Human biomonitoring in risk assessment: analysis of the current practice and 1st examples on the use of HBM in risk assessments of HBM4EU priority chemicals

Heinälä, M.; Bessems, J.; Buekers, J.; Cornelis, C.; Vermeire, T.; Woutersen, M.; van Engelen, J. ; Borges, T.; Rousselle, C.; Ougier, E.; Louro, H.; Alvito, P.; Martins, C.; Assuncao, R.; Silva, M. J.; Krul, L.; Pronk, A.; Schaddelee-Scholten, B.; Stierum, R.; Gonzalez, M. C.; de Alba, M.; Diaz, G.; Viegas, S.; Humar-Juric, T.; Abraham, K.; Vinggaard, Anne Marie

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Task leader	Tiina Santonen	FIOH	11.10.2017

Responsible author	Tiina Santonen	E-mail	tiina.santonen@ttl.fi
Short name of institution	FIOH	Phone	+358405390343
Co-authors	M. Heinälä, Finnish Institute of Occupational Health (FIOH), Finland J. Bessems, J. Buekers, C. Cornelis, Flemish Institute for Technological Research (VITO), Belgium T. Vermeire, M. Woutersen, J. van Engelen, National Institute of Public Health and the Environment (RIVM), Netherlands T. Borges, Directorate-General of Health (DGS), Ministry of Health, Portugal C. Rousselle, E. Ougier, Agency for Food, Environmental and Occupational Health & Safety (ANSES), France H. Louro, P. Alvito, C. Martins, R. Assunção, M.J. Silva, National Institute of Health Dr. Ricardo Jorge (INSA), Lisbon, Portugal L. Krul, A. Pronk, B. Schaddelee-Scholten, R. Stierum, Netherlands Organization for Applied scientific Research (TNO), Netherlands M.C. Gonzalez, M. de Alba, G. Díaz, A. Castaño Institute of Health Carlos III (ISCIII), Spain S. Viegas, Lisbon School of Health Technology/ Polytechnic Institute of Lisbon (ESTeSL/IPL), Portugal T. Humar-Juric, L. Kononenko, Ministry of Health, Chemicals Office of the Republic of Slovenia, Slovenia K. Abraham, Federal Institute for Risk Assessment (BfR), Germany A.M. Vinggaard, Technical University of Denmark (DTU), Denmark		

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1 Authors and Acknowledgements

Lead author

Tiina Santonen, Finnish Institute of Occupational Health (FIOH), Finland

Co-authors

M. Heinälä, Finnish Institute of Occupational Health (FIOH), Finland

J. Bessems, J. Buekers, C. Cornelis, Flemish Institute for Technological Research (VITO), Belgium

T. Vermeire, M. Woutersen, J. van Engelen, National Institute of Public Health and the Environment (RIVM), Netherlands

T. Borges, Directorate-General of Health (DGS), Ministry of Health, Portugal

C. Rousselle, E. Ougier, Agency for Food, Environmental and Occupational Health & Safety (ANSES), France

H. Louro, P. Alvito, C. Martins, R. Assunção, M.J. Silva, National Institute of Health Dr. Ricardo Jorge (INSA), Lisbon, Portugal

L. Krul, A. Pronk, B. Schaddelee-Scholten, R. Stierum, Netherlands Organization for Applied scientific Research (TNO), Netherlands

M.C. Gonzalez, M. de Alba, G. Díaz, A. Castaño Institute of Health Carlos III (ISCIII), Spain

S. Viegas, Lisbon School of Health Technology/ Polytechnic Institute of Lisbon (ESTeSL/IPL), Portugal

T. Humar-Juric, L. Kononenko, Ministry of Health, Chemicals Office of the Republic of Slovenia, Slovenia

K. Abraham, Federal Institute for Risk Assessment (BfR), Germany

A.M. Vinggaard, Technical University of Denmark (DTU), Denmark

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2 List of abbreviations

AB	Advisory Board
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AEL	Acceptable Exposure Level
AOEL	Acceptable Operator Exposure Level
AOPs	Adverse Outcome Pathways
ACSH	Advisory Committee on Safety and Health at Work
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
BBP	Benzyl butyl phthalate
BE	Biomonitoring Equivalent
BGV	Biological Guidance Value
BLV	Biological Limit Value
BMD	Benchmark Dose
BMDL	Benchmark Dose Lower confidence Limit
BPA	Bisphenol A
BPR	Biocidal Products
BOELV	Binding Occupational Exposure Limit Value
CAD	Chemical Agents Directive
CDC	Center for Disease Control
CICADs	Concise International Chemical Assessment Documents
CMD	Carcinogens and Mutagens Directive
DALYs	Disability Adjusted Life Years
DAR	Draft Assessment Report
DBP	Dibutyl phthalate
DEHP	Bis(2-ethylhexyl) phthalate
DFG	German Research Foundation
DGS	Directorate-General of Health (Pt)
DIBP	Diisobutyl phthalate
DMEL	Derived Minimal Effect Level
DNEL	Derived No-Effect Level
EBD	Environmental Burden of Disease
ECHA	European Chemicals Agency
EDC	Endocrine Disruptor

EEA	European Environment Agency
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
ESTLs	Lisbon School for Health Technology
EU	European Union
FAO	Food and Agriculture Organization
HBGV	Health-Based Guidance Value
HBM	Human Biomonitoring
HBM4EU	European Biomonitoring Initiative
HIA	Health Impact Assessment
IARC	International Agency for Research on Cancer
INSA	Instituto Nacional de Saúde Dr. Ricardo, Jorge, Portugal
IOELV	Indicative Occupational Exposure Limit Value
IPCheM	Information Platform for Chemical Monitoring
IPCS	International Programme on Chemical Safety
JRC	Joint Research Center
MDA	4,4'-Methylenedianiline
MOA	Mode of Action
MOCA	4,4'-Methylene-bis-(2-chloro-aniline)
MB	Management Board
NGO	Non-Governmental Organisations
NHCP	National Hub Contact Point
NO(A)EL	No Observed (Adverse) Effect Level
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
OSH	Occupational Safety and Health
PAHs	Polycyclic Aromatic Hydrocarbons
PBPK/PBTK	Physiologically Based Pharmacokinetic/Toxicokinetic
PBDEs	Polybrominated diphenyl ethers
PBT	Persistent Bioaccumulative and Toxic
PCBs	Polychlorobiphenyls
PFCs	Perfluorinated Compounds
PFO	Perflurooctanoate
PFOA	Perfluorooctanoic Acid or Pentadecafluorooctanoic acid
PFOS	Perfluorooctane Sulfonic Acid or Heptadecafluorooctane-1-sulphonic acid

POD	Point of Departure
PPPs	Plant Protection Products
PTR	Periodic Technical Report
RAC	Risk Assessment Committee
RCR	Risk Characterization Ratio
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RMM	Risk Management Measures
RP	Reference Point
RV	Reference Value
SCCS	Scientific Committee on Consumer Safety
SCOEL	Scientific Committee on Occupational Exposure Limits
SEAC	Socio-Economic Analysis Committee
SVHC	Substances of Very High Concern
TDI	Tolerable Daily Intake
UN	United States
VOCs	Volatile Organic Compounds
WP	Work Package
WHO	World Health Organization
WHOPES	WHO Pesticides Evaluation Scheme

3 Introduction

In chemicals risk assessment frameworks, the default approach is to assess external intake from different sources of exposure and via different routes of exposure. They are often assessed separately. This approach includes various uncertainties and often overestimates the real uptake since default, conservative estimates are used e.g. for the absorption of the chemical. At the same time, actual (real life) exposure may be underestimated by not taking into account that exposure to a chemical substance may occur from different sources, which may fall under separate legislative frameworks. Examples are triclosan that is used in biocidal products as well as in consumer products and importantly, most if not all chemicals that are produced by workers where at the same time these workers may be exposed as part of the general population. In some cases, other tools to assess exposure via all possible routes may be insufficient; an example is occupational exposure via hand-to-mount exposure, which has been shown to occur for example in the case of many metals, like lead, through contaminated hands. Without biomonitoring, exposure in these cases could become severely underestimated.

Human Biomonitoring (HBM) is an important tool to survey the real life body burden – or internal exposure – of humans resulting from 'total' exposure to chemicals via different routes (lung, skin, digestive tract) and 'via' different legislative frameworks on chemicals. By providing more accurate data on actual body burdens (internal exposure), inclusion of HBM data could improve human health risk assessment for both the general population (exposure via air, consumer products, drinking water and food) as well as for workers (exposure via inhalation and/or skin) separately or as part of the population.

HBM could be helpful in other areas as well, demonstrating for example increased blood levels because of accumulation of a chemical in the body following repeated exposure. In many frameworks, human absorption, distribution, metabolism, and excretion (ADME) and toxicokinetics data including the body half-life are not necessarily required for the safety assessment of the chemical. HBM has also been used to showcase that interindividual differences with respect to respiratory ventilation and use of personal protection equipment are reflected in internal exposure. These differences are not observed using ambient air monitoring. In addition, by using HBM data it could be possible to bridge with new conceptual developments such as AOPs (adverse outcome pathways) and to investigate direct linkages between internal exposure and the onset of AOPs resulting in adverse health effects.

Naturally, HBM has also limitations including the fact that it often gives only a snap shot of exposure due to the assessment of single time points, often metabolites and not the parent compounds are measured, and exposure biomarkers are only proxies measured in easily accessible tissues and fluids and are not necessarily the concentrations at target organs. In addition, total body burden may be in some cases difficult to link to specific exposure sources. These limitations need to be recognised when interpreting biomonitoring data.

Although the past few years have shown good examples on the use of HBM in the risk assessment of chemicals, there is still quite some work to improve its use in risk assessment and human impact assessment. 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" (US NAS, 2017), lays out recommendations to incorporate the emerging science into risk-based evaluations. In that capacity, HBM is described as an essential tool allowing for advances in exposure science and epidemiology.

Therefore, the HBM4EU project aims to deliver European wide quantitative information on levels of *internal exposure biomarkers* and *effect biomarkers*. Using thousands of individually linked pieces of information on exposure and health-effect biomarkers, the aim is to establish 'internal exposure-

health effect relationships'. If successful, this will provide molecular epidemiological (= legislative framework independent) knowledge that could be used alongside the classical toxicological, regulatory framework-driven risk assessment. Moreover and at the same time, using the newly developed 'internal exposure - health effect relationships', health impact assessment (HIA) of chemicals would become more feasible. Altogether, improvement and the combined use of human health risk assessment and HIA will provide the necessary tools for a significant step forward in the important domain of chemicals risk management.

In order to achieve this goal and to provide strong anchoring to current risk assessment practices, in this report, the current use of human biomonitoring in risk assessment of chemicals has been evaluated. Firstly, different global (World Health Organization (WHO), Food and Agriculture Organization of the United States (UN FAO)) and regional (EU) risk assessment schemes were screened for information on HBM including the availability of guidance on how to use HBM in risk assessment.

In addition, a survey was held to collect information from national regulatory risk assessors on their day to day risk assessment practices, the use of HBM, and obstacles and challenges related to the use of HBM (in EU, European non-EU as well as non-European countries).

Finally, we have presented good examples on the advanced use of human biomonitoring of a few selected chemicals from the HBM4EU prioritised substance groups. Based on these data some proposals are provided for the better inclusion of HBM in human risk assessment and health impact assessment.

4 Overview on risk assessment and health impact assessment schemes

4.1 International risk assessment schemes

International risk assessment schemes such as from WHO and UN FAO provide a wealth of information and concrete guidance on how to perform risk assessment. In many parts and countries of the world, actual and concrete risk assessment for a specific chemical in the sense of a concrete risk prediction (i.e. actual exposure divided by a safe level such as an acceptable daily intake (ADI)) is a national prerogative. International 'risk assessment' schemes do propose however safe exposure levels such as TDI's or linked to this, MRL's (maximum residue levels). By doing so, these international bodies support especially those countries for which national or regional expertise and capacity to do so is limited. By this, they also enable international comparability of feed and food risk assessments and thereby promote fair practices in food and feed trade. Another reason is that concrete risk predictions require adequate exposure levels and these are often country-specific.

4.1.1 WHO

Under WHO/International Programme on Chemical Safety (IPCS) umbrella, the paradigm of risk assessment process begins with problem formulation and includes four additional steps: 1) hazard identification, 2) hazard characterisation, 3) exposure assessment and 4) risk characterisation (IPCS, 2004) - see Table 1. A full description of the concepts presented in the table may be found in chapter 3 of WHO Environmental Health Criteria (EHC) 239 (IPCS, 2009a).

Table 1: WHO/IPCS Paradigm of Risk Assessment

Step	Description	Content
Problem formulation	Establishes de scope and objectives of the assessment	Defining the question Prior knowledge Desired outcomes
Hazard identification	Identifies the type and nature of the adverse health effects	Human studies Animal-based toxicology studies In vitro toxicology studies Structure-activity studies
Hazard characterization	Quantitative or qualitative description of the inherent properties of an agent having properties to cause adverse health effect	Selection of critical dataset Modes/mechanism of action Kinetic variability Dynamic variability Dose-response for critical effect
Exposure assessment	Evaluation of the concentration or amount of a particular agent that reaches the target population	Magnitude Frequency Duration Route Extent
Risk characterization	Advice for decision-making	Probability of occurrence Severity Given population Uncertainties

EHC 214 (IPCS, 2000) refers that human health risk assessments of chemicals can be performed to evaluate past, current and even future exposures to any chemical found in air, soil, water, food, consumer products or other materials and that can be quantitative or qualitative in nature. Human

health risk assessment for chemical hazards is a means of integrating the components of the environmental health chain in a manner that is useful for analysis and management of chemical-mediated risks.

In IPCS, 2004, human health risk assessment is described as a process intended to estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.

The WHO Human Health Risk Assessment Toolkit: Chemical Hazards (IPCS, 2010) has been developed to support especially developing countries and countries with economies in transition in the management of chemical risks. It is a very practical tool, which is meant to provide its users the basic information needed for the assessment of chemical risks. It gives guidance to identify, acquire and use the information needed to assess chemical hazards, exposures and the corresponding health risks in their given health risk assessment contexts at local and/or national levels.

Human biomonitoring in WHO risk assessment scheme

WHO/IPCS risk assessment scheme refers that besides the use of traditional exposure assessment, the use of biological markers represents another method to evaluate human exposure to a chemical, and that the selection of sampling media depends on the contaminant of interest, the pattern of exposure, the timing of exposure, the population studied, ease of collection and storage and participant burden. Human biological monitoring is frequently considered invasive; however, several media that can be collected in a non-invasive manner are available for exposure assessment. Blood and urine, as well as exhaled breath and saliva, can be used to document recent exposures; past exposure can be evaluated using blood and urine, as well as keratinized tissues (hair and nails), ossified tissue (teeth and bone), adipose tissue and breast milk. Adipose tissue and bone can also represent future sources of internal exposure. Further information on biomarkers of exposure is available in IPCS (1993a, 2000, 2001b) (see also Table 2).

Table 2: Some WHO sources of guidance on biomarkers

Document title	Reference
Biomarkers and risk assessment: concepts and principles (EHC 155)	IPCS (1993a)
Human exposure assessment (EHC 214)	IPCS (2000)
Biomarkers in risk assessment: validity and validation (EHC 222)	IPCS (2001b)

In WHO (2010), it is mentioned that the greatest uncertainties in risk assessment almost always arise from inadequate exposure data, inadequate understanding of mechanisms of toxicity, and insufficient understanding of the exposure-dose-response pathway (Becking, 1995; McClellan, 1995). Two additional factors that can lead to uncertainties in risk assessment include mixed or multiple exposures implicated in the disease pathway, and variability of both exposures and responses within and between individuals.

In specific guidance on biomarkers, e.g. IPCS (1993a) “Biomarkers and risk assessment: concepts and principles” (EHC 155), the relevance of using the different types of biomarkers in the different phases of the risk assessment process are discussed in specific sections of the document:

- Biomarkers of exposure can be used to confirm and assess the exposure of individuals or populations to a particular substance, providing a link between external exposures and internal dosimetry.
- Biomarkers of effect can be used to document either preclinical alterations or adverse health effects elicited by external exposure and absorption of a chemical. Thus the linkage

of biomarkers between exposure and effect contributes to the definition of dose-response relationships.

- Biomarkers of susceptibility help elucidate the degree of the response to exposure elicited in individuals.

