apel P, Angerer J, Wilhelm M, et al. (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(2 Pt A):152-166.

Apel P, Rousselle C, Lange R, et al. (2020) Human biomonitoring initiative (HBM4EU) - Strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. Int J Hyg Environ Health. 9;230:113622.

Aylward L, Kirman C, Schoeny R, et al. (2013) Evaluation of Biomonitoring Data from the CDC National Exposure Report in a Risk Assessment Context: Perspectives across Chemicals. Environmental Health Perspectives 121:3

Bevan R, Angerer J, Cocker J, et al. (2012) Framework for the development and application of environmental biological monitoring guidance values. Regul. Toxicol. Pharm. 63(3):453-460 doi:10.1016/j.yrtph.2012.06.002

Bevan R, Jones K, Cocker J, Assem FL, Levy LS. (2013) Reference ranges for key biomarkers of chemical exposure within the UK population. Int J Hyg Environ Health. 216(2):170-4.

Bolt HM, Thier R. Biological monitoring and Biological Limit Values (BLV): the strategy of the European Union (2006). Toxicol Lett. 162(2-3):119-24.

Hays SM, Aylward LL, LaKind JS, et al. (2008) Biomonitoring Equivalents Expert Workshop. Guidelines for the derivation of Biomonitoring Equivalents: report from the Biomonitoring Equivalents Expert Workshop. Regul Toxicol Pharmacol. 51(3 Suppl):S4-15.

Hays, S.M. and Aylward, L.L. (2009), Using Biomonitoring Equivalents to interpret human biomonitoring data in a public health risk context. J. Appl. Toxicol., 29: 275-288.

Hays S.M and Aylward L.L (2012) Interpreting human biomonitoring data in a public health risk context using Biomonitoring Equivalents. International Journal of Hygiene and Environmental Health 215 (2012) 145– 148

Hays SM, Becker RA, Leung HW, et al. (2007) Biomonitoring equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective. Regul. Toxicol. Pharmacol. 47 (1), 96–109.

Hays SM, Macey K, Poddalgoda D, et al. (2016) Biomonitoring Equivalents for molybdenum. Regul Toxicol Pharmacol, 77:223-9.

Hays SM, Poddalgoda D, Macey K, et al. (2018) Biomonitoring Equivalents for interpretation of urinary iodine. Regul Toxicol Pharmacol. 94:40-46

Health Canada (2016) Biomonitoring Equivalents as a Screening Tool for Population Level Biomonitoring Data: A Health Canada Perspective. Available at: https://www.canada.ca/en/services/health/publications/science-research-data/biomonitoring-equivalents-screening-tool-population-level-data.html

Schulz C, Angerer J, Ewers U et al. (2007) The German Human Biomonitoring Commission, International Journal of Hygiene and Environmental Health, 210(3–4):373-382.

SCOEL, 2014 SCOEL 2014 - Scientific Committee on Occupational Exposure Limits, List of recommended health-based biological limit values (BLVs) and biological guidance values (BGVs), 2014,

CC/2021/01 Annex A

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Development of Human Biomonitoring Guidance Values in the HBM4EU project

Summary of human biomonitoring

Secretariat
March 2021

Human biomonitoring

HBM has been defined as “a scientifically-developed approach for assessing human exposures to natural and synthetic compounds from the environment, occupation, and lifestyle” (Choi et al., 2015). The approach uses repeated, controlled measurement of chemical or biochemical markers in biological samples taken from subjects exposed to the substance of interest occupationally and/or through the general environment (Ladeira and Viegas, 2016).

Exposure assessment is a key factor in any framework used for the human health risk assessment (RA) of chemicals, however this step is often considered the weakest part of the RA process (IGHRC, 2010). The aim of exposure assessment is to determine the amount of a substance, or a metabolite, at target sites for toxicity in an individual. This level may then be compared with known values so enabling conclusions to be drawn regarding the level of risk, or to determine how well-controlled a particular exposure is or has been (Bevan et al., 2017). As an example of the latter, the reduction in population blood-lead levels following the policy decision in the UK to remove lead (lead tetraethyl) from petrol and to further reduce the amount of permitted lead in “lead free petrol” was clearly able to monitor and demonstrate the success of these actions (Quinn and Delves, 1987).

When assessing human exposure, it is not usually possible to obtain samples from target sites or organs of toxicity. The default approach to estimate human exposure is to either consider external exposure only or to model internal exposure from external measurements; both of these approaches are associated with a number of uncertainties which, when combined, may overestimate actual internal exposure. An underestimation of exposure can also occur if all sources and routes of exposure to a chemical, or mixture, are not understood or considered (Cherrie et al., 2006).

HBM assesses exposure through the measurement of internal levels of a chemical, its metabolites or a surrogate marker of its effects in a human biological sample, typically urine or blood; it is not however a measure of health (Bevan et al., 2017). Other tissues can be used for HBM purposes such as hair and nails but usually, urine or blood are the preferred tissues for most forms of routine occupational or general population HBM surveys or investigations for practical reasons. HBM data is a direct reflection of the total body burden or biological effects resulting from intake via all routes of exposure, i.e., inhalation, dermal absorption, and ingestion, including hand-to-mouth transfer in children. Importantly, interindividual variability in exposure levels, metabolism and excretion rates are also taken into consideration, together with other modifying influences in physiology, bioavailability, bioaccumulation and persistency, all of which can contribute to the levels of environmental chemicals present *in vivo* (Angerer et al., 2007; Ladeira and Viegas, 2016). Physiologically-based pharmacokinetics (PBPK) modelling can also help assess links between exposure to chemicals and observed HBM data (Sarigiannis et al., 2019).

As shown in Figure 1, HBM can be considered complementary to environmental monitoring for enabling exposure assessment. In HBM, it is possible to accurately quantify a substance, metabolite or a surrogate marker of its effect in a suitable sample of biological material obtained from an individual. In the same way as for

environmental monitoring, the aim is to relate the result to an internal dose of a substance available to cause toxic effects and so, similarly, there are a range of uncertainties involved. These principally involve metabolic variation, extent of bioaccumulation, elimination kinetics and, when using spot[5] urine samples, correcting for hydration may be important.

