Human biomonitoring in health risk assessment in Europe
Current practices and recommendations for the future

Louro, Henrique; Heinälä, Milla; Bessems, Jos; Buekers, Jurgen; Vermeire, Theo; Woutersen, Marjolijn; van Engelen, Jacqueline; Borges, Teresa; Rousselle, Christophe; Ougier, Eva

Published in:
International Journal of Hygiene and Environmental Health

Link to article, DOI:
10.1016/j.ijheh.2019.05.009

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

Link back to DTU Orbit

Citation (APA):
Human biomonitoring in health risk assessment in Europe: Current practices and recommendations for the future

Henriqueta Louro\textsuperscript{a,b}, Milla Heinälä\textsuperscript{c}, Jos Bessem\textsuperscript{d}, Jurgen Buekers\textsuperscript{d}, Theo Vermeire\textsuperscript{e}, Marjolijn Woutersen\textsuperscript{e}, Jacqueline van Engelen\textsuperscript{e}, Teresa Borges\textsuperscript{f}, Christophe Rousselle\textsuperscript{g}, Eva Ougier\textsuperscript{g}, Paula Alvito\textsuperscript{a,h}, Carla Martins\textsuperscript{a,h,l}, Ricardo Assunção\textsuperscript{a,h,l}, Maria João Silva\textsuperscript{a,b}, Anjoeka Pronk\textsuperscript{i}, Bernice Schaddeele-Scholten\textsuperscript{j}, Maria Del Carmen Gonzalez\textsuperscript{j}, Mercedes de Alba\textsuperscript{j}, Argelia Castaño\textsuperscript{j}, Susana Viegas\textsuperscript{a,i}, Tatjana Humar-Juric\textsuperscript{m}, Lijana Kononenko\textsuperscript{n}, Alfonso Lampen\textsuperscript{n}, Anne Marie Vinggaard\textsuperscript{o}, Greet Schoeters\textsuperscript{d}, Marike Kolossa-Gehring\textsuperscript{o}, Tiina Santonen\textsuperscript{c,n}

\textsuperscript{a} INSA - National Institute of Health Dr. Ricardo Jorge, Portugal
\textsuperscript{b} ToxOmics – Centre for Toxigenomics and Human Health, Nova Medical School/Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Portugal
\textsuperscript{c} FIOH - Finnish Institute of Occupational Health, Finland
\textsuperscript{d} VITO - Flemish Institute for Technological Research, Belgium
\textsuperscript{e} RIVM - National Institute for Public Health and the Environment, the Netherlands
\textsuperscript{f} DGS - Directorate-General of Health, Ministry of Health, Portugal
\textsuperscript{g} ANSES - Agency for Food, Environmental and Occupational Health & Safety, France
\textsuperscript{h} CESAM - Centre for Environmental and Marine Studies, University of Aveiro, Aveiro, Portugal
\textsuperscript{i} TNO - Organization for Applied Scientific Research, the Netherlands
\textsuperscript{j} ISCIII- - Instituto de Salud Carlos III, Spain
\textsuperscript{k} H&TRC - Health & Technology Research Center, ESTeSL- Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa, Portugal
\textsuperscript{l} Ministry of Health, Chemicals Office of the Republic of Slovenia, Slovenia
\textsuperscript{m} RIVM - National Institute for Public Health and the Environment, the Netherlands
\textsuperscript{n} UBA – Umweltbundesamt, Germany

ARTICLE INFO

Keywords:
Risk assessment
Human biomonitoring
Chemicals
Internal exposure
HBM4EU

ABSTRACT

Human biomonitoring (HBM) is an important tool to survey the internal exposure of humans which represents the real life chemical body burden to chemicals and/or their metabolites. It results from total exposure to chemical substances from different sources and via different routes. These substances may be regulated under different legislative frameworks on chemicals (e.g., environmental, occupational, food safety etc). In occupational health, HBM has long traditions to control the exposures at workplaces. By providing accurate data on internal exposure, HBM data can improve human health risk assessment (RA) for both the general population and workers. Although the past few years have shown good examples on the use of HBM in the RA of chemicals, there is still quite some work to be done to improve its use in a regulatory RA.

Under the scope of the European Human Biomonitoring Initiative (project HBM4EU, 2017–2021), the current study reviews the state-of-the-art of HBM use in chemicals RA with a special focus in Europe, and attempts to identify hurdles and challenges faced by regulators. To gather information on the use of HBM, including the availability of guidance on how to use it and the RA schemes applied by different European or international organizations were analysed. Examples of such use were identified for a few selected groups of chemicals of concern for human health. In addition, we present the results of a survey, aimed at collecting information from national regulatory risk assessors on their day-to-day RA practices, the use of HBM data, and the obstacles and challenges related to their use. The results evidenced and explained some of the current obstacles of using HBM data in RA. These included the lack of HBM guidance values or biomonitoring equivalents (BEs), limited toxicokinetic information to support the interpretation of HBM data and, in the occupational health and safety (OSH) field, the lack of legal enforcement. Therefore, to support the integration of HBM in regulatory RA, we recommend, on one hand, the elaboration of a EU level guidance on the use of HBM in RA and, on the other
1. Introduction

In the frameworks for human health risk assessment (RA) of chemicals, the default approach is either to consider only external exposure or to infer internal exposure from the external exposure measurements from different sources and via different routes (inhalation, dermal absorption, ingestion) by modelling. This approach embraces various uncertainties and may often overestimate the real internal exposure, since default, conservative estimates are used e.g. for chemical absorption. Conversely, current (real life) exposure may be underestimated if not taking into account that exposure to a single chemical substance or to mixtures of chemicals may occur from different sources, which may fall under separate legislative frameworks and therefore are not considered as a whole. Underestimation of real internal exposure also happens by insufficiently assessing all possible routes of exposure, e.g. the hand-to-mouth behaviour in occupational settings (Cherrie et al., 2006).