It is also highlighted in this document that the biomarkers in health risk assessment (measurements within the context of "biological monitoring") have been used to assess worker exposure and, in clinical settings, to evaluate the administration of therapeutic agents. These measurements, or biomarkers, provide the critical link between chemical exposure, internal dose and health impairment, and are of value in assessment of risk. However, it is said that there is a need to identify and validate for each organ system the characteristic parameter(s) that are indicative of induced dysfunction, clinical toxicity or pathological change, as well as to establish the specificity and sensitivity of each biomarker and its method of measurement (e.g. biological markers of effect and markers for susceptibility – please see figure Figure 1).

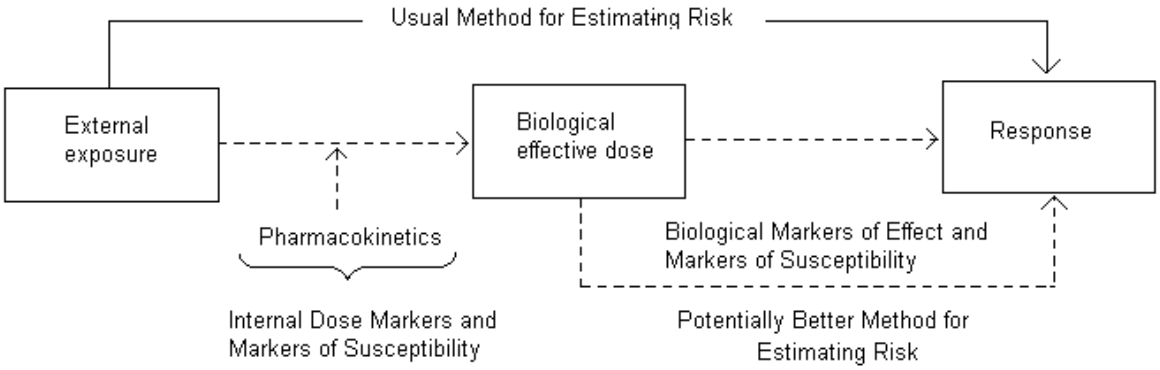

Figure 1: Rationale for using biomarkers to assess risk (from Schulte&Waters, 1999)

In IPCS (2001b) Biomarkers in risk assessment: validity and validation (EHC 222), biomarkers for risk assessment were considered and a framework for selecting and validating biomarkers was developed (Table 3). How the three types of biomarkers, of exposure, of effect and of susceptibility, could be validated for research and be used in risk assessments. It was considered that valid biomarkers can lead to biologically based risk assessments although there have been few cases where validated biomarkers have been used in **quantitative** risk assessments. Also, that the lack of validation of most biomarkers of intermediate effect was probably the most critical impediment to the broad use of biomarkers in risk assessment.

Table 3: Characteristics of valid biomarkers

Biomarker type	Characteristic of validity
Exposure	Consistently linked with exposure at relevant levels of exposure with confounding and background exposures assessed*
Effect	Consistently linked with increased risk with confounding and effect modifying factors assessed
Susceptibility	Can distinguish subgroups at risk given specific exposure

*Biomarkers of exposure may also be validated by establishing a constant link to an adverse health effect or to the concentration of the chemical in the target organ.

The main conclusions from this document include:

- Validation of biomarkers for research and risk assessment requires both laboratory and epidemiological studies.
- Successful use of biomarker data implies an understanding of mechanisms. The incorporation of mechanistic data in risk assessment is certainly important, but risk assessments and regulations should not wait for the development of mechanistic data nor should uncertainty about mechanism be used to block public health action.
- The contribution of biomarkers of susceptibility has great potential but has yet to be realised on a large scale in quantitative risk assessment.
- There is a need for a long-term commitment to the assessment of the validity of biomarkers for risk assessment, environmental health research and public health practice. Introduction of new and validated methods based upon new technologies to study biomarkers of exposure, effect and susceptibility at the different levels of the risk management process will be of great assistance to risk assessors.

Recommendations were made especially for research:

- to develop more incisive biomarkers to fill in the gaps in the continuum of events from environmental exposure to clinical disease expression, taking advantage of new, high-throughput technologies
- to study the genetic basis for different susceptibilities toward environmental exposures and how this exposure influences the phenotype
- to develop and use bioinformatics and advanced statistical methods to fully utilise existing and newly generated data

Also WHO Risk assessment toolkit (IPCS, 2010), meant for use especially in developing countries, recognises the role of human biomonitoring in chemical risk assessment and refers to specific WHO guidance on exposure assessment and the use of human biomonitoring data in risk assessment. In addition, under the umbrella of the WHO Chemical Risk Assessment Network, WHO organised a workshop on human biomonitoring to support chemical risk assessment in Bangkok, Thailand in November 2016 (http://www.who.int/ipcs/network/BKK2016/en/). The workshop was intended to provide a forum to exchange information and knowledge and facilitate future collaboration related to HBM in chemical risk assessment, especially in low resource settings.

HBM4EU priority substances evaluated by WHO

WHO has evaluated a wide range of chemicals in the past. These evaluations have been published under WHO EHC series or as Concise International Chemical Assessment Documents (CICADs). Latest CICAD published by this far is on hexavalent chromium, which is one of the priority compounds under HBM4EU (WHO, 2013). It describes some data on the human biomonitoring of chromium at the workplaces using urinary total chromium as an unspecific marker for the hexavalent chromium exposure. Sample risk characterisation is made for workers for lung cancer using air monitoring data for exposure assessment.

4.1.2 WHOPES

WHO pesticides evaluation scheme (WHOPES) has published generic risk assessment models to be used in the risk assessment of insecticides used for indoor residual spraying, larviciding, space spraying, treatment of mosquito nets and aircraft disinfection

(http://www.who.int/whopes/guidelines/en/). The described models are meant as first tier models to be used in the approval of new formulations and should be refined by using more advanced models or measured data if needed. No reference to the use of human biomonitoring data in the risk assessment or post-approval surveillance has been made, except regarding the possible use of human data on acetylcholinesterase inhibition in the hazard and dose-response assessment of organophosphates.

4.1.3 FAO

The UN FAO has published, in 2013, a document entitled “GUIDELINES ON THE APPLICATION OF RISK ASSESSMENT FOR FEED” (FAO 2013) that provides a description on the FAO risk assessment practices.

Considering that the presence of hazards in the feed of food-producing animals may imply subsequent transfer of hazards to edible products, the document provides a guidance for feed and feed ingredients risk assessment by governments in accordance with Codex principles for risk analysis. Risk assessment under the codex risk analysis framework is described to include:

- identification of a food safety problem arising from feed;
- establishment of a risk profile;
- ranking of the hazard for risk assessment and risk management priority (for further details see EFSA 2013);
- determination of a risk assessment policy for the conduct of the risk assessment;
- definition of the output form of the risk assessment;
- commissioning of the risk assessment, and
- consideration of the possible results of the risk assessment.

Human biomonitoring in FAO risk assessment scheme

The steps involved in Risk assessment procedure are enunciated in this document and do not account explicitly for HBM. However, international programs such as the WHO Global Environment Monitoring System (GEMS/Food), the Joint FAO/WHO International Food Safety Authorities Network (INFOSAN), and other reliable rapid alert systems, and industry self-monitoring programs are referred as important sources of useful information. In addition, the document refers that further information is provided in the WHO Principles and Methods for the Risk Assessment of Chemicals in Food.

In this document, human exposure assessment is seen as the qualitative and/or quantitative evaluation of the likely intake of the hazard(s) via food, while the aim of the exposure assessment in feed risk assessment is to estimate the level or prevalence of hazard(s) in edible product(s) after transfer from feed. Subsequently, these estimated levels of hazard in edible product arising from feed are used as input for human exposure assessment. The feed exposure assessment should result in the determination of the predicted level or prevalence of a hazard in edible product. This result is then incorporated as a starting point in the human exposure assessment for food. The evaluation of the human exposure to the hazard should be done using relevant foods and food groups and/or specific human populations to account for feed as a source of exposure, (e.g. by modelling).

HBM4EU priority substances evaluated by FAO

In the document, the hazards in feed can include biological and chemical agents (such as "heavy metals", dioxins, excessive levels of pesticides, veterinary drugs and additives), radionuclides and

other undesirable substances. Biotransformation products present in edible products also need to be considered.

A recent paper examined 564 feed samples over a period of five years (2010-2015) collected by Texas Feed and Fertilizer Control Service and provided a comprehensive analysis of heavy metals during the prescribed time period and ingredient/finished feed type to facilitate risk assessment and implementation of risk management techniques (Dai *et al.*, 2016).

Another paper described the review of chemical contaminants in byproducts in animal feed during 1998-2009 in Denmark (Mortensen *et al.*, 2014). Also, several samples of citrus pulp and dried distillers grains with solubles were additionally collected for analysis and risk assessment. The levels of contaminants in the samples from the official control were below maximum limits from EU regulations with only a few exceptions in the following groups; dioxins and dioxin-like polychlorobiphenyls (PCBs) in fish-containing byproducts and dioxins in vegetable and animal fat, hydrogen cyanide in linseed, and cadmium in sunflowers (Mortensen *et al.*, 2014)..

A European review about dioxins and PCBs in feed and food is described in another paper suggesting that fish, meat and dairy products appeared to be the highest contributing food groups to dietary exposure (Malisch and Kotz, 2014).

4.2 EU Risk assessment schemes

4.2.1 EU Chemicals legislation (REACH)

Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) requires from producers and importers to register all substances placed on the EU market above 1 tonne per year[1]. REACH obliges registrants who markets a substance at ≥10 t/year to conduct a chemical safety assessment (i.e. risk assessment), and provide it to the European Chemicals Agency (ECHA) as part of the Registration dossier. Both the environmental and health risk assessments are based on the fundamental assumption that risk is a function of hazard and exposure. If a hazard is identified, a relationship between exposure (dose) and the effect is sought, which can be used to estimate whether a risk exists and determine whether risk management measures are required.

Description

REACH introduced the concept of Derived No-Effect Level (DNEL), defined as the level of a substance above which a human should not be exposed. DNELs must be derived for all hazardous substances placed on the market in quantities exceeding 10 tonnes per year and should reflect route, duration and frequency of exposure. DNELs should be derived for occupational settings, consumer use, and for the general population for indirect exposure via the environment (Boogaard *et al.*, 2011).

The standard methodology involves setting a point of departure (POD), which is a modified dose descriptor, usually based on a no-observed-adverse-effect level (NOAEL) from an animal study. To the POD a series of default assessment factors is applied to compensate for variations as well as uncertainties with regard to the differences of sensitivity to the substance for which the DNEL is

[1] EC, Regulation (EC) No. 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repairing Council Regulation (EEC) No. 793/93 and Commission Regulation (EC) No. 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/ 105/EC and 2000/21/EC, vol. 1907/2006, 2006. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1907

derived. Substance-specific data can be used when available to refine the default factors recommended in the guidance. When an indicative or binding occupational exposure limit (IOEL or BOEL) has been adopted in the EU following a recommendation report prepared by the Scientific Committee of Occupational Exposure Limits (SCOEL) (see section 4.2.5) or when there is an adopted occupational exposure limit set by national authority in one of the Member states, these can be used as DNEL values for occupational settings, provided they are documented and health-based. As described in section 4.2.4 BOELs usually take socio-economic considerations into account, which may prevent their use as such as DNELs.

The risk assessment is more complicated for effects where there is no identified threshold concentration, particularly for genotoxic carcinogens. In these cases, a stringent level of acceptable risk is established, called the Derived Minimal Effect Level (DMEL).

The conditions of exposure are defined in REACH by the use of exposure scenarios, which comprise a set of operational conditions (e.g. process temperature, concentration of substance) and risk management measures (RMM) (e.g. local exhaust ventilation, protective equipment). For each exposure scenario, the assessor makes an estimate of the exposure, using measured or calculated data.

When risk assessment is performed, DNELs or DMELs are compared to exposure levels to derive a risk characterisation ratio (RCR). If the exposure estimate is equal to or higher than the DNEL or DMEL, the substance will be of concern with regard to the population considered. The assessor may decide that additional information, either concerning exposure or toxicity, is necessary to refine the chemical risk assessment. If the exposure cannot be controlled below the DNEL or DMEL, then the use pattern given in the exposure scenario is designated as a ‘use advised against’ which is recorded in the safety data sheet.

Human biomonitoring in REACH

For the characterisation of the dose-response relationship for human health, DNELs may be expressed as internal exposure biomarker values, applying to the substances for which internal exposure data are available and have been reliably associated with effects. In general, when both internal exposure (human biomonitoring) and external exposure monitoring data are available, and effects data corresponding to both types of exposure data are available, the most appropriate and/or reliable data/method should be used for setting the DNEL. When deriving an internal biomarker DNEL, it has to be clearly indicated that it is a biomarker value, e.g., by mentioning “biomarker” as subscript to $DNEL_{biomarker}$ (ECHA, 2008a).

However, REACH requirements do not include any incentive to understand the relationship between internal exposure biomarkers of the substance 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 common practice in the Registration dossiers. Unfortunately, REACH IUCLID system where dossier submitters have to file substance information contains no field reserved for a $DNEL_{biomarker}$. This does not encourage registrants to consider the possibility to set a $DNEL_{biomarker}$.

Human biomonitoring, which integrates all exposures regardless the route of exposure, is most helpful in: 1) the actual exposure assessment for complex scenarios and 2) the validation that operational conditions and RMM considered in the exposure scenarios result in safe exposures. However, guidance on how to use HBM in risk characterisation and management is limited (Boogaard *et al.*, 2011; ECHA, 2008a).

The authorisation procedure aims to assure that the risks from Substances of Very High Concern (SVHC)[2] are properly controlled and that these substances are progressively replaced by suitable alternatives while ensuring the good functioning of the EU internal market. After a two-step regulatory process, SVHCs may be included in the Authorisation List (Annex XIV) and become subject to authorisation[3]. These substances cannot be placed on the market or used after a given date, unless an authorisation is granted for their specific use, or the use is exempted from authorisation. SVHC are substances with a serious hazard profile and it is generally expected in the context of applications for authorisation that the exposure is not only modelled but also characterised by some representative measured data. HBM, on its own or in conjunction with monitoring data, can therefore be used in the authorisation process to demonstrate that the RMM in place are sufficient to appropriately control or minimise the risks. It may also validate a reduction of exposure when new RMM or changes in operational conditions have been put in place. HBM is particularly relevant when dealing with substances with systemic effects and when significant absorption is expected through different routes of exposure (e.g., dermal and inhalation routes).

Occupational human biomonitoring can also be required on an occasional or regular basis as a condition to grant authorisations. Examples in which occupational biomonitoring has been set as a condition for authorisation are available as ECHA's Risk Assessment Committee (RAC) opinions on authorisation for example for trichloroethylene (ECHA, 2015a) and 4,4'-methylenedianiline (MDA) (ECHA, 2017a). Additionally, ECHA document "How to apply for authorisation"(ECHA, 2016) also advices the applicants that when estimating worker exposure, biomonitoring is an important resource for the measured exposure dataset. In the same document there are examples of applications where human biomonitoring was used to clarify and demonstrate representativeness of exposure data.

The restriction procedure is a tool to protect human health and the environment from unacceptable risks posed by chemicals[4]. Restrictions may limit or ban the manufacture, placing on the market or use of a substance. It can apply to any substance on its own, in a mixture or in an article, including those that do not require registration. It can also apply to imports.

In the restriction process, human biomonitoring is used either as a basis or as supportive to the exposure assessment in the characterisation of an unacceptable risk that needs to be managed through a proposed restriction. HBM data could also be used to illustrate the impact or effectiveness of the restriction (i.e. reduction of the risks to human health of combined exposure to the substance), which is helpful to develop the benefit-cost analyse.

To be useful for risk management however, human biomonitoring data needs to be easily accessible, comprehensive, harmonised, recent and representative for the targeted population.

However, whilst human biomonitoring data integrates all exposures, HBM studies have limited capability in identifying the sources of exposure. Exposure modelling has been shown to be useful to better characterise the contributing sources of exposure and strengthen the demonstration that a proposed restriction will indeed reduce sources of exposure that contribute significantly to the risks (see example of the restriction dossier on 4 phthalates, section 5.2.1).