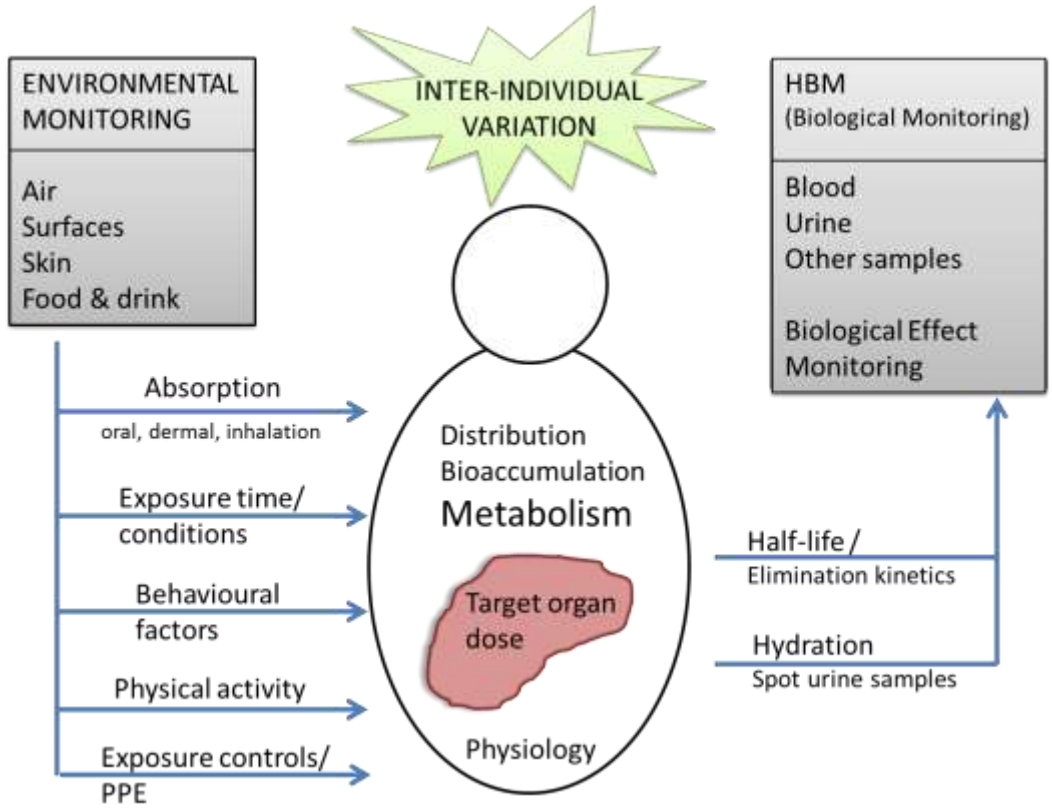

Figure 1: An overview of some of the tools available for exposure assessment. A variety of different sources can be measured using environmental analysis. Several factors determine an individual's actual exposure, while further biological variables (inter-individual variation) affect the internal dose available to exert toxic effects at target sites. HBM reflects the absorbed dose and a range of sample types have been used. However, factors such as elimination kinetics and hydration (for spot urine samples) can result in variation between individuals. Thus, biomarker levels are a substance-specific dynamic process, dependent on the route and duration of exposure and the time since cessation of exposure. PPE: Personal Protection Equipment.

The use of biomarkers in HBM

HBM analyses human tissues and fluids for biomarkers which have been defined as the chemical of interest or its metabolites or, "an alteration in cellular or biochemical components, processes, structure or functions that is measurable in a biological system or sample, but is not a measure of the disease, disorder or condition itself". Three main categories of biomarkers have been defined as biomarkers of exposure,

[5] A single untimed urine sample, voided spontaneously by the patient. This type of sample differs from a timed urinary specimen, which represents all the urine a patient produces over a set period, for example, 24-hr period.

effect, and susceptibility, depending on their toxicological significance (Ladeira and Viegas, 2016).

Biomarkers of exposure

These are more fully defined as “chemical substances, their metabolites, or reaction products in human tissues or specimens such as blood, urine, hair, adipose tissue, teeth, saliva, breast milk, and semen” (Choi et al., 2015). Biomarkers of exposure, when available, are the preferred choice for monitoring exposure to environmental pollutants (occupational or non-occupational) as they assess the aggregated exposure by all routes at an individual level and can be used in conjunction with standard environmental monitoring (Ladeira and Viegas, 2016).

Biomarkers of exposure are further divided into those reflecting ‘internal dose’ and those reflecting ‘effective dose’. The concentration of a chemical (or metabolite) in blood following exposure is a basic measure of the internal dose, indicating the likely level of chemical (or metabolite) at the target site. The effective dose is a more accurate measurement of the exposure levels associated with the target molecule, structure or cell itself (Ladeira and Viegas, 2016).

Biomarkers of effect

Defined by The International Programme on Chemical Safety as “a measurable biochemical, physiological, behavioural or other alteration within an organism that, depending upon the magnitude, can be recognised as associated with an established or possible health impairment or disease” (Barrett et al., 1997). Biomarkers of effect can occur as a result of exposure to a range of chemical, physical and biological agents and can be at the level of the whole organism, organ function, tissue, individual cell or subcellular. These biomarkers are widely used in HBM and should ideally reflect early reversible changes in an exposed organism (Ladeira and Viegas, 2016). Genotoxicity biomarkers are an important group of biomarkers of effect and include chromosomal aberrations, micronuclei and the comet assay, which can be effective in distinguishing exposed from non-exposed subjects at high exposure (typically in occupational studies). In addition, increases in these ‘surrogate’ genotoxicity biomarkers of effect are considered to indicate early disease-related changes where it has been shown that the surrogate biomarker mimics the disease-causing genotoxic events (Bonnassi et al., 2011).

Biomarkers of susceptibility

This group of biomarkers reflect individual characteristics (inherent or acquired) of an organism that make it more susceptible to the adverse effects caused by exposure to a specific substance or agent. Differences in response of an individual to the same exposure scenario may have several causes ranging from differences in genetic make-up to the influence of external variables such as diet (Manno et al., 2010). Biomarkers of susceptibility encompass factors linked to toxicokinetics including enzymes of activation and detoxification, repair enzymes, and changes in target molecules for toxic chemicals and are particularly useful in helping to explain interindividual variation. Biomarkers of susceptibility do not represent stages along

the dose-response mechanistic sequence, but instead represent conditions that alter the rate of transition between the stages or molecular events (Ladeira and Viegas, 2016).

All types of biomarker are the result of complex exposure pathways specific to the individual and other individual characteristics including variances in toxicokinetics and genetic susceptibility. To be relevant for widespread use, it is considered that biomarkers should be sensitive, specific, biologically relevant, feasible, practical and inexpensive to monitor (Angerer, 2007).

Strategic uses of HBM

HBM has evolved to be used for a number of different purposes in both occupational and general population settings, although the technical and analytical aspects may be the same for either. It may be used for research purpose to address specific questions or, for general population surveys. It can also be used for targeted surveys/investigations into specific sections of the population such as pregnant women or children. Probably the most well-developed use of HBM has been in occupational settings where exposures to a chemical of particular concern might be relatively high. Here routine HBM might be more informative about risk than air monitoring and, various types of reference values used for risk management might exist for the chemical of concern (Bevan et al., 2017). In the general populations, it is often used to inform on exposure to chemical of particular concern and also, for changes over time (increase or decrease) for substances of interest related to industrial or consumer usage to existing or newly-introduced substances.