Human biomonitoring (HBM) assesses typically internal concentrations of chemicals or their metabolites in human biological samples such as urine or blood. It aggregates exposure from different sources and by different exposure routes, hence providing a more accurate estimate of the body burden. Therefore, inclusion of HBM data can improve RA for both the general population and workers, separately, or as part of the population. From a policy angle, HBM can help to answer questions like: what is the total exposure to the substance from different sources, how does the chemical exposure evolve over time, are the measures to reduce exposure effective, are there differences in exposure between regions or population groups, what are the highly exposed groups etc. Since demonstrating regulatory efficacy is a critical component of regulatory frameworks, HBM data can assist in evaluation and demonstration of the effectiveness of policy actions, and the detection of emerging contaminants. In occupational health, HBM has long traditions to identify and control exposures at workplaces and to mixtures of chemicals may occur from different sources, which may fall under separate legislative frameworks and therefore are not considered as a whole. Underestimation of real internal exposure also happens by insufficiently assessing all possible routes of exposure, e.g. the hand-to-mouth behaviour in occupational settings (Cherrie et al., 2006).

Human biomonitoring (HBM) assesses typically internal concentrations of chemicals or their metabolites in human biological samples such as urine or blood. It aggregates exposure from different sources and by different exposure routes, hence providing a more accurate estimate of the body burden. Therefore, inclusion of HBM data can improve RA for both the general population and workers, separately, or as part of the population. From a policy angle, HBM can help to answer questions like: what is the total exposure to the substance from different sources, how does the chemical exposure evolve over time, are the measures to reduce exposure effective, are there differences in exposure between regions or population groups, what are the highly exposed groups etc. Since demonstrating regulatory efficacy is a critical component of regulatory frameworks, HBM data can assist in evaluation and demonstration of the effectiveness of policy actions, and the detection of emerging contaminants. In occupational health, HBM has long traditions to identify and control exposures at workplaces and in some European countries there are also biological limit values established for occupational exposure (RPA, 2017).

Naturally, HBM has also limitations since often the specific metabolites are measured, and not the parent compounds, and exposure biomarkers are only proxies measured in easily accessible tissues and fluids (Grandjean, 2012), not necessarily reflecting the concentrations at all target organs. Conversely, total body burdens may in some cases be difficult to link to specific exposure sources. These limitations need to be recognized when interpreting HBM data.

In addition to monitoring of internal exposure, HBM may also assess early biological effects (effect biomonitoring). The linkage of biomarkers between exposure and effect contributes to the identification of dose-response relationships (Fig. 1).

Although the past few years have shown good examples on the use of HBM in the RA of chemicals, there is still quite some work to be done to improve its use in regulatory RA. One of the policy targets in the Parma Declaration was the contribution 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, 2010). As a matter of fact, the US National Academies of Sciences, Engineering and Medicine in a recently released report on “Using 21st Century Science to Improve Risk-Related Evaluations” (USNAS, 2017) lays out recommendations to incorporate this emerging science into risk-based evaluations. HBM is described as an essential tool allowing for advances in exposure science and epidemiology. In addition, the role of different biomarkers is currently studied e.g. in the assessment of food and nutrient intake (Food Biomarkers Alliance, http://foodmetabolome.org/).

Under the scope of European Union (EU), the Horizon2020 European Joint Program HBM4EU (2017–2021) has been launched to coordinate and advance human biomonitoring of chemicals in Europe. HBM4EU aims to support policy making by providing better evidence of the actual exposure of citizens to chemical substances and mixtures, and to link this exposure to the possible health effects. The program involves collaboration between several European Commission services, EU agencies, national representatives of ministries and regulatory agencies, stakeholders and scientists, connecting the research and policy settings (Ganzleben et al., 2017). The overall objective is to minimize the human health impact of the use of hazardous substances.

Intending to provide strong anchoring of HBM to RA practises, in this study the information from three different approaches is described and integrated, namely: i) a state-of-the-art review of HBM use in existing RA schemes; ii) examples of the use of HBM for RA in a set of chemicals selected from the HBM4EU prioritized substances and iii) a survey to the regulatory risk assessors on the use of HBM in RA, obstacles, and challenges related to its use. Finally, proposals for a better inclusion of HBM in human RA are derived from the integration of the information provided by those different approaches.

2. Methods

2.1. Methodology for evaluation of RA schemes and examples

An expert group consisting of participants from 16 EU institutions enrolled in HBM4EU, with expertise in chemical risk assessment, co-
Table 1
International and EU RA schemes.

<table>
<thead>
<tr>
<th>RA Scheme</th>
<th>HBM recognized as an exposure assessment tool</th>
<th>Biomarkers of effect recognized as possible tools for e.g. hazard characterization</th>
<th>Specific guidance available for the use of HBM in RA</th>
<th>Examples on the use of HBM exist? (given in brackets, if include HBM4EU priority chemicals)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO</td>
<td>yes</td>
<td>yes</td>
<td>yes (toxic metals e.g. Hg/MethylHg, Cd, Cr), toluene, nitrobenzene, etc.)</td>
<td>GEMS; IPCS/INCHEM</td>
<td></td>
</tr>
<tr>
<td>FAO</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>*REACH guidance R8 mentions the possibility to derive DNELs based on biomarker levels</td>
<td></td>
</tr>
<tr>
<td>REACH</td>
<td>yes</td>
<td>no</td>
<td>+/− *</td>
<td>Guideline for RA of contaminants in food and feed</td>
<td></td>
</tr>
<tr>
<td>EPA</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (cadmium and lead)</td>
<td>WHO RA guidance is followed</td>
<td></td>
</tr>
<tr>
<td>EFSA review</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes (Metals, PCBs, cotinine; mycotoxins; perchlorate; nitrosamine; alkaloids; dioxines; phthalates; PAHs; furans; fluorocarbons; organochlorines; phenols; PFCs; PBDEs; organophosphates; pyrethroids; chlorinated phenols; acrylamides; carbanates)</td>
<td>Document focused on vulnerable groups</td>
<td></td>
</tr>
<tr>
<td>EFSA review</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Data from: HBM data collection from occupational exposure to pesticides -EFSA supporting publication 2017:EN-1185. 207 pp.</td>
<td></td>
</tr>
<tr>
<td>EU Pesticides</td>
<td>yes</td>
<td>yes</td>
<td>HBM has been used for monitoring worker exposure. Most studied pesticides: Herbicides (in order): 2,4-D &gt; atrazine &gt; metolochlor &gt; MCPA &gt; alachlor &gt; glyphosate. Insecticides (in order) were: chlorpyrifos &gt; permethrin &gt; cypermethrin &gt; deltamethrin &gt; malathion, Fungicides were: captan &gt; mancozeb &gt; folpet</td>
<td>Document focused on vulnerable groups</td>
<td></td>
</tr>
<tr>
<td>EU Biocides</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>Data from: HBM data collection from occupational exposure to pesticides -EFSA supporting publication 2017:EN-1185. 207 pp.</td>
<td></td>
</tr>
<tr>
<td>EU Cosmetics</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>Document focused on vulnerable groups</td>
<td></td>
</tr>
<tr>
<td>EU OSH</td>
<td>yes</td>
<td>no (legislation, however, SCOEL methodology recognises this possibility)</td>
<td>only B-Pb taken into the legislation, however, SCOEL recommendations available for several priority chemicals</td>
<td>Document focused on vulnerable groups</td>
<td></td>
</tr>
<tr>
<td>WHO- HIA</td>
<td>Yes</td>
<td>Not known</td>
<td>Yes (lead, dioxin, IDCs in general)</td>
<td>Document focused on vulnerable groups</td>
<td></td>
</tr>
</tbody>
</table>