[2] Substances with the following hazard properties may be identified as SVHCs: 1) Substances meeting the criteria for classification as carcinogenic, mutagenic or toxic for reproduction category 1A or 1B in accordance with Commission Regulation (EC) No 1272/2008 (CMR substances) ; 2) Substances which are persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) according to REACH (Annex XIII) ; 3) Substances identified on a case-by-case basis, for which there is scientific evidence of probable serious effects that cause an equivalent level of concern as with CMR or PBT/vPvB substances

[3] Substances included in Annex XIV of REACH ("Authorisation list") are available from : https://echa.europa.eu/fi/recommendation-for-inclusion-in-the-authorisation-list
Substances included on the Candidate list for Authorisation are available from: https://echa.europa.eu/candidate-list-table

[4] Substances restricted under REACH (Annex XVII) are available from: https://echa.europa.eu/fi/substances-restricted-under-reach

HBM4EU priority substances evaluated under REACH:

Several HBM4EU priority substances have been recently evaluated under REACH regulation. These are listed in the following table 4.

Table 4: HBM4EU priority substances evaluated under REACH

Substance group	Substance	CAS Number	Evaluation under REACH RA scheme	Use of HBM data
Phthalates	DEHP Bis(2-ethylhexyl) phthalate	117-81-7	SVHC requiring authorisation	No
			Application for Authorisation on Formulation of recycled soft PVC containing DEHP in compounds and dry-blends (ECHA 2014a)	Yes
			Restriction in toys & childcare articles (ECHA 2017b)	Yes
	BBP Benzyl Butyl phthalate	85-68-7	SVHC requiring authorisation	No
			Restriction in toys & childcare articles (ECHA 2017b)	Yes
	DBP Di butyl phthalate	84-74-2	SVHC requiring authorisation	No
			Application for Authorisation for DBP used as an absorption solvent in a closed system in the manufacture of maleic anhydride (ECHA 2014b)	Yes
			Restriction (toys & childcare articles) (ECHA 2017b)	Yes
	DIBP Diisobutyl phthalate	84-69-5	SVHC requiring authorisation	No
			Restriction in toys & childcare articles (ECHA 2017b)	Yes
	DINP Diisononyl phthalate	28553-12-0	Restriction (toys & childcare articles)	No
	DIDP Diisodecyl phthalate	26761-40-0		
	DNOP Di-n-octyl phthalate	117-84-0		
	DPP Dipentyl phthalate	131-18-0	SVHC included on the candidate list for authorisation	No

Substance group	Substance	CAS Number	Evaluation under REACH RA scheme	Use of HBM data
	DIPP Diisopentyl phthalate	605-50-5	SVHC included on the candidate list for authorisation	No
	Bis(2-methoxyethyl) phthalate	117-82-8	SVHC included on the candidate list for authorisation	No
	Diisobutyl phthalate	84-69-5	SVHC included on the candidate list for authorisation	No
	Dihexyl phthalate	84-75-3	SVHC included on the candidate list for authorisation	No
Bisphenol	BPA - Bisphenol A 4,4'-isopropylidene diphenol	80-05-7	Restriction in thermal paper (ECHA 2015b)	Yes
Per/Poly fluorinated compounds	PFOA Pentadecafluorooctanoic acid	335-67-1	SVHC on the candidate list for authorisation	No
	PFOS Heptadecafluorooctane-1-sulphonic acid	1763-23-1		
	APFO Ammonium pentadecafluorooctanoate	3825-26-1		
	PFNA Perfluorononan-1-oic acid	375-95-1		
	PFDA Nonadecafluorodecanoic acid	335-76-2		
	PFDoA Tricosafluorododecanoic acid	307-55-1		
Cadmium & Chromium	Cadmium	7440-43-9	Restrictions	No
	Chromium trioxide	1333-82-0	SVHC requiring authorisation	No

Substance group	Substance	CAS Number	Evaluation under REACH RA scheme	Use of HBM data
	Chromium VI compounds	-	SVHC requiring authorisation	No/ (yes*)
PAHs (Polycyclic Aromatic Hydrocarbons)	BaP Benzo[a]pyrene	50-32-8	Restriction	No
	BeP Benzo[e]pyrene	192-97-2		
	BaA Benzo[a]anthracene	56-55-3		
	CHR Chrysen	218-01-9		
	BbFA Benzo[b]fluoranthene	205-99-2		
	BjFA Benzo[j]fluoranthene	205-82-3		
	BkFA Benzo[k]fluoranthene	207-08-9		
	DBAhA Dibenzo[a,h]anthracene	53-70		
Anilines	MOCA 4,4'-methylenebis[2-chloroaniline]	101-14-4	SVHC requiring authorisation (ECHA, 2015c)	Yes
	MDA 4,4'-methylenedianiline	101-77-9	SVHC requiring authorisation (ECHA, 2015d & 2017a)	Yes
Flame retardants	Tris(2,3-dibromopropyl) phosphate	126-72-7	Restriction	No
	DecaBDE	1163-19-5	Restriction	No

Substance group	Substance	CAS Number	Evaluation under REACH RA scheme	Use of HBM data
	Bis(pentabromophenyl) ether			

(*) Some chromium(VI) authorization applications used occupational biomonitoring data in exposure assessment and in some cases biomonitoring of workers were added as an additional condition for authorization

4.2.2 Food safety

In 2012, EFSA published a guideline for risk assessment of contaminants in food and feed (EFSA 2012). It aimed to provide an overview of the working principles used by the EFSA Panel on Contaminants in the Food Chain (CONTAM Panel) and gave an outlook for future perspectives of risk assessments of contaminants in food and feed.

The CONTAM Panel's task is to assess whether or not exposure to a chemical contaminant in food is likely to be associated with adverse health effects in the European population, or in farm animals, fish and pets in Europe, or to represent a risk to the consumer of foods of animal origin. In contrast to EFSA Panels dealing with regulated substances, the CONTAM Panel relies on scientific information that is in the public domain.

The risk assessment of chemical contaminants in food relies on the integration of two components: knowledge about the human exposure to these substances via food and other routes (i.e. occurrence data in food and food consumption data), and their potential to cause adverse health effects (i.e. the hazard). Whenever possible, the CONTAM Panel establishes an exposure level at which there is no appreciable health risk, called a health-based guidance value (HBGV) such as a tolerable daily intake (TDI). In the identification and characterisation of the hazard the Panel takes into account all toxicological information available, including studies on humans, experimental animals, cell- and other systems. In the absence of toxicity data from humans, the HBGV is usually based on data from repeated-dose studies on experimental animals, such as chronic toxicity or multigeneration studies in rats and mice. For the establishment of an HBGV, a reference point (RP) needs to be identified, based, if possible, on mathematical modelling of the dose-response relationship. The EFSA Scientific Committee recommended the use of a benchmark dose lower confidence limit (BMDL) as the RP (EFSA, 2009). The BMDL is an estimate of the lowest dose that is 95 % certain to cause no more than a specified change in response over background. If modelling is not considered appropriate, another RP may be used such as the NOAEL, which is the highest dose not causing a statistically significant adverse effect compared to the controls. The HBGV is established by dividing the RP by uncertainty factors to account for extrapolation from animals to humans and for variability in human sensitivity.

For some substances the CONTAM Panel assesses if the substance could give rise to acute health effects in relation to short periods of intake (e.g. certain metals, opium alkaloids, some mycotoxins or marine biotoxins) and establishes, if possible, an acute reference dose (ARfD) as the HBGV for such substances (EFSA, 2012).This is usually based on short-term toxicity data from experimental animals (e.g. acute toxicity or developmental toxicity), but also based on human data when available (e.g. pharmacological activity of opium alkaloids, outbreaks of food poisoning caused by some marine biotoxins).

For substances that cause genotoxicity by a mechanism involving reaction with DNA, it is not possible to identify a dose threshold of effect. Until 2005, the advice given by the risk assessor to the risk manager was to reduce exposure to such substances to a level that is as low as reasonably achievable (known as the ALARA principle). However, it was long recognised that such advice does not provide risk managers with a basis for setting priorities for action, either with

regard to the urgency or to the extent of measures that may be necessary. To overcome this, the EFSA Scientific Committee proposed the margin of exposure approach as a harmonised approach for the risk assessment of substances that are both genotoxic and carcinogenic.

Human biomonitoring in the assessment of food contaminants

In some cases, the CONTAM Panel has been able to model human data and to incorporate information from biomarkers of exposure or of effect in the characterisation of the hazard, e.g. cadmium and lead (EFSA, 2009; EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010). This allows the use of a body burden approach, where an estimate of systemic exposure (body burden), rather than external dose, is used in the risk characterisation. HBM data are, however, currently not used for refinement of exposure assessment on a regular basis. Usually food monitoring data are used for refinement, when applicable.

On the other hand, EFSA has recently published overviews on the use of HBM in the risk assessment of food contaminants. That is the case of two recent papers, namely: “Review of the state of the art of human biomonitoring for chemical substances and its application to human exposure assessment for food safety” (Choi et al., 2015) and “Identification of exposure to environmental chemicals in children and older adults using human biomonitoring data sorted by age: Results from a literature review” (Choi et al., 2017).

The first document is an EFSA External Scientific Report that is based on a literature search performed in several databases and conference proceedings for 2002 – 2014. It comprises the following information:

- Definitions of HBM and biomarkers, HBM techniques and requirements, and the possible application to the different steps of risk assessment.
- Evaluation of the usefulness of HBM for exposure assessment of chemical substances from food source, and for the implementation of a systematic Post Market Monitoring approach for regulated chemical substances.

An inventory of HBM programmes (38) with detailed information about study design, analytical methods, and reference values (RVs) and biomarkers used is also made. Substances covered include metals, PCBs; cotinine; mycotoxins; perchlorate; nitrosamine; alkaloids; dioxins; phthalates; PAHs; furans; fluorocarbons; organochlorines; phenols; Perfluorinated compounds (PFCs); Polybrominated Diphenyl Ethers (PBDEs); organophosphates; pyrethroids; chlorinated phenols; acrylamide; carbamates. Environmental monitoring and associations between HBM values and food, as well as coverage of substances and remaining deficits are highlighted. The review of study results provides also information on emerging chemicals, higher exposed and particularly vulnerable populations.

In addition, in the second paper above referred, EFSA has conducted a separate literature study on the identification of exposure to environmental chemicals in children and older adults using human biomonitoring data sorted by age (Choi et al 2017). This is a review aimed at demonstrating the use of HBM to identify environmental chemicals that might be of concern for two vulnerable populations: children or older adults. Children are considered vulnerable populations when it comes to exposure of environmental chemicals for a number of reasons such as the children’s continuing development and behavioural activities, smaller body storage for compounds due to their smaller body size and blood volume capacity as well as less mature metabolic pathways, which might lead to longer half-lives in the body. Older adults and the elderly are particularly vulnerable to chemical exposure for a number of other reasons, such as physiological and cellular damages that may have accumulated over time, and metabolic processes that might have slowed down or be pathologically altered due to disease. The effect of aging on the decreased function of organ systems responsible for elimination of xenobiotics might result in longer half-lives of

environmental chemicals in the body, consequently allowing more time for these chemicals to elicit their deleterious effects on a physiologically-weakened older population.

Human biomonitoring has been presented by Choi et al. (2017) as a unique approach of monitoring the internal exposure to chemicals in these vulnerable populations. Since the objective of this review was to provide an overview of environmental chemicals identified from existing national HBM surveys/programs to be of concern for children or older adults and to further elaborate on the findings regarding these identified chemicals, national HBM programs from an EFSA survey were selected based on the following criteria: i) Cross-sectional HBM of the general population that is representative of the country; ii) Sample size of ≥ ~1000 subjects; iii) Analysis of environmental chemicals in biological matrices.

A total of 10 national HBM programs under these criteria were identified (Choi et al., 2017): GerES; CZ-HBM; NHANES; FLEHS; KorSEP; ENNS; BIOAMBIENT.ES; Slovenia's HBM; CHMS and PROBE. DEMOCOPHES' results are described in the text, but are not included in the tables, since it does not meet the above criteria.

Choi et al. (2015) gives some guidance how HBM can be used for RA. It is stated that, although HBM alone is not able to provide information about health risk from chemical exposure, it can be used in combination with other tools to serve this purpose. In the author's view, for interpretation in risk assessment, HBM data should be combined with other data and tools such as environmental and health registry data, modelling data from physiologically-based pharmacokinetic (PBTK/PBPK) models, or HBM-based guidance values such as Human Biomonitoring Values (HBM-I and HBM-II, Schulz et al., 2011; Apel et al., 2017) and Biomonitoring Equivalents (BE, Hays and Aylward, 2009) that translate established health-based guidance values (e.g., ADIs/TDIs and reference doses) or a POD from an animal toxicity study (BMDL or NOAEL) into a biomarker concentration. To this point, EFSA states that HBM can be used to raise awareness (Choi et al., 2015).

The example of the concern that was raised by DEHP metabolite levels of the children exceeding the HBM-I value in the GerES IV study or of the Cd exposure in China is described in this document, showing that these data indicated increased risk of adverse health effects and that intervention measures to reduce the body burden are urgently needed. Furthermore, it is exemplified how HBM data, along with personal information collected from participants or environmental monitoring, can provide important clues to identify potential sources of exposure and can explain exposure trends, which might help to explain the different findings observed in different countries or regions, especially concerning food consumption patterns.

EFSA concludes that large-scale cross-sectional national HBM programs can provide useful data and information on chemical exposure of the general population. The study designs of these large-scale programs should be well-planned, tested with pilot studies, adjusted, and appraised over time such that findings from these programs can serve as a useful and reliable basis for further investigation, e.g., allowing comparative analyses of chemical concentrations and/or exposure trends among different countries (Choi et al., 2015).

An advantage of HBM (especially large-scale national HBM programs) would be the assessment of internal dose in humans upon chemical exposure, and with recruitment of participants of all ages, HBM data can be stratified by age to identify chemicals that show higher body burden in children or older adults. Therefore, Choi et al. (2015) consider HBM as a powerful tool for exposure assessment of chemicals in humans. In addition, guidelines for a proper HBM study design are enunciated. HBM should include:

- recruitment of participants of all ages
- collection of sufficient data from participants
- conducting data analysis that can be stratified by various factors

In this way, HBM outcomes might provide useful and reliable information for identifying vulnerable populations such as children and older adults and the environmental chemicals that might be of concern for them (Choi et al., 2017). Such identification can facilitate policy makers to focus their efforts to ensure that the chemical exposure in vulnerable populations can be reduced as much as possible, thereby reducing their body burden and potential risks of adverse health effects.

By conducting analysis using age-stratified data from national HBM programs and studies can bring added value of identifying chemicals of potential concerns in children and older adults in general. This review focuses primarily on age to identify these two particular vulnerable populations and the chemicals of concern for these populations, but other factors such as gender, socioeconomic status, education, and lifestyle habits (e.g., smoking and alcohol consumption) can also be considered when stratifying and analysing HBM data in order to identify other vulnerable populations regarding chemical exposure.

In addition, the paper has reference to HBM4EU: Harmonisation efforts performed in DEMOCOPHES will continue as 26 countries and the European Commission will collaborate and work together in the European Joint HBM Initiative called HBM4EU with potential options of studying age-related exposures of environmental chemicals.

Considering the ageing world population, HBM is described as useful for the authorities by monitoring chemicals that might be of concerns (e.g., metals and some persistent pollutants) for older adults as well as providing additional information on concentrations of other environmental contaminants including emerging chemicals. An example where HBM data could help policy is the Third EU Health Program (“Health for Growth”) from 2014 to 2020, which one of the objectives is “fostering good health in an ageing Europe” (European Commission, 2016). There is currently a paucity of programs that specifically aim to investigate body burden in older adults, but recruitment of participants in national HBM programs often include older adults. Evaluation of chemical exposure in older adults can then be conducted using age-stratified data from the national HBM programs.

HBM4EU priority substances evaluated by Food safety RA schemes

Over the nine years since its inception, the CONTAM Panel has assessed human and animal health risks related to the presence of persistent organic pollutants, natural toxins and plant toxicants, metals and metalloids, reaction products from thermal food processing, cross-contamination of feed for non-target animals with chemicals authorised for use such as feed additives, or non-authorised substances such as hormones, and complex mixtures such as mineral hydrocarbons in food and/or feed.

The CONTAM Panel conducts risk assessments on an enormous range of different types of chemicals, adapting its approach depending on the types of data that are available, and the specific question that has been asked. It is anticipated that future work will include instances where previously uninvestigated environmental contaminants have been detected in food or feed.