Strengths and weaknesses of HBM

The discipline of HBM has existed for many decades with the establishment of numerous HBM studies, mainly concentrated in Europe and the USA, which initially focused on occupational exposure. There has been an expansion in the use of HBM into the field of environmental and consumer exposure analysis as the capability to measure small amounts of chemicals in human samples has increased (Choi et al., 2016; Bevan et al., 2017). At the present time, HBM is well-developed and widely used in both the occupational and environmental settings across Europe, North America and parts of Asia, particularly Japan, Korea, China and Australia. Indeed, as HBM is also beginning to be used in countries such as Brazil, India and South Africa it can now be considered worldwide, although limited in breadth in some continents. HBM as a tool for occupational and environmental exposure has been the subject of several recent reviews (Bean et al. 2015; Bevan et al. 2012; Bevan et al., 2017; Boogaard et al. 2011; Choi et al., 2016; Cocker et al. 2014; Exley et al. 2015; Faure et al., 2020; Ganzleben et al., 2017; Hays and Aylward 2012; Joas et al. 2015; Ladeira and Viegas, 2016; Scheepers et al. 2011; Scheepers and Smolders 2014; Scheepers et al. 2014; Smolders et al. 2015; Sobus et al. 2015).

The main strength of HBM is that it is the only direct method of determining whether exposure of an individual (or population) to a particular chemical has occurred, how large that exposure has been and whether the exposure has changed over time (Choi et al, 2015). This is particularly useful from a public health viewpoint to help

evaluate and demonstrate, in some cases policy and/or regulatory efficacy. Cross-sectional HBM data reflects current exposure (depending on the half-life of the substance of concern) and long-term trends in exposure patterns can be characterised through repetitive sampling over time in the same population. HBM can therefore identify where chemical exposures are occurring in regions or populations, what the total level of exposure is from all sources, whether the exposure is evolving over time and, if intended mitigation measures have indeed resulted in decreased exposure (RPA, 2017).

HBM has, of course, some limitations which should be considered when setting up sampling programmes and interpreting data. The measurement of metabolites represents a proxy for the parent compound which will introduce some uncertainty into the exposure assessment. In a similar way, biomarkers of exposure are proxies present in easily accessible tissues and fluids and so may not represent levels in the target organs. In addition, total body burdens may also be difficult to link to specific exposure scenarios, for example to assess whether the source of a chemical is occupational or non-occupational or, a mixture of both (RPA, 2017).

Some of the strengths and weaknesses of HBM in relation to their use in risk assessment are summarised in Table A.1. below. Although weaknesses are apparent, these can be minimised, if understood, through careful study design. In comparison to environmental monitoring, HBM additionally requires toxicological data (particularly metabolism data) and some knowledge of the dynamic nature of biomarker levels (Bevan et al., 2017).

Table A.1 Summary of strengths and weaknesses of HBM for use in risk assessment

Strength	**Weakness**	**Comment**
Measures actual internal exposure. Direct and objective exposure assessment	Cannot distinguish between different exposure routes into body even in the same environment	In the occupational setting, accounts for any exposure controls or protective equipment
Specific to an individual. Or can be applied to population exposure.	**Is a snapshot of exposure.** Biomarker levels are dynamic; related to half-life, exposure duration and time post-exposure	Useful for highlighting behavioural factors; essential that comprehensive behavioural observations are made
Incorporates inter-individual variability in toxicokinetics and physiology		HBM can be used to test the assumptions used in traditional exposure assessment models Important to consider kinetics to ensure appropriate exposure time frame is captured
Biological-effect markers allow detection of early, reversible, health effects	Not many validated biological effect markers in use. Need to be specific	Most effect biomarkers not specific so not possible to relate endpoint to a specific substance

Strength	Weakness	Comment
Use of benchmark values (e.g. P90 level) can identify individuals at increased risk even in the absence of detailed toxicology knowledge	Relation to environmental levels introduces several areas of uncertainty	Debate about the relevance of correlating to environmental levels; use of separate, specific reference ranges for HBM (e.g. bioequivalences)
Potential for use of computational modelling e.g. PBPK to improve understanding of the relationship between biomarker levels and dose	Limited availability of human exposure data. Where conducted, human volunteer exposure studies are extremely small-scale	Computational modelling can help to identify areas where better human toxicity data are required, which will then improve the model in a positive feedback loop

Source – Bevan et al. (2017)

Whilst HBM has been used in chemical RA, from a regulatory RA perspective it is considered there is a need "to develop a consistent and rational HBM approach as a complementary tool to assist evidence based public health and environmental measures, including awareness raising for preventive actions" (WHO/IPCS, 2010). The US National Academies of Sciences, Engineering and Medicine report on "Using 21st Century Science to Improve Risk-Related Evaluations" (USNAS, 2017) lays out recommendations to incorporate HBM into risk-based evaluations as an essential tool that allows for advances in exposure science and epidemiology (Ganzleben et al., 2017). An overview and comparative analysis of current national HBM survey programmes is presented in the following section.

Summary

- HBM is a scientifically-developed approach for assessing human exposures to compounds from the environment, occupation, and lifestyle.

- Biomarkers are used as an integrated method of measurement of exposure to a given agent (i.e., internal dose), resulting from complex pathways of human exposure; it also incorporates toxicokinetic information and individual characteristics such as genetically-based susceptibility.

- HBM programmes provide essential information for identifying chemicals that need to be assessed with regard to potential health risks in specific population subgroups or areas. It can be an important complement to the conventional sources of information for regulatory risk assessments and for supporting public and occupational health protection policies.

- HBM is the only available tool that integrates exposures from all sources and provides data for epidemiological studies of association strengths, dose response relationships, and others. However, it does not differentiate the exposure by source.

- It is important to note that HBM alone cannot provide information on how long a chemical has been in the body. It should be used in conjunction with exposure and health assessments. Linking biomonitoring data with dose,

exposure, and environmental concentrations requires refined modelling tools (e.g., PBPK models, probabilistic source-to-dose models, and interfaces between exposure and PBPK models), advanced statistical approaches, and information collection tools to improve the interpretation of linkages and to reduce uncertainties.

- Additional data should be collected (e.g., from questionnaires, interviews, etc) to provide information about potential sources, namely from patterns of dietary habits, hobbies and other possible confounder factors.

- The analysis of HBM data related with environmental monitoring and other data of pertinent environmental sources, such as lifestyle and diet, can reveal major sources and pathways of exposure, identify risk factors and provide support to targeted interventions.

- The implementation of standardised approaches to surveillance is mandatory to ensure international comparability of human biomonitoring data, support for policy actions and targeted interventions by identifying populations with elevated exposure levels, enabling follow-up monitoring to evaluate intervention effectiveness.

Annex A References

Angerer J, Ewers U, Wilhelm M (2007) Human biomonitoring: state of the art. Int J Hyg Environ Health 210: 201-228.

Barrett JC, Vainio H, Peakall D, et al. (1997) 12th meeting of the Scientific Group on Methodologies for the Safety Evaluation of Chemicals: susceptibility to environmental hazards, Environ. Health Perspect., 105 Suppl 4, 699–737.

Bean HD, Pleil JD, Hill JE (2015) Editorial: New analytical and statistical approaches for interpreting the relationships among environmental stressors and biomarkers. Biomarkers 20(1):1-4 doi:10.3109/1354750X.2014.985254

Bevan R, Angerer J, Cocker J, et al. (2012) Framework for the development and application of environmental biological monitoring guidance values. Regul. Toxicol. Pharm. 63(3):453-460 doi:10.1016/j.yrtph.2012.06.002

Bevan R, Brown T, Matthies F, et al. (2017). Human biomonitoring data collection from occupational exposure to pesticides. EFSA Supporting Publications. 14. 1185E-n/a. 10.2903/sp.efsa.2017.EN-1185.