authors of this work, was gathered to analyse the relevant global and EU risk assessment schemes. Global schemes were included since they have an impact also on European practices. The schemes identified included World Health Organization (WHO) and Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (JECFA) schemes, while national schemes inside and outside Europe were excluded. The RA activities of the Organisation for Economic Co-operation and Development (OECD) were also screened, but no currently active RA schemes were identified. EU practices included RA schemes related to the Regulation on Registration, Evaluation, Authorisation and restriction of CChemicals in the EU (REACH), the biocides and pesticides regulations as well as the food safety schemes by EFSA, occupational safety and health framework (EU-OSHA) and the cosmetics products regulations. The drug safety area was excluded from the assessment. Primary evaluation of each scheme was performed by nominated experts (experts from 1 to 2 different institutes per scheme). Experts were asked to 1) give a short description on the risk assessment scheme; 2) identify whether the scheme includes a guidance and describe whether the guidance has some reference to the use of HBM in RA, and if yes 3) describe how this guidance takes HBM into account; 4) identify whether HBM4EU priority substances have recently been evaluated under the scheme (or possibly coming under evaluation in future). These HBM4EU priority substances (the first list of HBM4EU priority substances, www.hbm4eu.eu/the-substances) included: phthalates and 1,2-Cyclohexane dicarboxylic acid diisononyl ester (Hexamoll® DINCH), bisphenols, per-/polyfluorinated compounds, flame retardants, cadmium and chromium VI, polycyclic aromatic hydrocarbons (PAHs), aniline family, chemical mixtures and emerging substances. These existing evaluations of HBM4EU priority substances were assessed within the expert group for their use of HBM data and good examples were identified and described.

2.2. Survey design and implementation

A questionnaire was developed under the HBM4EU project and conducted in the summer of 2017 using a web-based tool Webropol (www.webropol.com). The survey was divided in two parts: the first part addressed RA in general (under e.g. chemical, pesticides and food safety legislations) and the second part targeted specifically the use of HBM in occupational health. This division was made because it is recognized that occupational health has longer traditions in using HBM as a tool to assess the exposure and associated risks. It was also clear that national practices related to its use in occupational and safety health (OSH) are likely to vary since the current EU legislation gives very little guidance for its use. It was possible to reply to both parts of the survey or only the general population or occupational health parts. Answers could be given anonymously. The full questionnaire can be found as supplementary material and the results of both parts are presented altogether.

The survey was distributed among different EU member state experts working in the risk assessment of chemicals via HBM4EU National Hub Contact Points (NHCPs), who were responsible for the distribution of the survey in their country among the local regulatory risk assessors working in the different fields of chemical RA. In addition, the survey was distributed outside EU to national authorities in different countries using the contact list of the WHO chemical risk assessment network (www.who.int/ipcs/network/en/).

3. Overview of risk assessment (RA) schemes

3.1. Global RA schemes

Table 1 summarizes the existing risk assessment schemes evaluated. A wealth of information and concrete guidance on how to perform RA is provided by international RA schemes such as from WHO/International Programme on Chemical Safety (IPCS) and JECFA. In many parts of the world, the real RA for a specific chemical in the sense of a concrete risk prediction (i.e. actual exposure divided by a safe level) is a national prerogative. International RA schemes do propose, however, safe exposure levels such as tolerable daily intake (TDI) or linked to this, maximum residue levels. This enables international comparability and thereby promotes fair practices in trade.

3.1.1. World Health Organization (WHO)/International Programme on Chemical Safety (IPCS)

Under the WHO/IPCS umbrella, the paradigm of RA process begins with problem formulation and includes four additional steps: 1) hazard identification, 2) hazard characterization, 3) exposure assessment and 4) risk characterization (WHO/IPCS, 2009a). This RA scheme refers that use of biomarkers represents a valuable tool to evaluate human exposure to a chemical, besides the use of traditional exposure assessment (WHO/IPCS, 2009a). WHO (WHO/IPCS, 2009a) discusses the relevance of using different types of biomarkers in the different phases of the RA and concludes that biomarkers may provide the critical link between chemical exposure, internal dose and health impairment.

In the IPCS document (WHO/IPCS, 2001), a framework for selecting and validating biomarkers was developed. WHO considers that valid biomarkers, through laboratory and epidemiological studies, can lead to biologically based RA, although there have been only few cases where validated biomarkers have been used in quantitative RA. The role of HBM in chemical RA is also recognized in the WHO RA toolkit (WHO/IPCS, 2010), which refers to the earlier WHO guidance on exposure assessment and the use of HBM in RA (WHO/IPCS, 2001, 2000, 1993).