Concerning the papers described above (Choi et al., 20015, 2017), in the overviews on the use of HBM in the risk assessment of food contaminants, the following substances were mentioned: Metals; PCBs; cotinine; mycotoxins; perchlorate; nitrosamine; alkaloids; dioxins; phthalates; PAHs; furans; fluorocarbons; organochlorines; phenols; PFCs; PBDEs; organophosphates; pyrethroids; chlorinated phenols; acrylamide; carbamates. In addition, twelve classes of chemicals were identified to have higher body burden in either children or older adults. There is consistent evidence from multiple national HBM programs to show higher body burdens of BPA and some PAH metabolites in children and of heavy metals and persistent chemicals such as organochlorine pesticides in older adults. The 12 classes of environmental chemicals that were shown to have

higher body burden in children or older adults when compared to other age groups have been listed in (Table 5).

Table 5: Chemicals showing higher body burdens in children or elderly (Choi et al., 2017)

Chemicals showing higher body burden in children	Chemicals showing higher body burden in older adults or elderly
PCBs (PCB 28)	PBDEs (PBB 153)
PBDEs (BDE 28, BDE 47, BDE 99, BDE 100, BDE 153)	Metals (arsenic, cadmium, lead, mercury, palladium, selenium)
PFAS (PFOA)	PFAS (PFOS)
PAHs (1-hydroxypyrene, 3-hydroxyphenanthrene)	Organochlorine pesticides (DDE, p,p'-DDE, Hexachlorobenzene, β-Hexachlorocyclohexane, Mirex, cis-Nonachlor, trans-Nonachlor, Oxychlordane, Toxaphene parlar 50)
Parabens (Methyl paraben, propyl paraben)	
Perchlorate	
Bisphenol A	
Phytoestrogen (Daidzein, Genistein, O-Desmethylangolensin)	Parabens (Methyl paraben, Propyl paraben)
Volatile organic compounds (VOCs) (t,t-MA)	

4.2.3 EU plant protective products legislation

Plant protection products (PPPs) are pesticides used to keep crops healthy and prevent them from being destroyed by disease and infestation. They include herbicides, fungicides, insecticides, acaricides, plant growth regulators and repellents. PPPs contain at least one active substance (the active component against pests/plant diseases). Before an active substance can be used within a plant protection product in the EU, it must be approved by the European Commission. Member States evaluate and authorise the products at national level.

The process for deciding whether a new active substance can be approved for use in PPPs, in the EU, involves all Member States, the European Food Safety Authority (EFSA) and the European Commission. Members of the public and other interested parties can also provide comments for consideration in the process, specifically through the public consultation process of EFSA. Each active substance has to be proven safe in terms of human health, animal health and impact on the environment.

EU legislation

PPPs are mainly regulated by framework Regulation (EC) No 1107/2009. Data requirements are given in Commission Regulation (EU) No 283/2013 (for the active substance) and Commission Regulation (EU) No 284/2013 (for the PPP).

All matters related to legal limits for pesticide residues in food and feed are covered by Regulation (EC) No 396/2005. This regulation also contains provisions on official controls of pesticides residues in food of plant and animal origin that may arise from their use in plant protection.

Pesticide evaluations: overview and procedure

Active substances undergo an exhaustive evaluation process before a decision can be made on approval. To support an application for an active substance a complete 'dossier' must be submitted which must fully address the data requirements. The risk assessment of active substances evaluates whether, when used correctly, these substances are likely to have any direct or indirect harmful effects on human or animal health – for example, throughout the food chain and occupational exposure. In addition, the environmental risk assessment aims to evaluate fate and behaviour in the environment including the potential impact on non-target organisms.

Active substances

For the review of each active substance, applicants have to submit an application dossier, containing scientific information and studies, through a national contact point. A Member State is appointed as a “rapporteur” (RMS) to carry out an initial risk assessment and to prepare a Draft Assessment Report (DAR) which EFSA peer reviews.[5]

A similar process also operates for the renewal of active substances already approved for use in PPPs (Regulation (EU) No 844/2012).

The dossier should accomplished format requirements agreed by the OECD for regulatory dossier structure. The complete dossier is a very extensive set of documentation comprising not only the required tests and studies, but also a series of supporting documents providing background information on the active substance and its uses. A set of 'tiered' summaries detailing the applicant's evaluation and risk assessment for the active substance and product (the summary dossier) is required in addition to the complete copies of all the individual study reports.

To enable a risk assessment to be conducted, at least one PPP application must be supported by the dossier with comprehensive data required for approval of the active substance.

The dossier is evaluated by experts in the areas of: identity, physical chemical properties; analytical methods; mammalian toxicology; operator exposure; residues; efficacy; environmental fate and behaviour and ecotoxicology.

Mammalian toxicology of active substance is assessed on the basis of the standard toxicological data on acute and repeated/long-term toxicity as well as irritation, sensitising, mutagenic and reproductive effects. In addition, medical data (medical surveillance on manufacturing plant personnel and monitoring studies, diagnosis of poisoning) and other data collected on humans (direct observations, epidemiological studies) are taken into account.

Mammalian toxicology of PPP is assessed on the basis of following studies acute toxicity data on the product (oral toxicity, dermal toxicity, inhalation toxicity, skin irritation, eye irritation and skin

[5] http://www.efsa.europa.eu/sites/default/files/applications/apdeskapplworkflowpesticidesnasub.pdf
http://www.efsa.europa.eu/sites/default/files/applications/NewActSubstancesProcedure.pdf

sensitisation) supplementary studies on the PPP and supplementary studies for combinations of PPPs.

Operator exposure (occupational exposure) to PPP is assessed on the basis of modelled or measured operator exposure data and data on dermal absorption. Available toxicological data relating to co-formulants is also taken into account in the assessment.

The approval of plant protective products involves the comparison of estimated human exposure with RVs below which it is considered there are no expected adverse health effects. As we just described, pesticide producers must provide extensive animal (and environmental) toxicity test data to be used to assess the risk to occupational population (operator, worker) and general population (bystander, resident and consumer) under different use patterns. If a risk to operator, bystander, resident or worker is identified, risk management measures to reduce exposure should be assessed, e.g. use of personal protection equipment, mitigation measures and labelling.

Following detailed evaluation of the dossier, the RMS produces a report of their evaluation "the Draft Assessment Report (DAR)", which is *peer reviewed* by the other Member States and EFSA to reach consensus, based on which EFSA makes its conclusions.

The EFSA conclusion is a key document as it presents a comprehensive independent summary of the risk assessment process. It summarises the specific conclusions, RVs and endpoints; identifies particular conditions that may need to be considered in relation to the risk; and the critical areas of concern. The final conclusion is sent to the European Commission.

Human biomonitoring in pesticide evaluation

There's no a specific guideline that describes the use of HBM data. However, human biomonitoring as a tool for occupational exposure assessment related to the use of PPPs has been reviewed in a recent paper *(EFSA 2017: EN-1185. 207 pp*.).

The main objectives of the report were as follows:

1. To provide an overview on the use of HBM as a tool for occupational exposure assessment refinement, identifying advantages, disadvantages and needs for further development.
2. To provide a review of available HBM studies/surveillance programmes conducted in EU/US occupational settings to identify pesticides (or metabolites) both persistent and not persistent, for which biomarkers of exposure (and possibly effect) are available and validated.

A systematic review with defined inclusion and exclusion criteria according to EFSA methodology (EFSA 2010) of the literature databases Scopus, Web of Science and PubMed was performed for the period 1990 to 2015 (December). The search identified 2096 publications relating to the use of HBM to assess occupational exposure to pesticides (or metabolites). Additional information was collated from individual searches to identify grey literature and reports, international evaluations or monographs and conference proceedings of appropriate societies/organisations and any associated journals.

HBM is being used more frequently as part of an occupational health and safety strategy, as a tool for refined exposure assessment and in order to contribute to the evaluation of potential health risks from occupational exposure to pesticides. HBM essentially involves the quantification of either a substance, its metabolites, or a surrogate marker of its effects in a biological sample obtained from a person who may have been exposed. Thus, HBM is considered to be an estimate of exposure, rather than a measure of health, and should be employed alongside environmental monitoring as a tool to characterise exposure.

Under the previously described regulation for PPP, human data in the form of epidemiology studies, toxicokinetic and metabolism studies, or tests on skin irritation or skin sensitisation, are required to be submitted if available. However, RVs are established based on animal studies. The exception to this is where “appropriate scientifically valid and ethically generated human data are available and show that humans are more sensitive and lead to lower regulatory limit values”. This apparent contradictions within Regulation (EC) No 1107/2009 appear to deter manufacturers from producing, and therefore reporting, such data. There is also a requirement under 283/2013 that “Methods shall be submitted, with a full description, for the determination of non-isotope-labelled residues in all areas of the dossier, as set out in detail in the following points: in body fluids, air and any additional matrices used in support of operator, worker, resident and bystander exposure studies”, however it is not clear whether this requires data to be generated or just that methods are to be reported if data has been generated.

There are no established methods to estimate human exposure and therefore applicants may use measurements made during application or other steps in the process with the PPP, other analogous measurement data, or one of a number of data base or exposure models (e.g.UK-POEM, BBA model, EUROPOEM II, AOEM, SeedTropex, PHED, Southern Greenhouse model, ConsExpo, BREAM). A range of exposures are typically estimated, including for pesticide applicators, post application workers, and bystanders or neighbours and consumers. In reality, very few exposure measurements are submitted as part of the approvals process (and these are usually exclusively environmental data not HBM); the vast majority of the exposure assessments rely on modelled data.

The use of HBM-data for operator or bystander exposure assessment requires appropriate characterisation of background exposure.

An OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application (OECD /GD(97)148) has also looked to provide some harmonised guidance on exposure studies in this area. In this document, human biomonitoring is recommended as a potential “Tier 3” approach, for cases where generic exposure data plus information on dermal absorption and protective measures result in either insufficient data or unacceptable risk.

HBM has been extensively used for monitoring worker exposure to a variety of pesticides. A commonly reported problem when carrying out epidemiology studies is the difficulty in characterising exposure. Occupational exposure to pesticides may vary in relation to crop, climate, microclimate, task, application method, personal protection equipment, clothing, and personal hygiene. Epidemiological studies on occupational pesticide use (e.g. agricultural pesticide applicators, agricultural workers) are often limited by inadequate or retrospective exposure information, are typically obtained through self-reported questionnaires, which can potentially lead to erroneous exposure results. There are very limited data studying seasonal exposures.

Exposure assessment is a key part of all epidemiological studies and misclassification of exposure and use of simple categorical methods are known to weaken the ability of a study to determine whether an association between contact and ill-health outcome exists. At present, this limits integration of epidemiological findings into regulatory risk assessment.

The validity of regulatory exposure assessments (i.e. generated through use of models) has been investigated through comparison with exposures estimated from non-occupational biomarker studies (Cochran, 2002; Krieger et al., 2012; CDC, 2009). Findings suggested the models to be conservative, i.e. not realistic, in their estimates of exposure.

It is apparent that HBM has a role to play in the validation of exposure assessments models as well as in measuring actual exposures for the approvals process. As noted above, when checked, the

models have often been found to be over conservative – this may lead to inappropriate or overly proscribed control measures, which in themselves can increase exposure (e.g. sweating due to overly cumbersome personal protection equipment may increase skin absorption; reused gloves will increase contamination). If exposure assessment models are comprehensively validated against HBM studies then adjustments can be made to the parameter assumptions within the models, leading to more realistic evaluations of exposure. Such validation studies would also allow identification of the critical exposure parameters (e.g. application device or volatility of active etc.).

One important tool used for risk assessment of pesticide workers in the EU is the Acceptable Operator Exposure Level (AOEL). This is a health-based limit value against which non-dietary exposures to pesticides are currently assessed. It is intended to define a level of daily exposure (in milligrams/kilogram body weight/day) throughout a spraying season, year on year, below which no adverse systemic health effects would be expected. The AOEL is normally derived by applying an assessment factor (often 100, 10X Animal to Human Extrapolation and 10X Human Variability or Individual Sensitivity) to a NOAEL (corrected if appropriate for incomplete absorption) from a toxicological study in which animals were dosed daily for 90 days or longer. Less often, the critical NOAEL comes from a study with a shorter dosing period (e.g. a developmental study).

The concept of the AOEL as such has relevant legislative consequences, as exposure estimates exceeding the AOEL do not, for example, allow an inclusion of active substances in Annex I of Directive 91/414/EC. Draft guidance for the setting of AOELs was published by European Commission in 2005, and although there is a current formal harmonised approach for the derivation of AOEL in Europe, this is subject to ongoing review. The benchmark dose (BMD) approach, as an alternative to the traditionally used NOAEL, involves analysing dose-response data from experimental studies, and to look at the possible application of this approach to data from observational epidemiological studies.

There are very few health-based HBM values or biological equivalents (BEs) for occupational exposure to currently used pesticides which limits the use of human biomonitoring. A further consideration for HBM is the inability to differentiate exposure from sources other than the one(s) under investigation. Because HBM integrates exposure from all sources, in the occupational field, potential contribution from environmental or dietary sources should also be considered. Following application, pesticides may undergo breakdown in the environment due to both chemical and microbial action. This may result in the presence of hydrolysis products on and/or in food, which are available for dietary absorption. For example dialkylphosphates, which are frequently measured in urine to reflect exposure to organophosphates, have been reported at relatively high levels on a variety of fruit and vegetables, which have the potential to result in a significant overestimation of organophosphate exposure. Thus, it is not always comprehensible if biomarkers (often metabolites) found in urine are part of human or plant metabolism and whether consumers were exposed at all to the unchanged active substance. Consequently, these potential effects should be predictable and, therefore, suitable investigations should be carried out to assess any confounding effects on HBM results.

On the other hand, there is limited information on the exposure of residents living near agricultural land. Pesticide HBM studies could provide relevant information in this area of concern.

Post-approval occupational health surveillance for pesticides in the EU

There is currently no requirement in the EU 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 relationships between pesticide exposure and possible adverse health effects within agricultural cohorts, the data from which can be used to inform regulatory policies and practice. There are many examples of such studies in Europe and USA, and these

have been brought together in a consortium, AGRICOH, which was set up in 2010 by the US National Cancer Institute and is coordinated by the International Agency for Research on Cancer (IARC). The consortium was set up to encourage and support data pooling to study disease exposure associations that individual cohorts would not have sufficient statistical power to study.

Although there are many studies which can be called “post-approval assessment studies”, which look at occupational exposure to pesticides using HBM (as the active substance has been approved), in reality there are very few studies that compare actual exposure against assumed exposure during the approvals process.

Conclusions and future research needs and recommendations given by EFSA (2017)

In the regulatory framework for pesticide active substance approval, the vast majority of the exposure assessments rely on modelled data. In reality, very few exposure measurements are submitted as part of the approvals process (and these are usually exclusively environmental data not HBM).

It was proposed that the collection of human biomonitoring data for pesticide workers could be added as a routine component of existing occupational health surveillance programmes; for example, the European Human Biomonitoring Initiative could be a vehicle for gathering such data.

The authors used identified evidence to formulate recommendations on the implementation of HBM as part of the occupational health surveillance for pesticides in Europe, examples as follows:

- Priorities for the development of new biomarkers for all pesticides considering toxicological concern; conduction of cohort studies with focus on young farmers
- Derivation and adoption of health-based guidance values, as only few HBM values for occupational exposure of currently used pesticides are available
- Guarantee of the quality and comparability of occupational HBM data across the EU including developing and publishing of quality assurance schemes to validate inter-laboratory measurements and encourage confidence in data sharing.
- Design of Standard Operating Procedures (SOPs) for field work
- Design of questionnaires to support exposure assessment
- Implementation of strategies for establishing and co-ordinating biobanking
- HBM data and policy guidance and/or evaluation implying that HBM has a role to play in the validation of exposure assessment models allowing adjustments to be made to reflect more realistic evaluations and allow identification of critical exposure parameters. There is currently no requirement in the EU for post-approval monitoring of exposure to pesticides, through both occupational and environmental routes.

Although the use of volunteer studies is not permitted within the framework of Reg. (EC) No. 1107/2009 and Reg. (EU) No. 528/2009, information obtained from post-marketing epidemiological studies may be taken into account for the risk assessment for active substance re-approval. New guidance is to be expected from EFSA on the use of epidemiological data in pesticide risk assessment in the near future (currently under review).