Bonassi S, El-Zein R, Bolognesi C, et al. (2011) Micronuclei frequency in peripheral blood lymphocytes and cancer risk: evidence from human studies. *Mutagenesis*, Volume 26, Issue 1, January 2011, Pages 93–100, https://doi.org/10.1093/mutage/geq075

Boogaard PJ, Hays SM, Aylward LL (2011) Human biomonitoring as a pragmatic tool to support health risk management of chemicals - Examples under the EU REACH programme. Regul. Toxicol. Pharm. 59(1):125-132 doi:10.1016/j.yrtph.2010.09.015

Cherrie JW, Semple S, Christopher Y, Saleem A, Hughson GW, Philips A. How important is inadvertent ingestion of hazardous substances at work? Ann Occup Hyg. 2006 Oct;50(7):693-704.

Choi J, Morck TA, Joas A, et al. (2015) Major national human biomonitoring programs in chemical exposure assessment, Environmental Science, 5(2), 782-802.

Cocker J (2014) A perspective on biological monitoring guidance values. Toxicol Lett 231(2):122-125 doi:10.1016/j.toxlet.2014.09.010

Exley K, Aerts D, Biot P, et al. (2015) Pilot study testing a European human biomonitoring framework for biomarkers of chemical exposure in children and their mothers: experiences in the UK. Environmental Science and Pollution Research 22(20):15821-15834 doi:10.1007/s11356-015-4772-4

Faure S, Noisel N, Werry K, et al. (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. International Journal of Hygiene and Environmental Health, 223: 267-280.

Ganzleben C, Antignac JP, Barouki R, et al. (2017) Human biomonitoring as a tool to support chemicals regulation in the European Union. Int J Hyg Environ Health, 220(2 Pt A):94-97.

Hays SM, Aylward LL (2012) Interpreting human biomonitoring data in a public health risk context using Biomonitoring Equivalents. International Journal of Hygiene and Environmental Health 215(2):145-148 doi:10.1016/j.ijheh.2011.09.011

IGHRC (2010) Current Approaches to Exposure Modelling in UK Government Departments and Agencies (cr15). Institute of Environment and Health, Cranfield University, UK.

Joas A, Knudsen LE, Kolossa-Gehring M, et al. (2015) Policy recommendations and cost implications for a more sustainable framework for European human biomonitoring surveys. Environmental Research 141:42-57 doi:10.1016/j.envres.2014.10.012

Ladeira C, Viegas S. (2016) Human biomonitoring: an overview on biomarkers and their application in occupational and environmental health. Biomonitong, 3(1):15-24.

Manno M., Viau C., in collaboration with, Cocker J., Colosio C., Lowry L., et al., Biomonitoring for occupational health risk assessment (BOHRA), Toxicol. Lett., 2010, 192, 3–16.

National Academies of Sciences, Engineering, and Medicine; Division on Earth and Life Studies; Board on Environmental Studies and Toxicology; Committee on Incorporating 21st Century Science into Risk-Based Evaluations. Using 21st Century Science to Improve Risk-Related Evaluations. Washington (DC): National Academies Press (US); 2017 Jan 5. PMID: 28267305.

Quinn MJ, Delves HT (1987) UK Blood Lead Monitoring Programme 1984-1987: protocol and results for 1984. Hum Toxicol. 6(6):459-74.

RPA, HSL, IEH (2017). Human biomonitoring data collection from occupational exposure to pesticides – Final Report, EFSA supporting publication 2017:EN-1185. 207 pp.

Sarigiannis DA, Karakitsios S, Dominguez-Romero E, et al. (2019) Physiology-based toxicokinetic modelling in the frame of the European Human Biomonitoring Initiative. Environ Res.172:216-230.

Scheepers PTJ, Bos PMJ, Konings J, et al. (2011) Application of biological monitoring for exposure assessment following chemical incidents: A procedure for decision making. Journal of Exposure Science and Environmental Epidemiology 21(3):247-261 doi:10.1038/jes.2010.4

Scheepers PTJ, Smolders R (2014) Identifying a role for human biomonitoring in incidents involving hazardous materials. Toxicol. Lett. 231(3):291-294 doi:10.1016/j.toxlet.2014.11.003

Smolders R, Den Hond E, Koppen G, et al. (2015) Interpreting biomarker data from the COPHES/DEMOCOPHES twin projects: Using external exposure data to

understand biomarker differences among countries. Environmental Research 141:86-95 doi:10.1016/j.envres.2014.08.016

Sobus JR, DeWoskin RS, Tan YM, et al. (2015) Uses of NHANES Biomarker Data for Chemical Risk Assessment: Trends, Challenges, and Opportunities. Environ. Health Perspect. 123(10):919-927 doi:10.1289/ehp.1409177

WHO/IPCS (2010) WHO Human Health Risk Assessment Toolkit: Chemical Hazards. Available at: https://apps.who.int/iris/bitstream/handle/10665/44458/9789241548076_eng.pdf [accessed February 2021]

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Development of Human Biomonitoring Guidance Values in the HBM4EU project

Environmental and consumer exposure monitoring schemes

Secretariat
March 2021

Environmental and consumer exposure monitoring schemes

Human biomonitoring schemes and programmes in the general population for adults and children have been carried out for a wide range of purposes and for a wide range of natural and anthropogenic chemical substances; these may or may not include biomarkers of effect and naturally occurring endogenous substances (e.g., hormones) which may be perturbed by the excess uptake of chemicals and contaminants. These HBM schemes may be cross-sectional or longitudinal in nature and may be designed as investigations to test a specific hypothesis or, more of a general survey to assess human uptake to a wide range of substances, often of particular toxic or health concern. These later surveys often act a valuable source of reliable data that can be drawn upon to test various health-related hypotheses at a later date.

To determine whether the general population, or a subset thereof, is exposed to specific and potentially harmful chemicals, a number of national HBM survey programmes have been established worldwide. These surveys allow monitoring of the exposure of the general population to environmental contaminants, and some have allowed national reference values for certain chemicals which can then be used in public health policies in a number of ways (e.g., exposure reduction programmes, advice to the public etc.). The main programmes are described below and a useful fuller description of many is given by Choi and colleagues (Choi et al. 2015). Apart from chemical contaminants, some schemes may now also include cytogenetic biomarkers in the blood and other markers of DNA and oxidative stress.

The US National Health and Nutrition Examination Survey (NHANES)[6]

NHANES is considered the most extensive and comprehensive of the HBM programmes with great effort devoted to the development of sensitive and specific analytical methods and the refinement of HBM tools. It is an ongoing cross-sectional programme aimed to assess the health and nutritional status of adults and children in the US. Developed in the early 1960s, NHANES has now become a major programme of the National Centre for Health Statistics and a part of the Centres for Disease Control and Prevention (CDC). Since 1999, NHANES has been a continuous annual programme. One of the key components of NHANES is the analysis of chemical exposure in the general US population using blood and urine samples collected from the participants. The chemicals or classes of chemicals analysed in the recent NHANES round are wide and range from metals and pesticides to flame retardants and plasticisers. The NHANES database can be used by researchers, and many papers have been published using the data to test and explore exposure-response relationship or, to develop hypotheses for further targeted study (for example, Lewis et al., 2015). From a risk assessment perspective, there is increasing interest in addressing challenges related to NHANES data interpretation in health risk contexts (Sobus et al., 2015).