Regarding mixture risk assessment, the WHO/IPCS (WHO/IPCS, 2009b) has developed a framework for the RA of combined exposure to multiple chemicals. It is based on a hierarchical (tiered) approach that involves integrated and iterative consideration of exposure and hazard at all phases. The use of the HBM in this framework is mainly related to the problem formulation and exposure assessment, where the questions related to the nature of exposure, likely of the exposure and co-exposures are raised. Human biomonitoring allows to analyse the simultaneous presence of chemicals in the body, irrespectively of exposure sources or routes. This offers the potential to evaluate risks from combined exposures to chemicals, considering their toxicological properties and their potential to cause interactive effects (similar or dissimilar modes of action) in a specific organ or system (cumulative assessment groups). Such data may indicate the potential relevance of considering a mixture effect in a RA framework. Further development of the concept includes a tiered approach taking into consideration the hazard from combined exposure to multiple chemicals, including information on absorption, distribution, metabolism and excretion (ADME), common metabolite monitoring, mechanisms, common molecular target and Mode Of Action (MOA) (WHO/IPCS, 2009b). In the report of a WHO/IPCS international workshop on aggregate/cumulative RA (WHO/IPCS, 2009b), it is also identified that the support of HBM systems, exposure databases and disease registries is critical in order to provide better data, to help guide prioritization of assessments and to evaluate the benefits of cumulative assessments.

3.1.2. Food and Agriculture Organization of the United Nations

The Food and Agriculture Organization of the United Nations (FAO) has published a document focused on guidelines for RA of feed (FAO, 2013). RA under this framework is consistent to the WHO/IPCS RA paradigm. It includes, however, no reference to the use of HBM data. Also in the FAO/WHO Principles and Methods for the RA of Chemicals in Food (FAO/WHO, 2009), no HBM data are considered.
3.2. European risk assessment schemes

3.2.1. Industrial chemicals legislation (REACH)

Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals, commonly known as REACH, introduced the concept of Derived No-Effect Level (DNEL) for threshold substances defined as the level below which no adverse effects are expected based on the current knowledge. For non-threshold substances, Derived Minimal Effect Levels (DMELs), which are reference risk level considered to be of a very low concern, may be derived. The risk to humans is considered to be adequately controlled, if the exposure levels do not exceed the DNEL/DMEL derived using REACH guidelines (REACH Annex I, 1.0.1). DNELs must be derived for all hazardous substances placed on the market in quantities exceeding 10 tonnes per year, and should be used in occupational settings, consumer use, and for the general population for indirect exposure via the environment (ECHAs, 2012).

DNELs may be expressed also as internal exposure biomarkers (DNELbiomarker) (ECHAs, 2012). 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. However, REACH requirements do not include any incentive to understand the relationship between internal exposure biomarkers and effects. It is also noted that toxicokinetic studies or measurement of the internal dose of a substance and/or its metabolites is generally not part of the regulatory toxicological tests. The development of knowledge on the relationship between effects and the internal doses of substances is therefore not a common practice in the Registration dossiers. Unfortunately, REACH IUCLID system, where dossier submitters have to file substance information, contains no field reserved for a DNELbiomarker. This does not encourage registrants to consider the possibility to set a DNELbiomarker.

Under REACH, HBM could be helpful for actual exposure assessment for complex scenarios and for validating if operational conditions and risk management measures result in safe exposures. However, guidance on how to use HBM in risk characterization and management is limited (Boogaard et al., 2011; ECHAs, 2012).

3.2.2. Food safety scheme

In 2012, EFSA published a guideline for RA of contaminants in food and feed (EFSA, 2012). It provides an overview of the working principles used by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) and gives an outlook for the future perspectives of RAs of contaminants in food and feed. It notes that in some cases CONTAM Panel has been able to model human data and to incorporate information from biomarkers of exposure or effect in the characterisation of the hazard, e.g. for cadmium and lead (EFSA, 2010, 2009) allowing the use of a body burden approach, rather than external dose for the risk characterization. It states also that increasing availability of biomarker and physiologically-based pharmacokinetic (PBPK) modelling data will support further improvement of RA and the use so-called “margin of body burden” approach.

EFSA has more recently published an overview on the use of HBM in RA of food contaminants (EFSA, 2015). The document is an EFSA External Scientific Report that provides an evaluation of the usefulness of HBM in the exposure assessment of chemicals from food sources, and in the implementation of a systematic post-marketing monitoring approach for regulated chemicals. It describes how HBM can be used for RA in combination with e.g. environmental and health registry data, modelling data from PBPK models, or HBM-based guidance values such as Human Biomonitoring Values (HBM-I and HBM-II)(Apel et al., 2017) and Biomonitoring Equivalents (BEs)(Hays and Aylward, 2009). HBM is also considered useful to raise awareness and large-scale cross-sectional national HBM programs are considered to provide useful data on chemical exposure of the general population, allowing comparative analyses of chemical concentrations and/or exposure trends among different countries (EFSA, 2015).

A review based on an EFSA commissioned study (Choi et al., 2017) shows the advantage of conducting analysis using age-stratified data from national HBM programs and studies to identify environmental chemicals that might be of concern for vulnerable populations (e.g. children or older adults). The review was based on the analysis of studies performed in Germany (GerES), Czech Republic (CZ-HBM), USA (NHANES), Belgium (FLEHS), South Korea (KorSEP), France (ENNS), Spain (BIOAMBIENT.ES), Slovenia (Slovenia’s HBM), Canada (CHMS) and Italy (PROBE) as well as in several European countries (DEOMICOPHES).

3.2.3. Plant protection products (PPP) regulation

The safe use of plant protection products or pesticides in the EU is mainly regulated by framework Regulation (EC) No 1107/2009 in EU. Data requirements are given in Commission Regulation (EU) No 283/2013 (for the active substance) and Commission Regulation (EU) No 284/2013 (for the marketed PPP or formulations).

A range of exposure conditions and levels are typically assessed, including those for pesticide applicators (high semi-chronic), post-application workers (lower semi-chronic), and bystanders or neighbours and consumers (low but chronic). In reality, very few exposure measurements are submitted as part of the approval process (and these are usually environmental data, not HBM data) and the vast majority of the exposure assessments rely on modelled data.

There is no specific guideline that describes the use of HBM data in PPPs RA. However, a recent paper (EFSA, 2017) provides an overview on the use of HBM as a tool for occupational exposure assessment refinement of PPPs, identifying advantages, disadvantages and needs for further development. This document includes also a review of available HBM studies/surveillance programmes conducted in EU/US occupational settings to identify pesticides, for which validated exposure (and possibly effect) biomarkers are available. According to this review, HBM should be employed alongside environmental monitoring as a tool to characterize exposure.