HBM4EU priority substances evaluated under PPP legislation

Prioritised substances have not been evaluated under this scheme, but attention should be drawn to the risk assessment of mixtures of pesticides. The recently started H2020 EuroMix project will deliver a mixture test strategy and test instruments using novel techniques. In addition, the EFSA’s

scientific report (EFSA Journal 2013;11(7):3313) reviews the terminology, methodologies and frameworks developed by national and international agencies for the human risk assessment of combined exposure to multiple chemicals and provides recommendations for future activities at EFSA in this area.

4.2.4 Biocides

For the biocides risk assessment scheme, the following guidance has been published: "Guidance on the Biocidal Products Regulation - Volume III, Part B - Human Health Risk Assessment" (ECHA, 2013).

The risk assessment process for the biocides active substances follows the same principles of the EU risk assessment schemes which means, in case of human health, a sequence of actions starting with the (1) Assessment of effects (hazard identification: identification of the adverse effects which a substance has an inherent capacity to cause; and hazard characterisation: dose (concentration) - response (effects) assessment: estimation of the relationship between dose, or level of exposure to a substance, and the incidence and severity of an effect, where appropriate) (2) Exposure assessment: estimation of the concentrations/doses to which human populations (i.e. workers, consumers and man exposed indirectly via the environment) are or may be exposed.(3) Risk characterisation: estimation of the incidence and severity of the adverse effects likely to occur in a human population due to actual or predicted exposure to a substance, and may include "risk estimation", i.e. the quantification of that likelihood. Combined exposure to multiple chemicals and dietary risk assessment are also considered where relevant.

Human Biomonitoring in biocides evaluation

HBM is not part of active substance approval within the framework of Reg (EC) No. 1109/2006 and Reg (EU) No. 528/2012 under a regular basis however existing human data may be used in some cases to derive RVs for risk assessment. The Human Health risk assessment scheme for the biocidal active substances doesn't include a specific guidance on the use of HBM though several considerations to biological biomonitoring are made in the Guidance for Human Health Risk Assessment, Volume III, Part B.

It is to be noted that the Biocidal Human Health risk assessment is performed making use of a data package submitted by the applicants and evaluated by Member State Competent Authorities, in order to evaluate safe uses. These data can be generated by *in vitro* and/or *in vivo* experimental studies, justified waivers and read-across arguments, addressing an extensive list of toxicological endpoints.

Human biomonitoring data are not part of the core information requirements under the BPR but, when available, may be used to refine the assessment and support several decisions. It is accepted that the use of scientifically valid human 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. Biomonitoring studies, epidemiological data and medical poisoning records can be some of the sources of human data.

Human volunteer studies should not be performed for the purposes of the BPR however can be requested for products already authorised for use under the BPR. As a prerequisite for the consideration of the use of human volunteer studies that have been performed, clear statements that they were performed in accordance with internationally accepted ethical standards should be provided (Charnley et al, 2004), e.g. the Declaration of Helsinki (World Medical Association, 1997). In some cases, the use of human data in regulatory safety assessment might lead to more stringent exposure limits for some biocides than those that would have been derived on the basis of animal data only. It should be noted that modification of the dose descriptor is not appropriate in cases

where human exposure is evaluated based on human biomonitoring data. In such cases (availability of valid HBM data), the calculation of Acceptable Exposure Level (AEL)/ Acceptable Exposure Concentration values can be used straightforward if studies in animals or humans are available which relate the effect directly or indirectly to the biomonitoring metric.

There are specific endpoints in the biocides risk assessment where the inclusion of human biomonitoring studies are considered very useful, for instance, to refine the toxicokinetic assessment, namely, to provide dosimetric means for establishing aggregate and/or cumulative absorbed doses of chemicals following specific situations or exposure scenarios or for establishing baseline, population-based background levels (Woollen, 1993). Temporal situational human biomonitoring can provide a realistic description of human exposure. The routine analysis of human tissues or excreta for direct or indirect evidence of human exposures to substances, can provide unique insights into the relationship between dose and putative toxicity thresholds established in experimental animals, usually rats. On the other hand, HBM information is seen as equivalent (i.e. as having neither greater nor lesser importance) to other forms of exposure data and these results reflect an individual's total exposure (oral, dermal and inhalation) to a substance from any source, i.e. from consumer products, and/or from the environment and not just for a specific type of exposure (occupational exposure). Data from controlled human exposure studies are even more unlikely available due to the practical and ethical considerations involved in deliberate exposure of individuals. It is referred that the most appropriate way of assessing total systemic exposure is by human biomonitoring, however, the interpretation requires detailed pharmacokinetic information on the compound involved. In conclusion, HBM is considered as Tier 3 level of risk assessment.

In Carcinogenicity (chapter 7), Guidance for Human Health Risk Assessment, Volume III, Part B, it is referred that techniques for biomonitoring and molecular epidemiology promise to provide information on biomarkers of individual susceptibility, critical target organ exposures and whether effects occur at low exposure levels. Such ancillary information may assist in the interpretation of epidemiology study outcomes and the definition of dose response relationships. For example, monitoring the formation of chemical adducts in haemoglobin molecules (Albertini et al., 2006), the urinary excretion of damaged DNA bases (Chen, H.J. and Chiu, W.L. (2005), and the induction of genotoxicity biomarkers (micronuclei or chromosome aberrations; Boffetta et al., 2007) are presently being evaluated and/or validated for use in conjunction with classical epidemiological study designs. Such data are usually restricted in their application to specific chemical substances but such techniques may ultimately become more widely used, particularly when combined with animal data that defines potential mechanisms of action and associated biomarkers that may be indicative of carcinogenic risk. Monitoring of the molecular events that underly the carcinogenic process may also facilitate the refinement of dose response relationships and may ultimately serve as early indicators of potential cancer risk. However, as a generalisation, such biomonitoring tools have yet to demonstrate the sensitivity requisite for routine use.

In 'Human data on reproductive toxicity' (chapter 8.2.3), it is mentioned that epidemiological studies, conducted in the general population or in occupational cohorts, may provide information on possible associations between exposure to a chemical and adverse effects on reproduction. Clinical data and case reports (e.g. biomonitoring after accidental substance release) may also be available.

HBM4EU priority substances evaluated under biocides regulation

HBM data are only exceptionally used for the risk assessment of biocidal active substances. This was the case, for instance, of iodine where an upper intake level set from human studies was used to derive the AEL values for the different time frames and the ADI.

It is noticed that there are no biocidal active substances within the current HBM4EU priority substances groups. However, they can be included in studies with mixtures and can be part of emerging chemicals studies.

4.2.5 Occupational risk assessment

Legislation

According to the EU Occupational Safety and Health (OSH) legislation (directive 89/391/EEC) it is the responsibility of the employer to evaluate the risks to the safety and health of workers. This includes also risks arising from chemical substances or preparations used.

The Chemical Agents Directive 98/24/EC (CAD directive on the protection of the health and safety of workers from the risks related to chemical agents at work) lays down minimum requirements for the protection of workers from risks arising from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents.

The Directive provides the basis for the drawing up of indicative and binding occupational exposure limit values for workplace air (IOELVs and BOELVs, respectively) as well as biological limit values (BLVs) at European Community level. For any chemical for which an indicative occupational exposure limit value is established, Member States must establish a national occupational exposure limit value taking into account the Community limit value. For any chemical agent for which a binding occupational exposure is established at Community level, Member States must establish a national binding occupational exposure that is equivalent to or lower than the Community limit value.

In addition to BOELVs for air concentrations, according to Chemical Agents Directive (CAD) *binding* BLV may be drawn up on the basis of the scientific evaluation of the health effects and of the availability of measurement techniques. Similarly to BOELVs binding BLVs take into account feasibility factors (technical and economic feasibility). For any chemical agent for which a binding BLV is established, Member States shall establish a corresponding national binding BLV based on, but not exceeding, the Community limit value. Where a binding BLV has been set, health surveillance is a compulsory requirement for work with the hazardous chemical agent in question. Workers shall be informed on this requirement before being assigned to the task involving risk of exposure to the hazardous chemical agent indicated. There is no provision for indicative BLVs in the Chemical Agents Directive. The only binding BLV drawn up is the limit value for blood lead (B-Pb), which is 70 µg Pb/100 ml blood (Council directive 98/24/EC of 7 April 1998). This has not been updated since then although there is scientific evidence of adverse health effects at lower B-Pb levels and the EU Scientific Committee on Occupational Exposure Limits (SCOEL) already recommended a biological limit value of 30 µg Pb/100 ml blood in 2002 (SCOEL, 2002).

In addition to CAD, exposure to carcinogens and mutagens at work is regulated under Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (CMD directive). According to CMD the employer shall assess and manage the risk of exposure to carcinogens or mutagens. In addition, workers' exposure to carcinogens and mutagens must be prevented whenever possible. If replacement is not possible, the employer shall use a closed technological system. Where this is not technically possible, the employer shall reduce exposure to minimum. CMD Annex III lists the binding limit values for the carcinogens and mutagens. There are no BLVs given under CMD at this moment. However, it is stated under annex II of the CMD concerning health surveillance that health surveillance of the workers exposed to carcinogens and mutagens must include, where appropriate, biological surveillance, as well as detection of early and reversible effects. The Advisory Committee on Safety and Health at Work (ACSH) has recently released an opinion on a possible amendment of Directive 2004/37/EC on the

protection of workers from the risks related to exposure to carcinogens or mutagens at work to incorporate provisions regarding biomonitoring (EC, 2017). All interest groups of the ACSH support the use of biological monitoring in workers' health and safety protection provided biological indicators are scientifically valid and bring added value to worker protection and prevention of occupational ill-health. However, at present ACSH does not support the amendment of Annex II to directive 2004/37/EC (CMD) by including biomonitoring or biological limit or guidance values recommended by SCOEL. Instead, they recommend to develop EU level guidance on biological monitoring for both carcinogens and mutagens as well as other hazardous substances falling under CAD (98/24/EC). According to ACSH such guidance should indicate the significance of biological values and the manner in which these values could be used as part of an overall approach to chemical risk management at the workplace. It is also emphasised that it should be built on the experience in the Member States and guidance documents already developed at national level. Even though ACSH does not support the amendment of CMD to include the possibility to set binding limit values in Annex III of CMD, they have proposed to add a new point to Annex II of CMD which states that when biological surveillance is carried out, those undertaking such surveillance should take into consideration biological values recommended by SCOEL as well as other available guidance and information at national and EU level (European Commission, 2017).

SCOEL recommendations

SCOEL has prepared several recommendations on BLVs or biological guidance values (BGVs, see the definition below). SCOEL recommends BLVs or BGVs case-by-case basis whenever human biomonitoring is considered to be an appropriate way to assess the exposure and health risk due to the substance, and that there are analytical methods and enough data to set a value. SCOEL key (guidance) documentation includes a detailed description on the main principles used to give a recommendation for BLV or BGV (SCOEL, 2014a).

BLVs are derived on the basis of currently available scientific data, which indicate that concentrations or levels of activity equivalent to the BLV are unlikely to result in adverse effects on health. They can be derived in one of the following three ways (SCOEL, 2014a):

1. When studies in humans (occupational field studies or experimental laboratory studies on volunteers) are available, linking adverse effects with concentrations of the chemical or its metabolites in biological media, the NOAEL may directly be used to derive the BLV that is related to this level.
2. If such studies are not available but an OEL has been set and studies in humans provide a link between airborne concentrations of the compound and concentrations of the compound or its metabolites in biological media, a BLV may be recommended in a way that corresponds to the OEL. Supporting evidence may be drawn from toxicokinetic modelling. This implies that any re-evaluation of an existing OEL must be paralleled by a re-evaluation of the corresponding BLV. The two exposure limits (OEL, BLV) are generally based on equivalent effects of substances on the exposed worker.
3. In case of biological effect monitoring, the BLV is directly derived from suitable studies in humans. The documentation should then explicitly deal with the question of the adverse nature of this effect in view of standard setting.

Where toxicological data cannot support a health-based BLV (e.g. cases in which no health based OEL can be set), **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. If background levels cannot be detected, the BGV may be equivalent to the detection limit of the biomonitoring method, which then is to be specified in the document.

In 2014, SCOEL published a list of recommended health-based BLVs and BGVs (SCOEL, 2014b), which includes BLVs or BGVs for 22 substances, including e.g. cadmium, aniline, MOCA and MDA, which have been assigned to the group of the priority compounds within HBM4EU. This document has not been updated since then, but after 2014 SCOEL has published recommendations on o-toluidine, beryllium, hexachlorobenzene and PAH mixtures containing benzo[a]pyrene, which include either a BLV or BGV. For example, in the case of hexachlorobenzene, no OEL is proposed but only a BLV since the substance is very bioaccumulating, has a low vapour pressure and is well absorbed through the skin (SCOEL, 2016). In addition, health effects of hexachlorobenzene could be directly linked to blood levels. Therefore, biological monitoring was considered as the only reliable measure to assess occupational exposure and health risk. It should be noted that for non-threshold carcinogens (like o-toluidine), SCOEL does not propose any health based limit value, therefore, in these cases also for biomarkers only BGV can be recommended (SCOEL, 2016). Most of the biological limit or guidance values recommended by the SCOEL are based on the measurement of the parent compound or the metabolites in urine, some are based on blood levels (e.g. B-Pb) but there are also values based on e.g. adduct levels (acrylamide).

Table 6: Biological limit and Guidance Values recommended by SCOEL for HBM4EU priority substances

Substance	BGV	BLV	SCOEL SUM no
Aniline		0.2 mg aniline/l urine	153
Cadmium		2 µg Cd/g creatinine	136
DBP	70 µg mono-n-butyl phthalate/l urine		143
Bisphenol A	7 µg/l		113
4,4'-Methylene-bis-(2-chloro-aniline) (MOCA)	Detection limit of the method (end of shift)		174
4,4'-Methylenedianiline (MDA)	1 µg/l urine		107
o-toluidine (belongs to the group of aniline compounds)	0.2 µg/l		301
PAH mixtures containing benzo[a]pyrene	0.5 µg 1-hydroxypyrene in urine		404

As described earlier, none of the SCOEL recommendations on the biological guidance or limit values have been taken forward into the legislation. Since there are no EU level BLVs given, it is currently up to the Member States how they apply human biomonitoring in the exposure and health risk assessment of workers. Practices related to the human biomonitoring vary between different countries. These practices in different countries have been surveyed by the questionnaire which results are presented in chapter 4.4.4. In addition, DG Employment has recently published a study entitled: “Second study to collect updated information for a limited number of chemical agents with

a view to analyse the health, socio-economic and environmental impacts in connection with possible amendments of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (RPA, 2017)". Also this includes some information on the use of biomonitoring in the occupational exposure and risk assessment in the different member states.

4.2.6 Risk assessment of cosmetics in EU

In general, the safety evaluation of cosmetic ingredients by the Scientific Committee on Consumer Safety (SCCS) [6] is based upon the principles and practice of the risk assessment process usually applied for chemical substances in the EU (SCCS, 2016). This risk assessment procedure is subdivided in 4 parts:

1) Hazard identification is carried out to identify the intrinsic toxicological properties of the substance, i.e. whether it has the potential to damage human health. It is based on the results of in vivo tests (performed before 2013, due to animal testing ban afterwards), in vitro tests, clinical studies, case reports, epidemiological studies, data from post-marketing surveillance and in silico methods. Intrinsic physical and chemical properties of the substance under consideration are also taken into account.

2) Dose-response assessment: In this part, the relationship between the exposure and the toxic response is evaluated. In the case of an effect with a threshold, usually the highest dose at which no adverse effects are observed (NOAEL) is determined. A dose without any effect may also be observed (NOEL). If the NOAEL cannot be derived, the lowest dose at which an adverse effect is observed (LOAEL) may be used. The BMD may be used as an alternative for the NOAEL, NOEL or LOAEL value. In the case of non-threshold carcinogens, the BMD or the T25 (chronic dose rate that will give 25% of the animal's tumours at a specific tissue site after correction for spontaneous incidence) is used as a dose-descriptor. Dose-response assessment is not restricted to in vivo data: if sufficiently robust, relevant and justified, also in vitro data could be used on a case-by-case basis.