[6] https://www.cdc.gov/nchs/nhanes/index.htm

The Canada Health Measures Survey (CHMS)[7]

This is an ongoing cross-sectional survey carried out biannually and includes participants aged from 3 to 79 and living in Canada. It began in 2007 by Statistics Canada in partnership with Health Canada and the Public Health Agency of Canada, and collects data on lifestyle habits, medical history, demographics, socioeconomic status. For food intake data collection, a semi-quantitative food frequency questionnaire (FFQ) is administered, particularly collecting data on the consumption frequency of various food groups (e.g., meat, dairy, vegetables consumed per day, week, month, or year). The participants also report to one of the CHMS collection sites for direct health measures, and blood and urine samples from the participants are collected for testing of health and nutritional markers as well as chemical levels from environmental exposure. In this respect, it has a strong similarity to the US NHANES programme.

In recent years, there has been a greater emphasis on collecting blood and urine data to a wide range of chemical substances similar to the range of those in the US NHANES programme. It is interesting to note that the diversity of lifestyles in Canada requires targeted HBM programmes to address sub-sections of the population. An example is a study which demonstrated an excess of heavy metals (Cd and Pb) and persistent organic pollutants (e.g., PCBs, DDT & DDE, toxaphene, chlordane, PBDEs) in Inuit living in the Arctic (Laird et al. 2013). As discussed in paragraph 36, Health Canada is utilising BEs to help interpret CHMS data from a risk perspective (Health Canada, 2016; Hays et al., 2016; Hays et al., 2018).

The German Environmental Survey (GerES)[8]

GerES is a nationwide cross-sectional HBM and health programme that has been periodically conducted in Germany since the mid-1980s. The survey is conducted by the German Federal Environmental Agency (Umweltbundesamt; UBA) in close collaboration with the Robert Koch Institute, which is responsible for the health examination component of the survey. Each survey focuses on a specific population of people living in Germany such as residents of the former East or West Germany and children, and the study populations are recruited from local resident registries to represent age, sex, community size, and locations. The three parts of the GerES are the biomonitoring using collected blood and urine, environmental factors (home exposure conditions including tap water and indoor air contaminants) and a detailed lifetime and dietary questionnaire.

Chemicals are selected based on the likelihood of exposure from the environment in children and adolescents. As examples, phthalates and their substitutes are analysed due to their use as plasticizers in food packaging, toys, etc. The GerES has had a major impact on the environmental health in Germany with particular focus on consumer safety and establishment of reference values for many chemical contaminants. GerES has been able to demonstrate temporal trends (e.g., decline in

[7] https://www.statcan.gc.ca/eng/survey/household/5071
[8] https://www.umweltbundesamt.de/themen/gesundheit/belastung-des-menschen-ermitteln/deutsche-umweltstudie-zur-gesundheit-geres

blood lead levels over time and decline in prohibited phthalates after regulations as well as the rise in exposure to alternatives introduced in place of the prohibited substances) and, importantly regional differences. GerES is considered the most extensive HBM program in Europe and has served as a model for the protocols developed and the reference values used for the EU COPHES/DEMOCOPHES study.

The French National Survey on Nutrition and Health (ENNS)[9]

This is an ongoing cross-sectional survey aimed to examine patterns of diet, nutritional status, and physical activity and to measure a number of nutritional and environmental biomarkers in the general population (aged 3–74). The ENNS programme is run by the French National Institute for Public Health Surveillance, along with the French National Program on Health and Nutrition. ENNS is comprised of data collection (e.g., of socioeconomic and demographic information), a food consumption survey, and a clinical examination including the collection of urine, blood, and hair samples. Around 40 substances including chlorophenols, metals (e.g., As, Cd, Co, Pb, Hg, Ni, U), PCBs, and several classes of pesticides (e.g., organochlorines, organophosphates, and pyrethroids) are measured. The findings for these have generated reference values of exposure to various metals and chemicals in the French adult population. The use of the reference values derived from the ENNS data for risk assessment purposes is unclear.

The Program for Biomonitoring the Italian Population Exposure (PROBE)[10]

PROBE was a cross-sectional population study to specifically determine the exposure of the healthy general population (aged 18–65) to metals in five urban regions Italy. It was commissioned and funded by the Italian National Institute of Health (Istituto Superiore di Sanità) and ran from 2008 to 2010. A total of 20 metals (i.e., Sb, As, Be, Cd, Cr, Co, Ir, Pb, Mn, Hg, Mo, Ni, Pd, Pt, Rh, Tl, Sn, W, U, and V) were analysed directly in the blood and serum samples. The 95th percentile values from this study were established as the reference values that can be used for comparisons with higher exposure scenarios in Italy. The use of the reference values derived for risk assessment purposes is unclear.

The Czech Republic, Human Biomonitoring Project (CZ-HBM)[11]

This was a limited cross-sectional study of the urban/suburban population in the Czech Republic covering two time periods and was a part of the nationwide environmental health monitoring system funded by the Czech Ministry of Health. The purpose of CZ-HBM was to assess population exposure to environmental pollutants and to follow up long-term time trends and their possible changes as a result of any preventive measures introduced. It was also used to establish a database from which reference values were derived that allowed subsequent characterisation of the

[9] http://ghdx.healthdata.org/record/france-national-nutrition-and-health-survey-2006-2007
[10] http://old.iss.it/binary/publ/cont/11_9_web.pdf
[11] http://www.szu.cz/uploads/documents/chzp/biomonitoring/democophes/Prednaska_Brusel.pdf

general population exposure. The use of the reference values derived for risk assessment purposes is unclear.

Three population groups were included in the CZ-HBM: adults aged 18–58, children aged 8–10, and breastfeeding primiparas. Information collected included biological specimens such as blood, urine, breast milk, hair, and teeth and food intake data collected for two 24-hour recall periods. Three groups of biomarkers were analysed: (1) selected heavy metals (Cd, Pb, and Hg) and essential elements (Cu, Se, and Zn), (2) the contaminants PCBs and organochlorine pesticides, and (3) cytogenetic changes in peripheral lymphocytes in blood. Reference values for Cd, Hg, and Pb levels as well as for PCBs and organochlorine pesticides in breast milk samples were established.

The BIOAMBIENT.ES project in Spain

A cross-sectional study (2009-10) with a stratified cluster sampling designed to cover all geographical areas, sex, and occupational sectors to obtain a representative sample of the Spanish workforce aged 16 and over (Pérez-Gómez et al., 2013). Blood and urine samples were collected for analyses of PBDEs, cotinine, metals (Cd, Pb, and Hg), organochlorine pesticides, PAH metabolites, and PCBs. The survey was conducted to generate reference values of chemical exposure (namely PCBs, Pb, and Hg) and confirmed high mercury levels attributable to fish intake. The use of the reference values derived from the BIOAMBIENT.ES data for risk assessment purposes is unclear.