According to EFSA (EFSA, 2017) it is apparent that HBM has a role to play in the validation and adjustment of parameter assumptions of exposure assessments models (often over-conservative) as well as in measuring actual exposures for the approvals process. There is currently no EU regulation for post-approval monitoring of exposure to pesticides, through either occupational and/or environmental routes. However, long-term health effect studies have been set up to look at the relationship between pesticide exposure and possible adverse health effects within agricultural cohorts in Europe and the USA, examples of which are brought together in a consortium, AGRICOH (A Consortium of Agricultural Cohort Studies) set up in 2010 by the US National Cancer Institute and coordinated by IARC. Although there are many studies published in the peer-reviewed and grey literature which can be called “post-approval assessment studies” and which look at occupational exposure using HBM, in reality, there are only very few studies that compare actual exposure against assumed exposure during the pre-marketing approval process and as part of the registration dossiers.

Overall, it was proposed by (EFSA, 2017) that the collection of HBM data for pesticide workers could be added as a routine component of existing occupational health surveillance programmes and HBM4EU could be a vehicle for gathering such data. Further recommendations included e.g. defining priorities for the development of new biomarkers for all pesticides considering toxicological concern; conduction of cohort studies with focus on young farmers or the derivation and adoption of health information -based Human Biomonitoring Guidance Values (termed HBM GV in HBM4EU), and the design of Standard Operating Procedures (SOPs) and questionnaires for field work.

Importantly, the Group of Chief Scientific Advisors to the European Commission recently recommended mandatory monitoring of exposure and health directly following the market authorisation of a PPP (EC,
2018).

3.2.4. Biocidal products regulation

The RA process for the biocide active substances follows the same principles of the EU RA schemes (ECHA, 2017). HBM is not part of active substance approval within the framework of Reg (EC) No. 1109/2006 and Reg (EU) No. 528/2012 on the Biocidal Products Regulation (BPR) on a regular basis. However, existing HBM data may be used in some cases to refine the assessment and support decisions. The human health RA scheme for the biocidal active substances does not include a specific guidance on the use of HBM, though several considerations to HBM are made in the Guidance for Human Health RA (ECHA, 2017). It is accepted that the use of scientifically valid human data, including HBM data, may reduce the level of uncertainty in comparison to extrapolation from animal models and is seen as a valuable contribution to science-based decision making.

So far, the human data have been only exceptionally used for the RA of biocidal active substances. This was the case of iodine used in biocidal products where an upper intake level from dietary human studies, was used to derive the systemic AEL reference value (European Commission, 2002). This Upper Intake Level was used in the EU risk assessment of a biocidal active substance (European Commission, 2013).

3.2.5. Occupational risk assessment

The Chemical Agents Directive 98/24/EC (Chemical Agents Directive, CAD) on the protection of the health and safety of workers from the risks related to chemical agents at work provides the basis for the drawing up of indicative occupational exposure limit values (IOELVs) and binding occupational exposure limit values (BOELVs) for workplace air. According to CAD also binding biological limit values (BLVs) may be drawn up. However, only one binding BLV exists in the EU to date. It is set for blood lead (B–Pb)) (Council directive 98/24/EC of 7 April 1998).

Exposure to carcinogens and mutagens at work is regulated under Carcinogen and Mutagens Directive (CMD). CMD Annex III lists the BOELVs for the carcinogens and mutagens. There are no BLVs given under the CMD but it is stated under annex II of the CMD that a health surveillance of the workers exposed to carcinogens and mutagens must include, where appropriate, biological surveillance. The recent opinion of the Advisory Committee on Safety and Health at Work (A/CHS) on the possible amendment of Directive (2004)/37/EC (EC, 2017) supports in principle the use of biological monitoring in workers' health and safety protection, but does not support inclusion of biological limit or guidance values in CMD. Instead, it recommends to develop EU guidance on HBM for hazardous substances falling both under the CAD and CMD.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) has recommended BLVs or biological guidance values (BGVs) for several substances. SCOEL methodology documentation includes a detailed description on the main principles used to give a recommendation for BLV or BGV (SCOEL, 2017, 2014). BLVs are derived on the basis of currently available scientific data, and are setting internal exposure levels under which adverse health effects are unlikely to result (SCOEL, 2017). Whenever the toxicological data cannot support a health-based BLV (e.g. cases in which no health based OEL can be set), only a BGV might 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 certain percentile (generally 90 or 95 percentile) in a defined reference population (preferably non-occupationally exposed working aged population).

In 2014, SCOEL published a List of recommended health-based BLVs and BGVs (SCOEL, 2014b), which includes BLVs or BGVs for 22 substances. This document has not been updated since then, but after 2014, SCOEL has published recommendations on o-tolidine, beryllium, hexachlorobenzene and PAH mixtures containing benzo[a]pyrene, which include either a BLV or BGV. Since there are no EU level BLVs given in CAD or CMD (except for blood lead), it is currently up to the member states how they apply SCOEL BLVs and BGVs in the exposure and health RA of workers.

3.2.6. Cosmetics regulation

In general, the safety evaluation of cosmetic ingredients by the EU Scientific Committee on Consumer Safety (SCCS) is based upon the principles and practice of the RA process usually applied for chemical substances in the EU (SCCS, 2015). For most cosmetic ingredients the producers are responsible. For certain classes of ingredients (such as hair dyes, preservatives, UV-filters), the SCCS is responsible.

For cosmetic ingredients, the risk of systemic side effects is largely determined by the absorption across the skin. In case of a significant absorption, that may be a cause of concern for low-dose biologically active molecules. In that situation, HBM studies or studies in volunteers may be valuable by providing an accurate estimate of the systemic effective dose in humans under in-use conditions. However, the SCCS guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation mentions that HBM data should rather be used as support in RA and risk management, because they are as such not suitable for the assessment of exposure of a (cosmetic) substance when other (non-cosmetic) sources for uptake and exposure are involved. Still, back-calculation from biomonitoring data to external exposure data are possible but requires additional information (e.g. type of biomarker, exposure modelling). Especially in view of the prohibition of in vivo animal studies on cosmetic substances, HBM makes it possible to gain important in vivo information, also directly in humans without the need for interspecies extrapolation, or the limitation of a small number of subjects involved in human volunteer studies (SCCS, 2018).