3) Exposure assessment: In this part, the amount of the substance and the frequency of human exposure to the substance are determined (including specific groups at potential risk, e.g., children, pregnant women, etc.). Exposure due to cosmetic products is estimated based on exposure scenario defined by the SCCS in its Note of Guidance (SCCS , 2016).To calculate the amount of cosmetic ingredient applied on the skin, the concentration of the ingredient in the products is multiplied by the amount of the cosmetic products used every day. To estimate systemic exposure, skin penetration is measured, usually *in vitro*, in conditions representative of the usual use of the products.

4) Risk characterisation: In the case of a threshold effect, the margin of safety is mostly calculated from oral toxicity studies and only in some cases from a dermal toxicity study. Where the NOAEL is a dose descriptor for an external dose, the $NOAEL_{sys}$ is a dose descriptor for the systemic exposure to a substance and is calculated from the NOAEL by use of the proportion of the substance systemically absorbed, which can be either based on oral bioavailability data (on Caco-2 cells model for example) or by assuming default values for oral bioavailability depending on the physico-chemical properties of the ingredient. For non-threshold effects (e.g. a non-threshold carcinogenic effect), the lifetime risk is often based on the T25 as above. Alternatively, the margin of exposure approach, for instance based on the BMD approach, can be used.

Human Biomonitoring in the Cosmetic Safety Evaluation

[6] Website: https://ec.europa.eu/health/scientific_committees/stub-for-f2a15b9438331568855209dc941b28691f940f4cc1aec4a7d18df58d_en

For cosmetic ingredients, the risk of systemic side effects is determined by the absorption of cosmetic ingredient across the skin as estimated by in vitro dermal/ percutaneous absorption studies, but also depending on the use of the product and the possibility of oral ingestion (toothpastes for example) or exposure by inhalation (spray products for example). If no experimental data are available, default values proposed in the SCCS note of Guidance are used to estimate the exposure. In case of uncharged small-size lipophilic substances, there may be a significant absorption, which may be a cause of concern for low-dose biologically active molecules. In that situation, studies measuring the unchanged compound or its metabolite in urine or blood of volunteers may be valuable. These studies may provide an accurate estimate of the systemic effective dose in humans under in-use conditions by integrating exposure from all routes. They may also provide insight into the biotransformation and elimination rate of the substance, i.e. toxicokinetic aspects that with the ban of animal studies will be increasingly difficult to document.

However, as HBM accounts for all sources (air, water, diet, consumer products etc.) and all routes of uptake, HBM data as such are not suitable for the assessment of exposure of a (cosmetic) substance when other (non-cosmetic) sources for uptake and exposure are involved. They should rather be used as support in risk assessment and risk management. Back-calculation from biomonitoring data to external exposure data is possible but requires additional information (e.g. type of biomarker, exposure modelling).

If adequately applied (i.e. toxicokinetics and metabolism of a substance is taken into account), HBM data can support and complement information on all aspects of ADME of a cosmetic substance, which are addressed in the safety evaluation dossier (e.g. results from in vitro and in vivo dermal absorption studies, results from toxicokinetic studies). HBM may also complement the results of further *in vitro* methods and animal studies, which are used for hazard and for risk assessment. 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 (no inter-species extrapolation, limited number of people involved). HBM data can be also combined with information from non-animal methods and PBTK modelling to generate more reliable information on toxicokinetics and to provide linkages between AOPs and human internal levels. If sufficient animal data is available, intraspecies variation can also be addressed using HBM.

When using HBM in the context of safety evaluation of consumer product ingredients, aspects which limit its field of application should be taken into account:

- HBM is applicable to substances that are systemically taken up and where the half-life of the exposure biomarker enables sampling and analytical determination.
- HBM is not appropriate when the relevant biomarker is an endogenously formed substance, present in much higher concentrations than those caused by uptake from the environment or consumer products.
- Various factors influence HBM results, including age, gender, lifestyle, consumer habits, diet, place of residence etc. as they modify the amounts of chemical substances taken up. Inter-individual differences in the metabolism of chemical substances, excretion of metabolites, health status as well as different compositions of biological materials like varying dilutions of urine etc., even under identical conditions of exposure, may provide different HBM results.
- Other error sources are contamination of samples during collection and handling of the biological samples if no specific metabolite is used as marker

HBM4EU priority substances recently evaluated under the scheme

Prioritised substances were not evaluated yet under the Cosmetic Safety Evaluation scheme.

HBM data were used in the evaluation of parabens for cosmetic use as supportive data. Results of biomonitoring studies were indeed indicating that the (average) systemic exposure dose was considerably lower than estimated in the previous paraben opinion for adults who use all types of cosmetic products with parabens at the authorised concentrations. Exposure estimates based on biological monitoring data were considered, therefore, by SCCS as useful additional information in their overall evaluation on the safety of parabens.

4.2.7 Risk assessment schemes for mixtures

The WHO/IPCS (2009) framework for the risk assessment of combined exposure to multiple chemicals is a widely accepted framework designed to aid risk assessors in identifying priorities for risk management for a wide range of applications where co-exposures to multiple chemicals are expected. It is based on a hierarchical (phased) approach that involves integrated and iterative consideration of exposure and hazard at all phases. Its use is often hampered by large data gaps on exposure as well as hazard information phases, with each tier being more refined (i.e., less cautious and more certain) than the previous one, but more labour and data intensive. It includes reference to predictive and probabilistic methodology in various tiers in addition to tiered consideration of uncertainty.

Application of the framework (see Figure 2) is not confined to any particular type of chemical or effect. However, it is intentionally concise, based on the recognition that more extensive guidance on specific technical aspects, including data quality, is available (ATSDR, 2004; US EPA, 2000; IGHRC, 2006. The framework is designed to be additionally developed through pragmatic application in specific case studies.

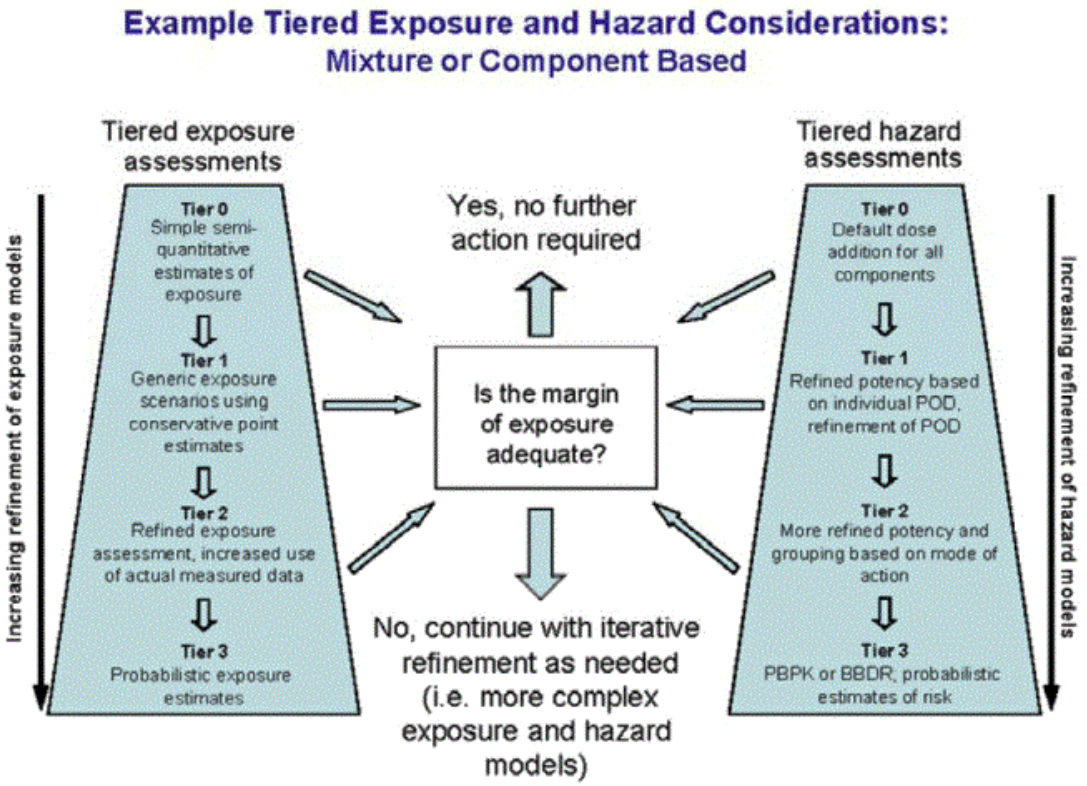

Figure 2: A conceptual representation of the WHO/IPCS framework (from Meek et al., 2011)

The terminology used in the context of the WHO, IPCS, ILSI/HESI initiatives (Meek et al., 2011; IPCS, 2009b) is an important aspect of the framework application. Exposure to multiple chemicals is defined as a “combined exposure”, should it be by a single route or by multiple routes (which has sometimes been referenced as “cumulative” exposure, e.g. by US EPA, 2003). Exposure to a single chemical from multiple sources and by multiple pathways and routes is defined as an “aggregate exposure”. Substances grouped together for evaluation of combined exposure are referenced as an ‘‘assessment group.”

Additionally, the “mode of action (MOA)” is an important concept to take into account. A postulated MOA is a biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data. It describes key cytological and biochemical events—i.e., those that are both measurable and necessary to the observed effect (Sonich-Mullin et al., 2001). Combined exposure to multiple chemicals can be defined in the context of whether or not the components act by similar or different MOAs in induction of critical effects (i.e., ‘‘single MOA or ‘‘multiple MOA). It does not imply full understanding of mechanism of action at the molecular level. Chemicals that act by the same MOA and/or at the same target cell, tissue or organ often act in a potency-corrected ‘‘dose additive’’ manner. Alternatively, chemicals may act independently, by discrete MOAs or at different target cells, tissues or organs (independent joint action).

Methods are based on different approaches on the assumptions of dose additivity (where components are considered to be toxicologically similar), response additivity (where components are considered to act independently) and interaction (where effects of combined exposure to components are expected to be greater than or less than those based on the assumption of dose additivity). For dose additivity, approaches are normally based on summed indices of comparison of estimated exposure with hazard for components (e.g., the hazard index). Alternatively, they are based on summed estimated exposure to components adjusted by potency, relative to an index compound (i.e., relative potency factors).

Human biomonitoring in WHO framework guidance

The relevance of the HBM in this framework, as in other risk assessment frameworks, is related to the problem formulation, Tier 1, Exposure Assessment, where the following questions are raised:

1. What is the nature of exposure?
2. Is exposure likely, taking into account the context?
3. Is there a likelihood of co-exposure within a relevant timeframe?
4. What is the rationale for considering compounds in an assessment group?

In relation to question 3) additional information can be triggered which may relate to the use of HBM in the context of the evaluation:

- Do temporal aspects of external exposure, toxicokinetics and toxicodynamics preclude co-exposure to the compounds of interest?
- Specifically, do the compounds in the “assessment group” have short half-lives (kinetics) or effects of short duration (dynamics)?
- Also, is the time between initial and subsequent exposures for such compounds sufficient so as to preclude co-exposures?

Exposure assessment (including aggregate exposure assessments) can be conducted at various scales, in which only the total exposure is of interest. This is done when using general intake fractions (e.g. the intake assessments for food additives) or actual human biomonitoring. In these cases, it is not important to know which routes or which products lead to exposure, but only whether the exposure is at a certain overall level (order of magnitude). As known, human

biomonitoring data may indicate co-occurrence of substances in the human body or elimination products. Such data indicate the potential relevance of their consideration in a framework analysis for an assessment group.

As future needs, in the report of a WHO/IPCS international workshop on aggregate/cumulative risk assessment (IPCS, 2009b), it is identified that the support of human biomonitoring systems, exposure databases and disease registries is also critical in order to provide better data, to guide prioritisation of assessments and to evaluate the benefits of cumulative assessments.

It is also noticed, that the draft framework prepared after the workshop reflects the further development of the concepts and includes an “approach to tiered consideration of hazard for exposure to multiple chemicals”. It includes subsequent considerations on ADME, common metabolite biomonitoring, mechanisms, common molecular target and MOA as depicted in Figure 3. Common metabolite biomonitoring (HBM) is increasingly important when going from modified tier 1 to tier 3.

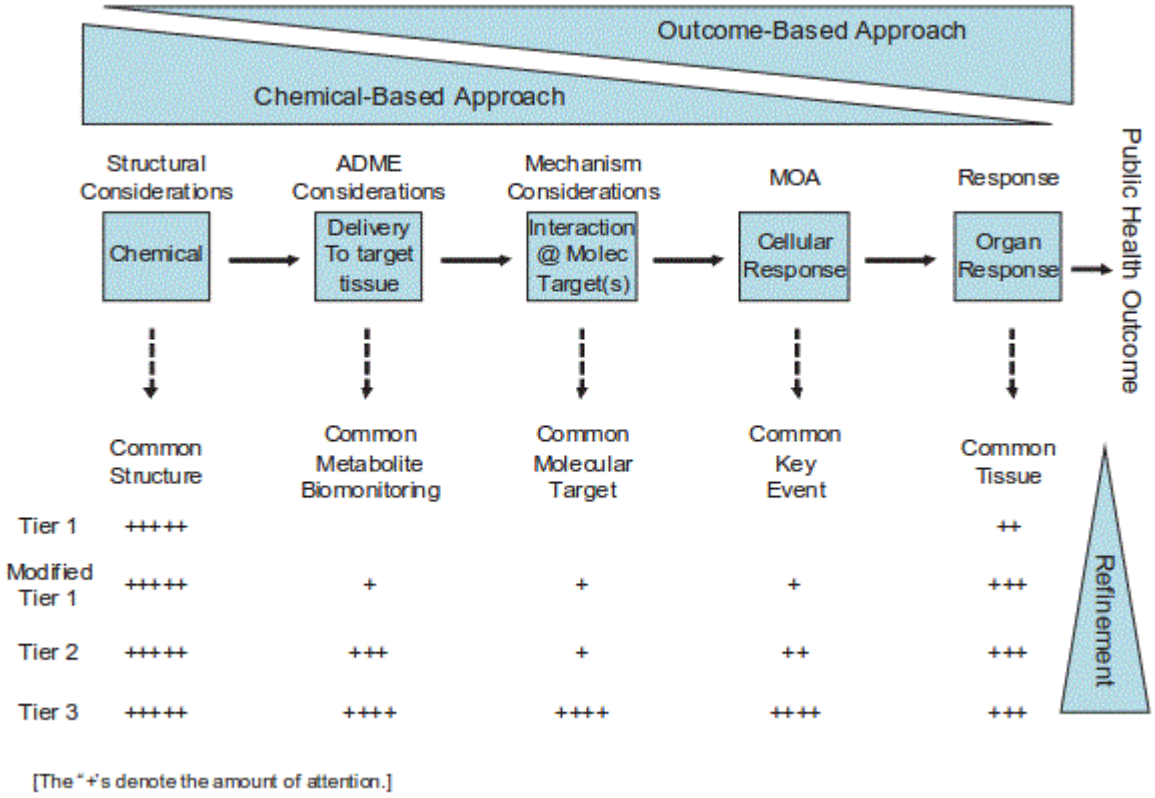

Figure 3: A proposed approach to tiered consideration of hazard for exposure to multiple chemicals (from WHO/IPCS 2009b)

As a concluding remark, there are several EU 2020 Initiatives focusing on the risk assessment of chemical mixtures, mostly directed to consumers and general public i.e. EDC-MixRisk, http://edcmixrisk.ki.se/, an EU project designed to improve a safer environment for children and concerned about their quality of life being threatened by environmental chemicals or their mixtures. In this context, risk assessment strategies with inclusion of HBM data and reference values are considered more and more relevant to allow estimation of the real body burden of chemical mixtures.

4.3 Health impact assessment schemes

4.3.1 Introduction to Health Impact Assessment (HIA)

WHO defines an HIA as *"a combination of procedures, methods and tools by which a policy, programme or project may be judged as to its potential effects on the health of a population, and the distribution of those effects within the population"* (WHO, 1999). Other definitions also exist. For example, the Center for Disease Control (CDC) in the US for example sees an HIA as a systematic process that uses an array of data sources and analytic methods, and considers input from stakeholders to determine the potential effects of a proposed policy, plan, program, or project on the health of a population, but also whether the health effects are distributed evenly within the population. An HIA may be part of an environmental impact assessment in case the health topic is dealt with in the assessment. In terms of policy, an HIA is a tool to promote health within all policies. It helps decision-makers to make choices about alternatives and improvements to prevent disease/injury and to actively promote health. Within this context it is important to consider the definition of "health" used in the HIA. Most often, HIAs are used in the public health domain (e.g. described by the WHO) and health is defined in holistic terms, including social and mental well-being and not only the absence of disease or infirmity. The socio-environmental model of health by Dahlgren and Whitehead (1991) is usually used. In this concept, where health is defined by both biophysical and social factors. The aims of HIAs based on the model of Dahlgren and Whitehead are:

- To reduce or eliminate negative health impacts and maximise the positive health impacts of policies, programmes or projects.
- To reduce health inequalities.