The Flemish Environment and Health Study (FLEHS)[12]

This is an ongoing series of cross-sectional surveys that began in 2003 in Belgium (Flanders). The survey population are categorised into mothers and newborns, adolescents (aged 14–15), adults (aged 20–40), and older adults (aged 50–65). They are selected in urban, rural, and industrial areas and only qualify if they have resided for at least 10 years in Flanders. Apart from extensive questionnaires, blood (including cord and maternal blood from mothers and their newborns), urine, and hair (only from mothers and adolescents) samples are also collected from the participants. The substances analysed include chlorophenols, cotinine, dioxins, fluorocarbons, furans, the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), metals (e.g., As, Cd, Cu, Pb, Mn, Hg, and Tl), organochlorine pesticides, organophosphate metabolites, PAH metabolites, PBDEs, PCBs, phenols such as BPA, phthalate metabolites, and pyrethroid metabolites. Measurements of 8-hydroxydeoxyguanosine (8-OHdG; a biomarker of oxidative DNA damage) and the single cell gel electrophoresis to determine the amount of DNA damage have been included in some surveys. HBM data derived from the study has been used for risk assessment purposes (for example, Bastiaensen et al., 2021). Although reference values were established from FLEHS, it is unclear whether these are used for risk assessment purposes.

[12] https://www.milieu-en-gezondheid.be/en/homepage-eng

The Korea National Survey for Environmental Pollutants in the Human Body (KorSEP)

KorSEP is an ongoing series in South Korea of cross-sectional HBM surveys which started in 2005 to measure the levels of environmental pollutants across the general population in South Korea. The surveys entail questionnaire-based lifestyle and dietary interviews and sample collection. Blood and urine specimens are collected, and analysed for BPA, cotinine, metals (As, Cd, Pb, Mn, and Hg), and metabolites of PAHs, phthalates, and pyrethroids (Lee et al., 2012). The data have been used to determine background levels of pollutants in the Korean population. It is unclear if reference values were derived and whether these are used for risk assessment purposes.

Some observations on national HBM Schemes

Several similarities and differences of the HBM parameters are seen among these and other HBM programs. For instance, all the national HBM programs are initiated by their respective governments and are cross-sectional in nature. The survey volunteer populations vary from infants to the elderly and many endeavour to establish national reference values for contaminants. Unlike occupational HBM, for the general population, much of the exposure and uptake of contaminants is derived from the diet and water and so many of these surveys are linked to detailed nutritional and lifestyle surveys. Most collect blood and/or urine and some hair and teeth. The number of chemicals and other biomarkers measured range from 20 metals in the case of PROBE in Italy, to over 400 chemical contaminants in the case of NHANES in the US. There is much of an overlap in the chemical contaminants measured as, unsurprisingly, many of the same chemicals occur on the national priority list for concern across different counties.

Annex B References

Bastiaensen M, Gys C, Colles A, et al. (2021) Exposure levels, determinants and risk assessment of organophosphate flame retardants and plasticizers in adolescents (14-15 years) from the Flemish Environment and Health Study. Environ Int. 147:106368.

Choi J, Morck TA, Joas A, et al. (2015) Major national human biomonitoring programs in chemical exposure assessment, Environmental Science, 5(2), 782-802.

Hays SM, Macey K, Poddalgoda D, et al. (2016) Biomonitoring Equivalents for molybdenum. Regul Toxicol Pharmacol, 77:223-9.

Hays SM, Poddalgoda D, Macey K, et al. (2018) Biomonitoring Equivalents for interpretation of urinary iodine. Regul Toxicol Pharmacol. 94:40-46

Health Canada (2016) Biomonitoring Equivalents as a Screening Tool for Population Level Biomonitoring Data: A Health Canada Perspective. Available at: https://www.canada.ca/en/services/health/publications/science-research-data/biomonitoring-equivalents-screening-tool-population-level-data.html [accessed February 20121]

Laird BD, Goncharov AB, Chan HM. Body burden of metals and persistent organic pollutants among Inuit in the Canadian Arctic (213). Environ Int. 59:33-40.

Lee JW, Lee CK, Moon CS, et al. (2012) Korea National Survey for Environmental Pollutants in the Human Body 2008: Heavy metals in the blood or urine of the Korean population. International Journal of Hygiene and Environmental Health, 215(4): 449-457.

Lewis RC, Meeker JD. (2015) Biomarkers of exposure to molybdenum and other metals in relation to testosterone among men from the United States National Health and Nutrition Examination Survey 2011–2012. Fertil Steril., 103:172–8.

Pérez-Gómez B, Pastor-Barriuso R, Cervantes-Amat M, et al. (2013) BIOAMBIENT.ES study protocol: rationale and design of a cross-sectional human biomonitoring survey in Spain. Environ Sci Pollut Res Int. 20(2):1193-202.

Sobus JR, DeWoskin RS, Tan YM, et al. (2015) Uses of NHANES biomarker data for chemical risk assessment: trends, challenges, and opportunities. Environ Health Perspect 123:919–927.

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Development of Human Biomonitoring Guidance Values in the HBM4EU project

HBM4EU case studies

This paper is attached. The information on BBzP, BPA and DINCH is not being made publicly available as the information within it has been provided in confidence as a pre-publication material.

Secretariat
March 2021

HBM4EU Case Study - Cadmium and its Inorganic Compounds

The following information was determined from the HBM4EU case study document[13].

Why is it of interest from HBM perspective?

Cd is a heavy metal found as an environmental contaminant both through natural occurrence and from industrial and agricultural sources (use of Cd containing sewage sludge as fertiliser and build-up of Cd-containing sediments in floodplain areas of polluted streams and rivers). Cd is found naturally in low concentrations, usually combined with zinc and lead as sulphide ores. It occurs in the environment in its inorganic form as a result of volcanic emissions and weathering of rocks.

Although Cd has been heavily regulated in the EU and elsewhere, and many uses gradually reduced and replaced over the years, anthropogenic sources have increased the background levels of Cd in soil, water and organisms. Cd is released into the environment by wastewater and waste incineration, and the contamination of agricultural soils can occur by the use of fertilisers, by air deposition and by Cd-containing sewage sludge There is a widespread contamination of soil in many areas of the world, from natural geological sources, and from pollution by Cd-containing fertilisers or industrial emissions releases.

Human exposure to Cd is occurring mostly via the respiratory and the gastrointestinal tracts. Important non-industrial sources of exposure are cigarette smoke and food, since Cd is taken up by plants. A high Cd content in tobacco leaves and a comparatively high absorption of Cd via the lungs results in a substantially higher concentration of Cd in blood and urine in smokers compared to never-smokers. In the non-smoking general population, food accounts for approximately 90% (mainly from cereals and vegetables) and less than 10% occur due to inhalation of the low concentrations of Cd in ambient air and through drinking water. The rate of Cd uptake in crops is influenced principally by the Cd chemical forms present, the soil physico-chemical properties and the plant species.