4. Examples of the use of HBM in RA with specific focus on HBM4EU priority substances

Next to the review of RA methodologies, some examples on the use of HBM in regulatory RA context were identified. The focus was specifically on the substances or substance groups selected as priority for research activities under the HBM4EU project. Several HBM4EU priority substances have been recently evaluated under REACH regulation. These include several phthalates, bisphenol A, PFOA, cadmium, chromium(VI), benzo[a]pyrene, aniline compounds such as 4,4′-methylenebis[2-chloroaniline] (MOCA) and 4,4′-methyleneedianiline (MDA) and flame retardants tris(2,3-dibromopropyl)phosphate and bis (pentabromophenyl)ether (DecaBDE) (see further in Supplementary Table 1).

Among these, phthalates and bisphenol A restrictions and MOCA authorization provide good examples on how HBM data can be used to strengthen exposure assessment in the regulatory risk assessment. More detailed descriptions of these cases are given as supplementary information.

PFOA and related substances have been also in a focus of regulatory risk assessments lately. PFOA is a key compound within the large group of per- and polyfluorinated substances, which is persistent, bioaccumulative and toxic, and has been recognized as a Substance of Very High Concern under REACH. PFOA, its salts and PFOA-related substances - which are considered to have the potential to degrade or be transformed to PFOA - are restricted in a number of consumer products (REACH annex XVII restricted substances list by Commission Regulation (EU) 2017/1000).

A wealth of HBM based data on exposure and health effects of PFOA exist either from the general population, from workers or from specific highly exposed populations for instance in the US, the Netherlands and Sweden, who have had their drinking water and outer environment contaminated due to industries in the vicinity producing Teflon or firefighter training areas.

Most PFOA RAs that have been performed to date are based on either animal or human data and show very large differences in their
conclusions. In general, the health based limit values based on animal experiments are much higher than those derived in RAs based on human data. One key issue is the major differences in toxicokinetics and toxicodynamics of PFOA between animals and humans.

The HBM data for the general population and workers were used in an EU restriction proposal prepared by Norway and Germany (ECHA, 2014). DNELbiomarker values for highly exposed workers and the general population were derived in order to assess risk to human health. Various epidemiological studies that have suggested associations between PFOA exposure and adverse health effects such as reduced birth weight and elevated cholesterol levels were used. With available LOAEL data, DNELs were calculated for the different effects based on animal external intake data as well as human exposure data. The risk characterization suggested that the highest exposed individuals in the general population are not protected towards the hazardous effects of PFOA, with Risk Characterization Ratios exceeding one. ECHA’s RA committee evaluated this restriction proposal (ECHA, 2015a), but based its opinion on PBT properties of PFOA, which were alone sufficient for restriction. DNEL was, however, derived to support the restriction but this was based mainly on animal studies since it was considered that a DNEL cannot be reliably derived from human data (ECHA, 2015a).

The German Human Biomonitoring Commission re-assessed the HBM value for PFOA in 2016 (UBA and GEA, 2016). The HBM I value represents the concentration of a substance in human biological material below which no risk for adverse health effects over a lifetime is expected. The German Commission decided to use the existing POD ranges of 1–10 ng/ml in blood plasma as a basis and selected 2 ng/ml comprising the HBM I value for PFOA (UBA and GEA, 2016). This value of 2 ng/ml was two-orders of magnitude lower than animal data based TDI or DNELs proposed earlier by EFSA and ECHA.

Recently, EFSA has updated its opinion on PFAS and PFOA and recommended a tolerable weekly intake for PFOA which is based on two epidemiological studies on the effects on serum cholesterol levels showing very similar BMDL5 levels expressed as serum/plasma PFOA (9.2–9.4 ng/ml (Knutsen et al., 2018).

Outside EU regulatory context, a good example on the use of HBM data under the mixtures framework is given in the publication by Meek et al. concerning PBDEs (Meek et al., 2011). In this case, conservative upper-bounding estimates of total intake of PBDEs were derived based on maximum levels in air, water, dust, food and human breast milk, and standard intake values for six age groups within the Canadian population. Comparison of the critical effect level with the upper-bounding deterministic estimate of exposure for the intake of total PBDEs resulted in a margin of exposure of approximately 300 whereas margins based on HBM data were approximately 10-fold less. There are also other illustrative cases outside the EU, such as human biomonitoring data used in regulatory risk assessment under Canada’s Chemicals Management Program (Zidek et al., 2017; St-Amand et al., 2014).

5. Survey: national RA practices and the views of risk assessors on the use HBM

The current RA practices in different countries (EU and non-EU countries) and the current use of HBM in the RA of chemicals were evaluated using a questionnaire sent to national risk assessors throughout the European Union. The aim of the survey was to understand how risk assessors, working in different fields of chemical RA, consider HBM, what they think about the use of HBM in RA and what they consider to be the main reasons and obstacles for (not) using HBM in health RA and HIA.

There were 71 respondents from 18 EU countries, 2 non-EU countries in Europe that participate in HBM4EU and 5 non-European countries. For 4 out of 71 respondents, the country was not indicated. Furthermore, about 50% of the EU respondents were located in just 5 EU countries. The higher response numbers were received from Austria (8 responses), Belgium (7) and Netherlands (5), followed by 4 responses from Finland, Latvia, Slovenia and Germany. From the rest of the countries the number of responses was 1–3, while no answers were obtained from Czech Republic, Greece, Hungary or Ireland (see further Supplementary Fig. 1). This means that extrapolation and generalisation of the results of this survey needs to be made with caution; especially for those questions that had a limited number of respondents.
Of the total of 71 respondents, 55 responded to the first part of the questionnaire concerning risk assessment in general and, among these, 12 responded also to the second part of the questionnaire focused on OSH. In addition, 16 responded exclusively to the field of OSH.

Concerning the regulatory frameworks of the respondents, 42% referred to be active in REACH, 39% in OSH and 31% in the food safety domain, while other areas included cosmetic products, biocides, plant protective products, pharmaceuticals and circular economy (further details in Supplementary Fig. 2).