While there is no single agreed method for an HIA, a general pattern has emerged amongst methods (Sweden: FHI, 2005; United Kingdom: Herriott and Williams, 2010; Ireland: Metcalfe et al., 2009) and there is much overlap between the various methods. Figure 4 gives an overview of the different steps which should be followed in an HIA by WHO. Sectors in which HIAs are applied according to WHO are for example transport (effect of air pollution, noise, accidents, active mobility), food (use of pesticides), waste management (exposure to chemicals) and energy production (air pollution).

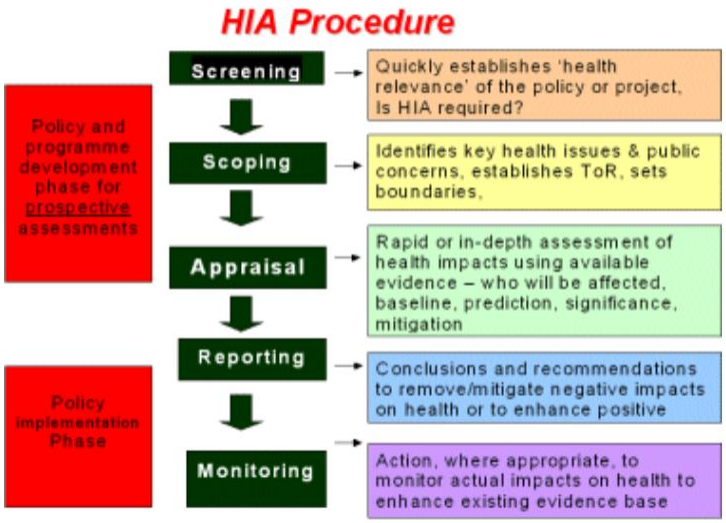

Figure 4: HIA procedure according to WHO (http://www.who.int/hia/tools/en/)

Different steps in HIA explained in brief:

1) **Screening**: Description of policy, plan, program or project; Questioning whether it affects health; Questioning whether the whole population is affected or vulnerable groups; Decide if HIA is necessary and possible; Rapid or comprehensive HIA; etc.
2) **Scoping**: Identify what to do and how to do it and who will do it; Setting aims and objectives; Which evidence should be collected; Search for evidence (interviews, in depth reviews, off the shelf evidence, surveys, etc.); Setting boundaries; Involvement of specialists; Setting up focus groups; Potential health impacts which should be investigated; etc.
3) **Appraisal**: Large amount of HIA work is carried out in this step: assessment of health impact using available evidence; Baseline, predictions, mitigation, significance, uncertainty; etc.
4) **Reporting**: Developing recommendations to reduce hazards and/or improve of health. A key output of HIA is the set of recommended changes to the proposal.
5) **Monitoring**: Monitoring the implementation of the proposal to ensure that any recommendations that decision-makers agreed upon, actually occur; As with any intervention, evaluation is required to see if it has worked is required

4.3.2 HIAs in toxicological risk assessment and environmental epidemiology

Within the toxicological and epidemiological framework, an HIA is more focussed on the description of absolute changes in (sub) clinical effects due to a policy measure and focusses less on health inequalities, stakeholder appraisal, perception, distribution effects and the maximisation of positive health impacts due to policy. The steps taken when performing HIA within a more toxicological and epidemiological context do not differ significantly from the WHO HIA procedure (for additional information see Figure A1 in Annex A).

When estimating the impact of air pollution on health, HIA is generally used. Well-known projects are APHEIS and APHEKOM[7], in which the impact of air pollution on health in 25 European cities was assessed (Medina et al., 2009). Also at the EU level HIA is used to calculate different air pollution scenarios and to set goals for air pollution reduction: EU Clean Air Package (IIASA et al., 2014; Holland, 2014). For energy production at the EU level, HIA is also often used to calculate the impact of different energy systems on health (Bickel and Friedrich, 2005; CASES project[8]). Dose-response or exposure-effect curves are mainly based on external exposure to air pollution (particulate matter).

Results from a human health risk assessment (Hazard identification -> dose-response assessment -> exposure assessment -> risk characterisation) can be used within an HIA to predict human health effects of specific exposures. However, several uncertainties arise with the extrapolation of human health risks to human health effects (being at risk does not equal having a health effect).

Two indicators used by the OECD and the EU for presenting health impact among the general population are DALYs (Disability Adjusted Life Years) and external costs, however in an HIA it is not obligatory to make such extended calculations. Other indicators or calculations are valid as well. In the framework of European Environmental Burden of Disease (EBD) studies, the health impact (DALYs) of 9 stressors was calculated in a consistent way (as far as possible) in 6 EU countries (Belgium, Finland, France, Germany, Italy, the Netherlands) (Hänninen et al., 2011). Considered stressors were: particulate matter, second hand smoke, radon, traffic noise, lead,

[7] http://aphekom.org/
[8] Cost Assessment for Sustainable Energy Systems: http://www.feem-project.net/cases/downloads_deliverables.php

ozone, dioxins, benzene and formaldehyde. When calculating the impact of dioxins different exposure data were used, depending on available data. Different ways to estimate daily intake of dioxins and dioxin-like PCBs were surveys on food consumption, total diet studies, human biomonitoring (investigation of human milk and blood levels). For lead, the health impact in terms of DALYs due to IQ loss in children and blood pressure elevation in adults was calculated based on Pb body burden results: blood lead levels (Hänninen et al., 2011). Similarly, Remy et al. (in preparation), estimated the reduction in external costs related with decreasing human lead levels over time in Flanders, Belgium.

4.3.3 Role of human biomonitoring in HIA

Within an integrated environmental HIA framework (see Figure A2 in Annex A), HBM serves as a pivotal point between environment and health, on the one hand leaning on environmental data to provide information on sources and pathways of exposure, and on the other hand clarifying hypotheses on the relationship between internal dose and prevalence of disease clusters (INTARESE: Integrated Assessment of Health Risk of Environmental Stressors in Europe: Briggs, 2008; Smolders et al., 2009; Liu et al., 2012).

Human biomonitoring is not commonly used in HIA. Often HIA include the application of dose-response or exposure-effect curves in which exposure is external exposure to pollutants or exposure based on environmental sources. The use of internal exposure through HBM could lead to a refinement of exposure information as accurate information on integrated personal exposure is provided. HBM data have proved to be a valuable addition to, or have even surpassed, estimates of exposure based on environmental measures (Suk et al., 1996; Bates et al., 2005). In the following paragraphs some examples are given on the uses of HBM data in HIA.

The WHO estimated the health impact of mercury through neurodevelopmental toxicity. The disease burden was addressed using the distribution of hair mercury concentrations of pregnant women or women of childbearing age as a measure of infant exposure. The rate of mild mental retardation caused by methylmercury-related IQ loss and the resulting number of DALYs lost were calculated from the exposure distribution (Poulin and Gibb, 2008). Similarly, the health impact of chronic mercury intoxication in artisanal small-scale gold mining in Zimbabwe was estimated based on mercury hair and urine concentrations (Steckling et al., 2014).

A recent WHO study investigated the burden of disease of foodborne chemical toxins, including dioxin and dioxin-like compounds. The results of the breast milk concentrations (exposure assessment) and BMD analyses (toxicity assessment) from 50 countries were compared, taking account of possible differences between experimental animals and humans, as well as intra-individual differences among humans. This comparison provided country-specific estimates of the incidence of dioxin induced prenatal and postnatal hypothyroidism and impaired fertility. It was calculated that dioxin exposure alone globally leads to 3 (3–20) DALYs in 100.000 people (Gibb et al., 2015).

In the US, Lanphear et al. (2005) performed a large scale study on the association between intelligence test scores and blood lead concentrations, especially for children who had blood lead levels under 10 µg/dL. To this end, they examined data collected from 1,333 children who participated in seven international population-based longitudinal cohort studies. The lead levels were determined in venous or fingerstick capillary blood samples and cord blood lead in a subsample of the subjects. The primary outcome was the full-scale IQ, which is a composite score of verbal and performance tests. The lead-associated IQ deficits observed in this pooled analysis were significantly greater at lower blood lead concentrations. The larger sample size of the pooled analysis permitted the authors to show that for a given increase in blood lead, the lead-associated intellectual decrement was significantly greater for children with a maximal blood lead

concentration of < 7.5 µg/dL than for those who had a maximal blood lead concentration of ≥7.5 µg/dL.

In the studies of Trasande et al., external costs (non- internalised costs or costs for society) were calculated for the exposure to endocrine disruptors (EDCs) in Europe based on HBM data (Trasande et al., 2015; Legler et al. 2015). According to their calculations EDC exposures in the EU contribute substantially to obesity and diabetes, with a moderate probability of €18 billion costs per year (this was considered as a conservative estimate by the authors). However, since the evidence on the association between EDCs and these diseases in humans is still debatable, these EBD risks and cost calculations include severe uncertainties even though population biomonitoring data based exposure estimates can be considered reliable.

Recently Tobolik et al. (2016) presented the start of the UKAGEP project in Germany. This project aims at estimating the EBD of 16 risk factors for children aged between 3 and 17 years in Germany. Current HBM data derived in the population-representative German Environmental Survey (GerES V, 2014-2017) are used to estimate the internal exposure of German children for eight hazards (e. g. lead in blood, arsenic in urine, EDCs in urine). Combined with exposure-response functions, which are derived or updated by meta-analysis, and data on the related health effects, DALYs will be calculated.

Another useful approach of HBM data for impact assessment is the comparison of HBM effect biomarker data (birth weight, eosinophil count, etc.) with health based RVs (from occupational exposure, medical data, reference groups). They allow to visualise whether there is any concern with regard to health-based criteria, how time trends look relative to these reference values and if population groups differ in their proportion above or below the values (FLEHS I, 2006; Engel et al., 2014).

4.4 Survey: National risk and HIA practices and the views of risk assessors on the use HBM in risk assessment

4.4.1 Aims of the survey

The ultimate goal of this task is to improve human risk assessment by more efficient application of HBM. In order to achieve this goal, the current risk assessment practices in different countries (EU- and non-EU countries) and the current use of human biomonitoring in the risk assessment of chemicals were evaluated using a questionnaire to national risk assessors. The aim was to find out how familiar risk assessors working in different field of chemical risk assessment are with HBM, how they find the use of HBM in risk assessment, what are the main reasons and obstacles for using HBM in health risk assessment and HIA.

The questionnaire was conducted in summer 2017 using a web-based tool Webropol (www.webropol.com). It was divided in two parts; first part was targeted for risk assessment in general (under e.g. chemical, pesticides and food safety legislations) and the second part was targeted specifically to the use of biomonitoring in occupational health. This division was made since biomonitoring has long traditions in occupational health and safety as a tool for workplaces and occupational health care to assess the exposure and risks, and the role of national OSH authorities is only to provide guidance for its use at workplaces. It was also clear that national practises related to its use in OSH are likely to vary since the current EU legislation gives very little guidance for its use. The first part included questions both on risk and HIA, the second part addressed only the use of HBM in the risk assessment at workplaces.

4.4.2 Respondents

There were 71 respondents from 18 EU countries, 2 non-EU countries in Europe that participate in HBM4EU and 5 non-European countries (Figure 5 and Figure 6). 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. This means that extrapolation and generalisation of the results of this survey needs to made by caution; especially for those questions that had a limited number of respondents.

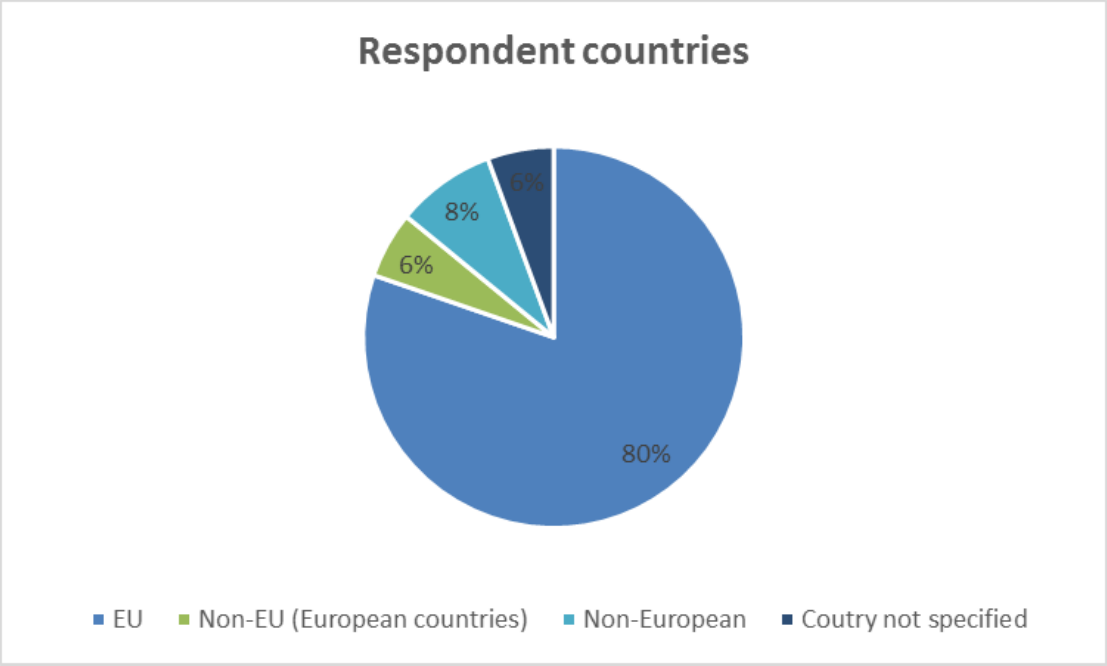

Figure 5: Responses from European and non-European countries (N=71)

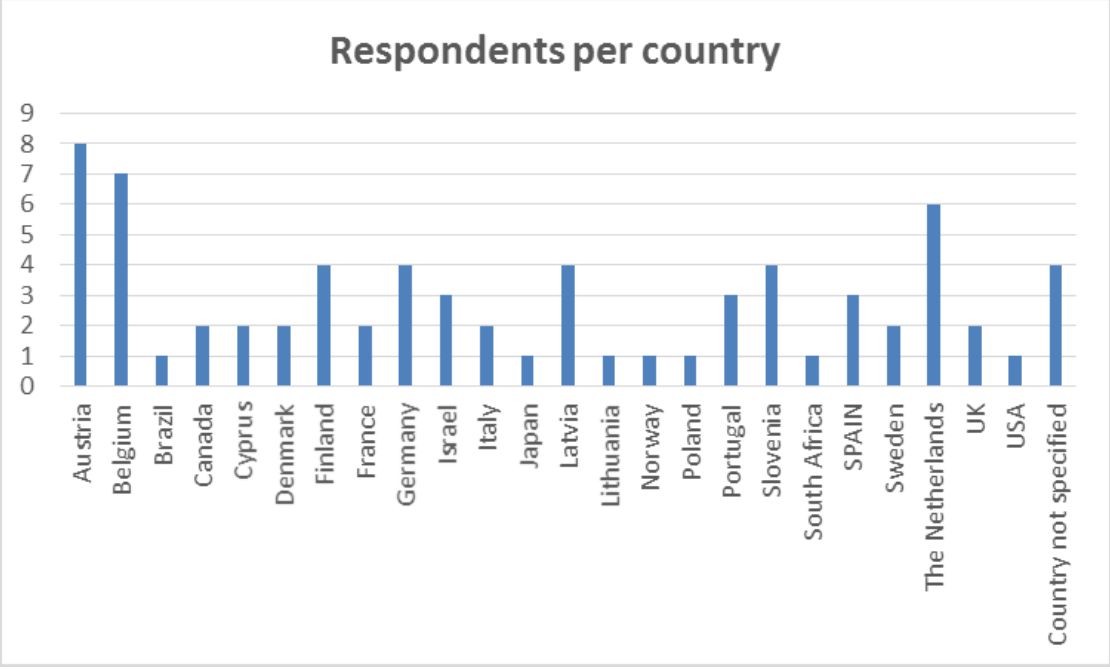

Figure 6: Country distribution of responses (N=71)

The most abundant regulatory areas the respondents are active in were REACH, OSH and the food safety domain (each >30%) (Figure 7). 23% of the respondents were working only in the OSH domain, and responded only to the second part of the survey.