The mining, smelting and industrial usage of Cd has caused considerable exposure of workers to Cd, but it is now fairly well controlled in most industrialised countries, but problems exist in developing countries and in some recently industrialised countries. In processes that involve extremely high temperatures (e.g., the iron and steel industries), Cd can volatilise and be emitted as vapour (CdO).

What is the chemical/metabolite of interest?

Cadmium (Cd) and its inorganic compounds including cadmium chloride, cadmium oxide, cadmium sulphide, cadmium sulphate, cadmium hydroxide and other

[13] Derivation of HBM guidance values (HBM-GVs) for Cadmium: HBM-GV_{GenPop} for the general population & HBM-GV_{Worker} for workers. The information has now been published: Lamkarkach F, Ougier E, Garnier R, Viau C, Kolossa-Gehring M, Lange R, Apel P (2020) Human biomonitoring initiative (HBM4EU): Human biomonitoring guidance values (HBM-GVs) derived for cadmium and its compounds. Environment International, 147, 106337.

compounds encountered occupationally or from anthropogenic and natural sources to the general population.

Urinary Cd is a well-known reliable biomarker of exposure of long-term exposure to Cd. It is the most extensively studied and used biomarker of exposure. For the general population, as well as for occupationally-exposed adults, it is the most reliable biomarker of exposure and its long half-life means that the timing of collection of the urine sample is less critical.

Cd concentration in blood can also be a useful biomarker of exposure during the relatively recent exposures (last month's i.e. 3-6 months); following accumulation of Cd, the blood level is dependent on the body burden and this may represent a useful biomarker to monitor the Cd occupational exposure, especially for new employees at the workplace. Therefore, blood Cd can be also recommended as a biomarker of exposure to complement urine Cd, for workers.

For biomarkers of effect, there are a range of options that have been developed following studies in workers occupationally exposed to Cd. For glomerular kidney effects, useful biomarkers of effect are glomerular filtration rate (GFR) and albumin in urine and for tubular effects, the most sensitive biomarkers are retinol-binding protein (RBP), alpha-1, beta-2-microglobulin (α1M and β2M and N-acetyl-β-D-glucosaminidase (NAG). Probably β2M is a widely studied low molecular weight protein (LMWP) for relating urinary concentrations of Cd to the tubular cytotoxicity of Cd in the absence of renal disease. However, its lack of stability in acidic urine could result in false results and underestimation of the actual excretion. α1M protein is another LMWP that can be measured in urine for detection of tubular dysfunctions.

There are a number of other biomarkers of effect providing an early indication of tubular cytotoxicity that may be related to Cd exposure such as, α-glutathione S-transferase, 6-keto prostaglandin F1, sialic acid, transferrin and more recently, Kim-1 protein but these are less well developed for consideration at the present time.

The data that can be used to relate urinary Cd concentrations to biomarkers of renal effects are somewhat limited and, as a result, only β2M and RBP were selected in the case study as possible biomarkers of effect in the case study of Cd.

How robust/sensitive are the analytical methods for different biological matrices?

The validated use of mass spectrometry after excitation in inductively coupled plasma (ICP-MS) is well-established and recommended for the determination of Cd concentrations in blood and urine of persons with low Cd exposure for both occupational and environmental populations. This reduces, in the case of urinary CD, any molybdenum-based polyatomic interferences. For very low concentrations (close to the limit of detection), an analytical uncertainty of 20% has to be included in the assessment. There are a number of quality control schemes for both urine and blood with both LoDs and LoQs for the available published methods.

β2M can be reliably measured in urine using an enzyme immunoassay (Kawada *et al.*, 1990; Chaumont *et al.*, 2011), by radioimmunoassay (Roels *et al.*, 1978), by simple immunodiffusion test (Garçon *et al.*, 2004 and 2007) or by immunonephelometry (Bernard *et al.*, 1981). RBP can be measured in urine by simple immunodiffusion test (Nozawa *et al.*, 1979), by the automated immunonephelometric technique (Roels *et al.*, 1978) or using the enzyme immunoassay (Garçon *et al.*, 2004 and 2007; Chaumont *et al.*, 2011).

Strength of toxicity data base - are there any remaining issues that require further studies?

Cd and its inorganic compounds have been extensively studied for both occupational and non-occupational populations for over 60 years so the human data base is fairly comprehensive and the experimental data base tends to be used in a more supportive fashion.

There are many fairly recent authoritative reviews which address all aspects of human exposure including: a detailed overview of the studies provided by the European Food Safety Authority (EFSA, 2009), the German Human Biomonitoring Commission (Kommission Human-Biomonitoring, 2011), the US Agency for Toxic Substances and Disease Registry (ATDSR, 2012), the French Agency for Food, Environmental and Occupational Health and Safety (ANSES, 2018), IARC (IARC, 2012) and by the International Union on Pure and Applied Chemistry (IUPAC, 2018).

The toxicokinetics, including long half-life and tissue and organ concentrations is well-described, particularly for occupational exposures and groups. Binding of Cd to metallothionein has been well-studied and is fairly summarised in the HBM4EU dossier. In the absence of kidney damage, the Cd excreted is only a small portion of the total amount of Cd which accumulates over time in the body. The Cd that is filtered by the glomerulus is almost entirely reabsorbed by the proximal tubule epithelial cells; little or no Cd is then excreted in the urine and its half-life may be between 10 and 20 years or even 40 years according to some researchers. However, when renal damage induced by Cd occurs, a dramatic increase in the proportion of Cd excreted in urine is seen. Non-occupational exposure to Cd occurs almost exclusively from food, with the average daily Cd content in faeces being a good indicator of the daily intake, as most the ingested Cd passes through the gastrointestinal tract unabsorbed and reaches the faeces. Faecal excretion in workers occupationally exposed to Cd reflects mainly Cd dust swallowed from industrial air and/or incidentally ingested from contaminated hands. EFSA (2009) reported that in breast milk, only 5 to 10% of the Cd content of maternal blood levels is found.

Toxicology of both occupational and non-occupational groups has been well investigated and evaluated in recent authoritative reviews and well reported in the HBM4EU dossier.

Acute toxicity to the lungs has been reported at high levels of inhalation (5mg/m^3). It may initially cause irritation of the upper respiratory tract, but symptoms may be delayed for a number of hours. Dyspnoea, chest pain and muscle weakness may

also occur. Pulmonary oedema, bronchitis, chemical pneumonitis, respiratory failure and death may occur within days of such high acute exposure. However, such case reports are essentially historical and related to fumes of CdO.