5.1. Current practices of HBM in RA

Across different frameworks, out of the 55 respondents concerning general RA, only 27% replied that HBM is regularly applied in their regulatory domain in their country (Supplementary Fig. 3). Thus, in most cases, it is either not used, or used only to a limited extent. Those who answered that it is used only to a limited extent mentioned occasional HBM campaigns such as following an incident (i.e. independent of regulatory framework), societal unrest (like recently with PFOA around the Chemours (previously DuPont) factory in Dordrecht in NL) or pertaining to only one chemical, i.e. lead, for which HBM is obligatory by law under OSH framework.

HBM seems to be more regularly applied in the OSH field since 56% of the respondents in this area referred to it. However, also in the OSH field, 44% of the respondents mentioned that it is either not used or it is used only to a limited extent. In this case the answer was justified due to the fact that HBM is legally required only when monitoring exposure to lead.

With respect to the existence of any guidance for the use of HBM for general RA in their country, out of 55 respondents about general population, 64% responded that no guidance is available (Fig. 2A). In case there is guidance available, it is usually specific for a single regulatory domain. In open comments it was mentioned that even if e.g. REACH guidance refers to HBM, more guidance on its use in RA is needed. Also for the technical and organisational application of HBM it became clear that guidance is largely missing (Fig. 2B).

Conversely, most of the 28 respondents from the occupational health field (73%) indicated that there is a guidance (regulatory, institutional) for the use of HBM in the workplace (Fig. 2A). Only three of them (representing different countries) said that there is no guidance in his/her country. Similarly, most of the respondents (77%) stated that there is a specific guidance for the technical application of HBM in workplaces/occupational health care (Fig. 2B). However, when asked about the most important obstacles when using HBM in RA, lack of official guidance was the second most important obstacle, just after the lack of legal enforcement (Fig. 3), both in the context of general population and OSH. Other important obstacle in OSH were the ethical aspects such as acquiring informed consent (44%) or the inexistence of validated HBM methods (44%) or no guidance values (39%), the latter also relevant for general population (47%).

Related to the legal enforcement, most of respondents (69%, n = 26) answered to the question on the effectivity of the regulations, that current OSH regulations are not effective enough to support the use of HBM in occupational health and safety (Supplementary Fig. 4). Lead was again mentioned by several respondents as an exception.

In respect to the absence of HBGV or population-based reference values (RVs), also the inability to interpret or use HBM data was high.

5.2. Perspectives on the use of HBM

The main drivers to perform HBM in the general population were identified as: to confirm exposure (54%), to assess internal exposure level (52%) and to support RA and define priorities for intervention (50%) (Fig. 4).

The main drivers to perform HBM in occupational settings were: health surveillance performed by occupational health care (67%) and the existence of regulations (e.g. B–Pb measurements required by law)” (67%), (Fig. 4). In a separate question, only 37% of 24 respondents indicated that HBM data are available for use in exposure assessment and management at the workplace. Thus, the results of the HBM in many cases are used only for individual health RA and not for the workplace RA and management, which is the responsibility of the employer. A reason for this, as mentioned by several participants, is the privacy concern.

When questioned how HBM could contribute to RA and management, the following answers were given more frequently: providing
realistic exposure data (60%), aggregating routes of exposure (47%), risk management prioritization (42%) and comparing subpopulations and identifying vulnerable populations (36%). Other answers included the assessment of the effectiveness of policy/risk management actions, integrate single chemical exposure due to aggregate exposure, using more biological effect markers in HBM to detect early effects, assessing temporal exposure trends, characterizing geographical patterns of exposure or effect, assess combined exposure or historical/retrospective exposure data (Supplementary Fig. 5).

In respect to the criteria for using HBM in RA, the existence of validated methods for HBM, the existence of health-based biological limit or guidance values and the ability to relate biomarker levels to external exposure were judged as the most important criteria to be met before HBM can be used in both the general population and OSH RA (Supplementary Fig. 6). However, other possible criteria, i.e. ability to estimate BE, existence of population based HBM RVs, a sufficient population size, and relation biomarker of exposure to health effect were also considered relevant. Additional linked points mentioned in the comments were appropriate knowledge about ADME, the appropriate metabolite to monitor as well as appropriate size of relevant sub-populations (men and women, children, pregnant women). It appears from the responses that the criteria set upfront are often not met.

Regarding the criteria for using HBM data in occupational RA, the information on that human HBM level can be related to the exposure source (85%) was emphasized. Approximately half of the respondents (54%) stated that HBM results of workers are compared to occupational BLVs or BGVs. Lead was the substance mentioned more frequently as useful tool, which can be used as a third tier method for the refinement of exposure assessment. In most regulatory areas (e.g. REACH), the data requirements for registration in practise do not support the use of HBM, although in principle it is given as an option for exposure assessment. This is mainly because there has been no real need to understand the relationship between internal exposure and health effects for regulatory purposes, and because toxicokinetic data, which plays a vital role for the use of HBM data, does not belong to the basic data requirements. In addition, the IUCLID database, meant for the registration of chemicals does not currently include an entry for DNELs based on biomarkers. Furthermore, in some regulatory areas (pesticides, biocides) the use of HBM results of workers is usually communicated to the Occupational Health Service and to the worker (60%). Less than half (44%) indicated that an overview of the results is communicated directly to the employer. Although 50% of the respondents stated that the occupational health service has an obligation to give an overview of the HBM results to the employer, 22% did not know if this is a reality or not. The way this information is presented to the employer is also very diverse since all participants (n = 9) responding to this question expressed different forms for presenting this information.

6. Discussion

In this study we have evaluated the role of HBM in several international and EU RA schemes and collected information from national regulatory risk assessors on the use of HBM in their day-to-day RA practices.

On the basis of this evaluation, HBM is generally considered as a useful tool, which can be used as a third tier method for the refinement of exposure assessment. In most regulatory areas (e.g. REACH), the data requirements for registration in practise do not support the use of HBM, although in principle it is given as an option for exposure assessment. This is mainly because there has been no real need to understand the relationship between internal exposure and health effects for regulatory purposes, and because toxicokinetic data, which plays a vital role for the use of HBM data, does not belong to the basic data requirements. In addition, the IUCLID database, meant for the registration of chemicals does not currently include an entry for DNELs based on biomarkers. Furthermore, in some regulatory areas (pesticides, biocides) the use of volunteer studies in the approval of new substances has not been allowed. This may limit the use of HBM data in those areas.

Although examples of the use of HBM data in chemicals RA can be found in almost all regulatory areas, the guidance on such use is generally either limited or missing. This was also noted as an outcome of the survey amongst risk assessors. The main findings of this survey were:

- HBM is mostly used under OSH framework, less under other RA frameworks. However, also under OSH, the use of HBM is sometimes limited only to B–Pb which is legally binding in EU. Outside the OSH domain, HBM is often incident driven (regulatory framework independent).
In OSH framework, HBM is seen as a health surveillance tool and not as an exposure assessment tool. Additionally, when HBM data are available, there is no guidance regarding the minimal data that should be available and reported to employers and enforcement bodies to allow RA and risk management at workplaces.

A key obstacle for using the HBM in risk assessment is the lack of guidance both in general population risk assessment and in OSH field. This pertains both to the more scientific part of HBM (biomarker selection, information on toxicokinetics, relation between exposure biomarker and health effects, sufficient sample size including subpopulations of concern) and to the technical and organisational part (not specified in the survey but includes e.g. validated sampling and analytical methods, how and to whom to communicate the results of HBM).

Another key obstacle was the lack of legal enforcement followed by the lack of guidance/limit values. Under OSH, also ethical aspects were raised, which is a bit surprising but may reflect the concerns of the workers related to the possible analysis of other markers (e.g. related to the use of drugs etc) from the samples collected by occupational health care.

It is recognized that practices related to HBM vary between different countries. Variability in HBM practices in occupational health have been shown also in recent EU DG Employment funded study (RPA, 2017). In the present survey, most participants were from EU countries but the frequency of respondents from a specific EU country varied from 0 to 8. About half of the respondents from the EU were from only 5 EU-countries. Therefore, care should be taken when generalising the results of this survey. However, for some questions, the results obtained from the survey were traced back to individual countries in order to ensure that some specific results do not represent a particular situation in a single country but are general issues.

Health based biological limit/guidance values (or biological equivalents) are considered extremely important for the use of HBM. This applies to all RA fields. The lack or paucity of toxicokinetic data may, however, hamper the derivation of HBM limit or guidance values. Fortunately, Biomonitoring equivalent approach requiring limited amount of toxicokinetic information and PBTK/PBPK modelling may be helpful (Angerer et al., 2011; Boogaard et al., 2011). Since in occupational context legal enforcement of biological limit values is an important driver to conduct HBM, inclusion of more BLVs in EU OSH legislation concerning chemicals (CAD/CMD) is emphasized. Also, even though HBM is commonly done by occupational physicians as part of health surveillance, aggregated results of the exposed workers could be used in many cases to review the workplace RA and the efficiency of the risk management measures.

In future, new possibilities to use biomonitoring data need also be considered; as the reduction in animal testing (3Rs) is already reality and experimental information on e.g. toxicokinetics may be lacking, the existing HBM data could be integrated with data using non-animal methods (in vitro, in silico and HTT screening) in combination with computational modelling (PBTK) to generate more reliable information on toxicokinetic and to provide linkages between AOPs and human internal exposure levels should be initiated. Well-designed and harmonised HBM studies should be considered for this development with selection of priority groups of chemicals. HBM data should also be used to validate integrated and aggregated external and internal exposure models. The link between external exposure sources and internal exposure should be better assessed. At the same time, these iterative efforts that will include adjustments to parameter settings (input data on exposure factors and time-activity patterns) will allow identification of critical exposure parameters.

Concerning OSH, efforts for the legal enforcement of biological limit values in EU should be initiated. The roles of worker’s health surveillance and HBM supporting workplace exposure assessment and risk management should be clarified. The collection of HBM data for example for pesticide workers should be considered as a routine component of existing occupational surveillance programs in Europe.

HBM has to be incorporated almost by default in European studies addressing exposure to mixtures, since it is probably the only way to obtain realistic exposure data regarding multiple exposures and also aggregate exposure to chemicals from different sources.

Reinforcing the capabilities of HBM and starting discussions with regulators on better anchoring HBM as a tool in the various EU legislative RA frameworks is critical to increase the frequency of use of the HBM tool and to improve the quality of regulatory RA by realistic, EU-specific exposure information.

7. Conclusions

The growing body of HBM data in Europe from the HBM4EU program as well as other studies presents an opportunity for the regulatory risk assessment community to improve and refine their high-impact assessments with high quality HBM data. There are already reliable, sensitive and specific HBM methods available for several substances of concern. When these HBM methods are applied using harmonised guidance for the various phases of HBM (recruitment, sampling, analysis, data evaluation, communication, follow-up strategy) we can ensure the high quality of the data collected. However, for the better use of HBM data in chemical RA we recommend following actions which are based on the findings of this study.

First of all, an EU level guidance applicable to different regulatory schemes on the use of HBM in RA should be prepared to better support the integration of HBM in regulatory RA. This can be drafted e.g. under HBM4EU project. The guidance should build on existing knowledge and it should consider also the new approaches for integrating HBM with in vitro in silico data and adverse outcome pathways (AOP).

Secondly, scientifically sound health-based biological limit/guidance values (such as derived via the biological equivalents approach), preferably with at least some regulatory recognition should be developed at EU and/or global (e.g., WHO, FAO) level.

Thirdly, research efforts for the development of approaches to integrate existing HBM data, data using non-animal testing methods (in vitro, in silico and HTT screening) in combination with computational modelling (PBTK) to generate more reliable information on toxicokinetic and to provide linkages between AOPs and human internal exposure levels should be initiated. Well-designed and harmonised HBM studies should be considered for this development with selection of priority groups of chemicals. HBM data should also be used to validate integrated and aggregated external and internal exposure models. The link between external exposure sources and internal exposure should be better assessed. At the same time, these iterative efforts that will include adjustments to parameter settings (input data on exposure factors and time-activity patterns) will allow identification of critical exposure parameters.
Acknowledgements

This project has received funding from the European Union’s Horizon 2020 research and innovation program under grant agreement No 733032 HM4EU, and received co-funding from the author’s organizations. The authors thank all other participants that contributed to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2019.05.009.

Declarations of interests

None.

References