Nephrotoxic effects: The main critical effects reported after repeated Cd exposure are those relating to the kidney, which generally occur after many years of oral and/or inhalation exposure and result from Cd accumulation in the kidneys (especially in the renal cortex). Accumulation of Cd in cells of the proximal tubules causes dose-dependent dysfunction and damage to the tubule cells (Fanconi syndrome). The earliest sign of incipient renal dysfunction is a reduction in the reabsorption function of the tubule which results increased excretion of LMWPs in urine. Characteristic is the appearance of LMWPs such as α1M and β2M, as well as markers of cell damage in the urine and these form the basis for biological effect monitoring for Cd; the relationship of these biomarkers with the reversibility of renal damage has been defined and measures of renal tubular dysfunction are the most sensitive markers of an adverse effect on the kidneys. At higher exposure levels Cd is also responsible for glomerular damage with high occupational or environmental exposures to Cd giving rise to decreased glomerular filtration rate (GFR) and increased serum creatinine. Often there is a combination with tubular dysfunction, but isolated glomerular dysfunction may also occur. The best markers for glomerular damage are albuminuria and GFR, however, GFR is rarely measured in clinical practice because of the complexity of the measurement. GFR can be indirectly assessed through the measurement of serum creatinine, LMWPs or cystatin C levels; recent evidence has suggested that cystatin C may be useful as a marker for glomerular filtration and its serum concentration is independent of gender, age, or muscle mass (Onopiuk et al., 2015). Interestingly, the HBM 4EU case study notes that the associations observed between very low-levels of urinary Cd and increases in urinary protein excretion may not be causal with associations observed at urinary Cd <2 nmol/mmol creatinine (i.e. 2 $\mu g.g^{-1}$ creatinine) likely to have been influenced by physiological factors (e.g. diuresis) and/or smoking status (IUPAC 2018).

Effects on Bone: Long-term exposure to Cd results in a higher risk of osteoporosis and osteomalacia as a result of changes in the composition of the bone substance.

Respiratory effects: Cd compounds cause adverse effects on the respiratory tract through direct action on tissues following deposition of inhaled aerosol. Long-term, i.e. years, of exposure by inhalation may give rise to respiratory disorders including chronic inflammation of the nose, pharynx, and larynx, as well as olfactory disturbances. In the lower airways, chronic obstructive lung disease of varying severity and emphysema are found. The observed effects are fairly dependent on exposure levels and can include functional changes such as reduction in FVC and FEV1.

Effect on the cardiovascular system and blood pressure: Although Cd showed hypertensive effects after long-term administration in the drinking water in animal experiments, epidemiological studies in humans have provided contradictory results. The weight of evidence does not suggest that cardiovascular effects are important outcomes at exposure levels that are likely to occur in the general population.

Carcinogenicity: The carcinogenic effects of Cd and its compounds were re-evaluated by IARC in 2012 and a classification of '*carcinogenic to humans'* (Group 1) was established.

Reproductive toxicity, diabetes, neurotoxicity and hepatotoxicity: Although some reports on these effects had been published, none could be linked to exposure to Cd alone.

What are the proposed HBGVs?

The current epidemiological data on Cd is robust and allows for the derivation of HBM-GVs for the general population and for workers, based on a relationship between human internal concentrations (parent compound or biomarker(s)) and health effects. As Cd accumulates in the human body throughout life, the case study proposes biological threshold values according to age, that would prevent an exceedance of the HBM-GV_{Genpop} at later age (over 50 years).

The basis of the proposed HBM-$GV_{GenPop(adults\ over\ 50\ years)}$ was a substance-specific adjusted benchmark concentration for urinary cadmium that is suitable to prevent an excretion of β2M that is elevated by 5% in 95% of the population (BMD_5L_{95}) (EFSA, 2009). This (4 $\mu g.g^{-1}$ creat of urinary Cd) was used as a PoD to derive the HBM-$GV_{GenPop(adults\ over\ 50\ years)}$ using an AF of 3.9.

HBM-$GV_{Genpop(adults\ over\ 50\ years)}$ = 1 $\mu g.g^{-1}$ creat

Attributed level of certainty – high/medium

In deriving an HBM-GV for workers, a PoD from an occupational study was used based on elevated urinary RBP and β2M concentrations. The lowest BMD_5L_{95}, in the non-smoker subgroup (i.e. 5.5 $\mu g.g^{-1}$ creat) was considered as the PoD, rounded to the lower value i.e. 5 $\mu g.g^{-1}$ creat. No AF's were required as workers are considered as a homogeneous group.

HBM-GV_{Worker} = 5 $\mu g.g^{-1}$ creat

Attributed level of certainty – high/medium

As the average age of workers in the study used was 45 years (± 10 years), using this study to establish a HBM-GV_{Worker} could mean that this value offers less protection to workers with a longer exposure. An alert value was calculated from a BMD_{10} of 1.5 $\mu g.g^{-1}$ creat (rounded to 2 $\mu g.g^{-1}$ creat of urinary Cd) estimated in workers over 60 years of age. **Alert Value = 2 $\mu g.g^{-1}$ creat of urinary Cd -** recommended as the threshold for initiating monitoring of renal function biomarkers such as β2M and RBP (in urine).

Blood cadmium (B-Cd) can be recommended as a biomarker of exposure, in addition to urine Cd, for workers and especially for new employees. In an occupational study, a large number of blood and corresponding urine samples (600 workers across 16 industries) were analysed to assess any correlation. The authors reported that a urinary Cd concentration of 5 µg.g^{-1} creat corresponded to a calculated Cd blood concentration of 4 µg/L. This was recommended as the HBM-GV.

HBM-GV$_{Worker}$ for Cd in whole blood = 4 µg.L^{-1}.

Attributed level of certainty – high/medium

Comparison of proposed with existing health-based evaluations – do they differ?

There are a number of existing internal toxicological reference values or critical values for the general population:

- EFSA (2009) has derived a 'critical value' of 1 µg.g^{-1} creat for Europe.
- In Germany, UBA (2011) has derived a HBM-I children (3-14y) of 0.5 µg.L^{-1} and a HBM-II children (3-14) of 2 µg.L^{-1}; For adults, a HBM-I of 1 µg.L^{-1} and an HBM-II of 4 µg.L^{-1} have been derived.
- ATSDR (2012) has set a reference value of 0,5 µg.g^{-1} creat.

The HBM-GV$_{Genpop(adults\ over\ 50\ years)}$ of 1 µg.g^{-1} creat is equivalent to the critical value derived by EFSA on which a TWI was calculated. It is also equivalent to the HBM-I value for adults (age unspecified) however ATSDR use a smaller value (0.5 µg.g^{-1} creat) (determined for chronic inhalation exposure) as the basis for deriving an MRL.

There are several occupational biological limit values:

- SCOEL (2017) has determined an biological limit value (BLV) of 2 µg.g^{-1} creat in urine.
- ANSES (2018) has determined a BLV of 5 µg.g^{-1} creat and 4 µg.L^{-1} in blood.
- ACGIH (2001) has determined a biological exposure indices (BEI) of 5 µg.g^{-1} creat in urine and 5 µg.L^{-1} in blood.
- FIOH has determined a biological action level (BAL) of 20 nmol.L^{-1} (2.2 µg/L) in urine and 50 nmol.L^{-1} (5.6 µg/L) in blood.

The HBM-GV$_{Worker}$ of 5 µg.g^{-1} creat in urine is higher than the OELs determined by SCOEL and FIOH but equivalent to those proposed by ANSES and ACGIH. The HBM-GV$_{Worker}$ of 4 µg/L in blood is equivalent to that proposed by ANSES and lower than those proposed by ACGIH and FIOH.

Application of HBM4EU value

The biomarkers discussed here have been utilised in large scale occupational and epidemiology studies. These studies are well described in the HBM4-EU dossier. There is no discussion regarding application of the HBM-GV's that were determined.