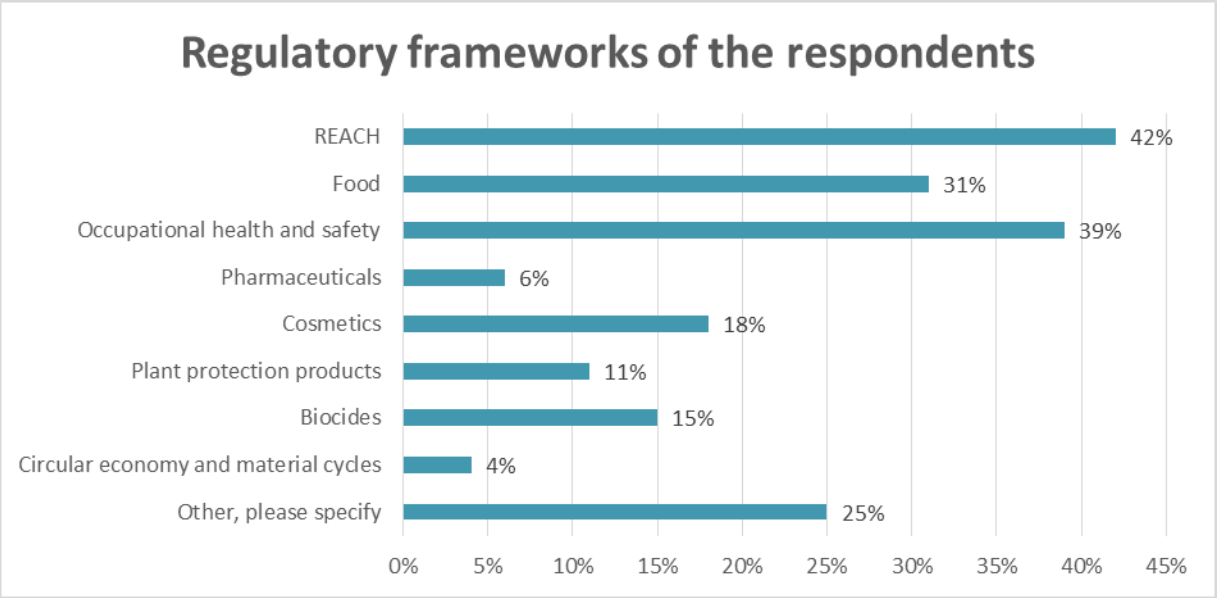

Figure 7: Regulatory areas of the respondents (N=71)

4.4.3 Results: Use of HBM in risk and health impact assessment

The first part of the questionnaire was related to the use of HBM in risk and HIA in general, including different risk assessment frameworks, like REACH, food safety, cosmetics, pesticides etc. Out of 55 respondents, only 27% replied that HBM is regularly applied in their regulatory domain in their country (Figure 8). Thus, in most cases it is either not used or used only to limited extent. Those who answered that it is used only in limited extent mentioned incidental 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. Pb, for which HBM is obligatory by law under OSH framework.

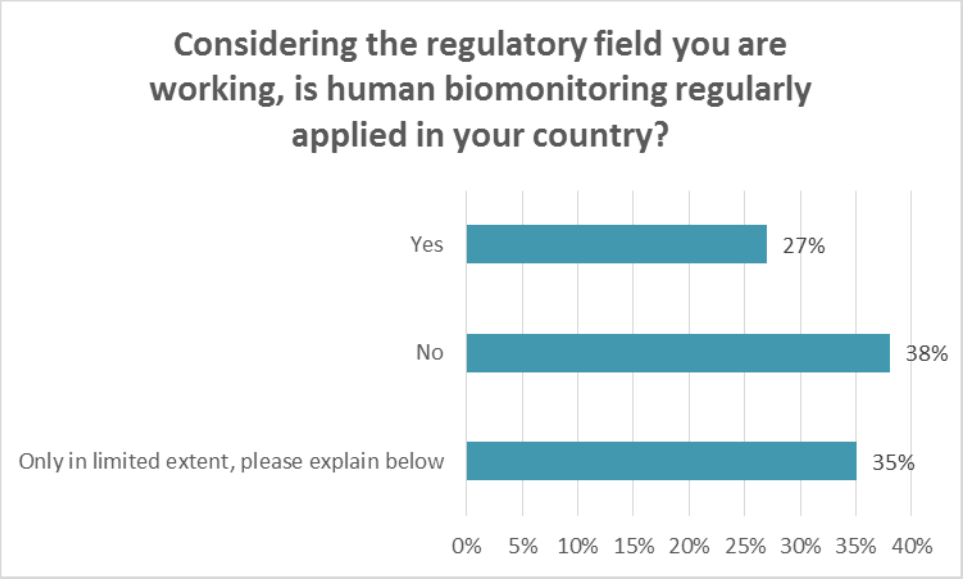

Figure 8: Use of human biomonitoring on general population (N=55)

With respect to guidance for the use of HBM for risk assessment in their country, out of 55 respondents, >60% responded that no guidance is available (Figure 9). In case there is guidance available, it is usually specific for a single regulatory domain: REACH, Cosmetic Product Regulation, OSH, small scale incidents handled by local environmental health services or e.g. for Pb in workers. In open comments it was mentioned that even if e.g. REACH guidance refers to biomonitoring, more guidance on its use in risk assessment is needed. Also for the technical and organisational application of HBM it became clear that guidance is largely missing (Figure 10).

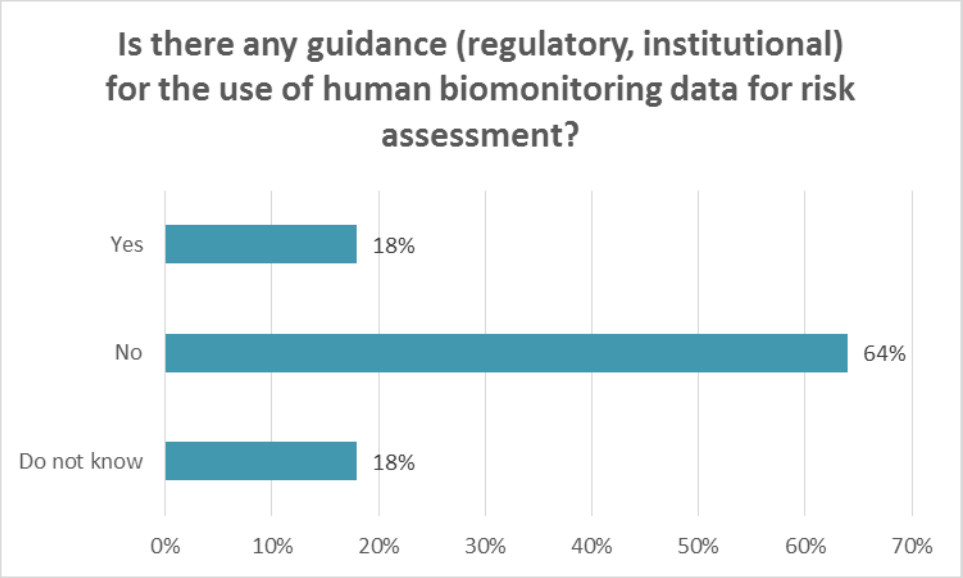

Figure 9: Existence of guidance for the use of human biomonitoring data for risk assessment on general population (N=55)

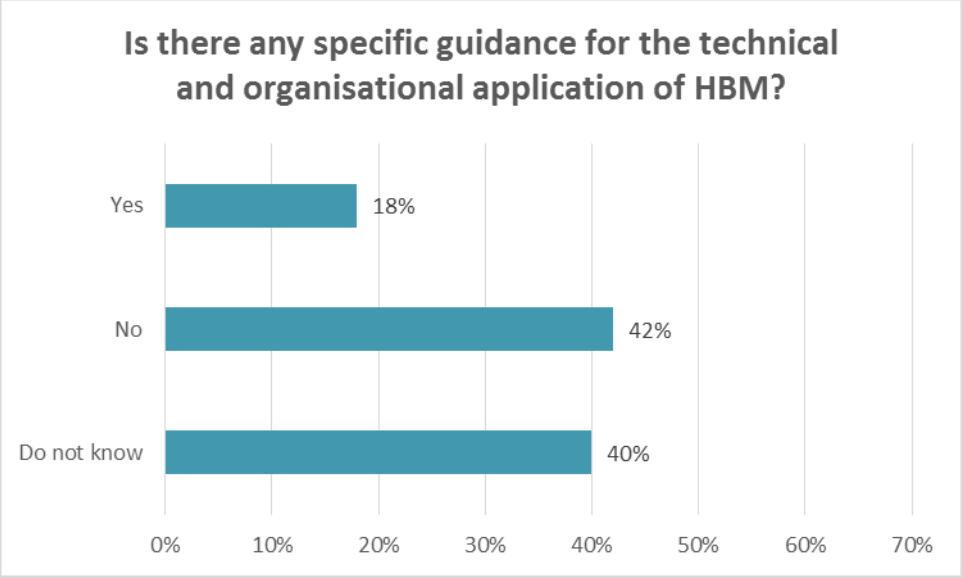

Figure 10: Existence of specific guidance for the technical and organisational application of HBM on general population (N=55)

Main drivers to start HBM are (50 respondents) to confirm exposure (54%), assess internal exposure level (52%), and to support risk assessment and define priorities for intervention (50%) (Figure 11). Although health surveillance is the one of the main drivers in occupational biomonitoring (see next chapter), in other risk assessment fields exposure assessment and priority setting are more emphasised. 8 respondents out of 50 (16%) responded that HBM is not usually performed for this question, whereas for a very comparable question (Figure 8) 21 out of 55 respondents (38%) responded that HBM is not usually performed. This difference is most likely explained by the way how questions were phrased; even though HBM is not usually performed in the respondents' country, he/she may have selected drivers on the basis of some infrequent cases in which biomonitoring has been used.

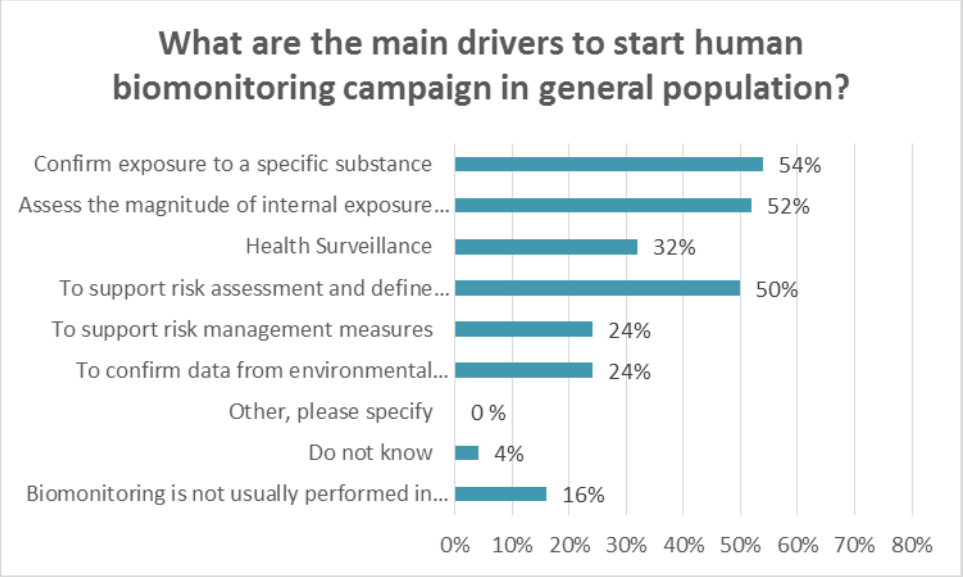

Figure 11: Main drivers to start human biomonitoring campaign in general population (N=50)

When questioned how HBM might contribute best now and in the near future to risk assessment and management, the following answers were given: realistic exposure data, aggregating routes of exposure, risk management prioritisation (policy, intervention), comparing subpopulations and identifying vulnerable populations. According to the respondents, DNA and protein adducts are not widely used as exposure biomarker (20%) and effect biomarkers are only marginally used (10%).

From the answers it appeared that in addition to existence of validated methods for biomonitoring, existence of health-based limit or guidance values and the ability to relate biomarker levels to external exposure were judged of most important criteria to be met before HBM can be used in the risk assessment. However, no large difference to other possible criteria, i.e. ability to estimate biological equivalent (BE, Hayes and Aylward, 2009), existence of HBM RVs, a sufficient population size, and relation biomarker of exposure to health effect were observed (Figure 12). Additional linked points mentioned in the comments were appropriate knowledge about ADME and 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 given that the criteria set upfront are often not met.

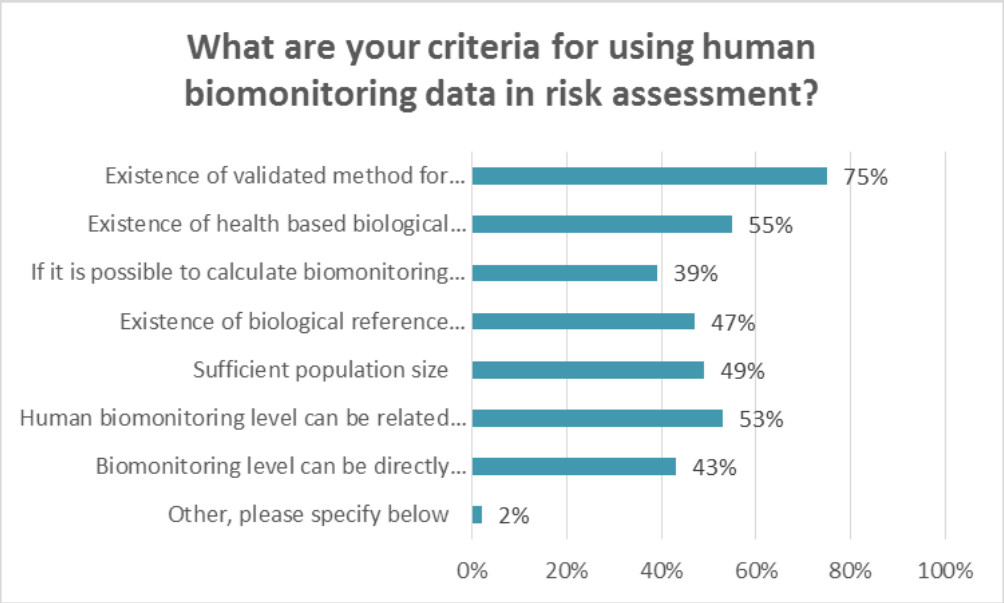

Figure 12: Criteria for using human biomonitoring data in risk assessment on general population (N=51)

According to the responses received, generally in risk assessment frameworks, HBM data is not compared to any health based limit or guidance values nor to HBM RVs (population distribution based guidance values). This most probably reflects the fact that there are only few limit values for general population, with the exception of German HBM I and II values or biological equivalents published for some substances in literature. This differs from the OSH framework where there are BLVs/BGVs or RVs available for commonly biomonitored substances. In the open responses German HBM I and II values were mentioned. Next to this, some internal (laboratory, institutional, like BEs by Summit Toxicology) recommendations approaching the status of guidance values were indicated. Furthermore, EFSA has published some epidemiologically-based guidance values, such as for B-Pb. Also with respect to Cd, there is a biomonitoring guidance value regarded as safe by EFSA and expressed as urinary Cd level. For contaminants in food, HBM levels are compared with levels used as basis for setting TDIs at EFSA.

When no national BLV or BGV were available mostly values from other countries are used. But as noted earlier, in many countries HBM for the general population is rarely used.

Only a small part of 53 respondents mentions ongoing work to elaborate health-based limit values for biomarkers. Majority of the respondents does not know if there are these kind of activities going on in their country. Also on those experts working in the field of OSH, less than half recognises these activities in their country.

The three most important obstacles (Figure 13) for applying HBM data in risk assessment mentioned:

- No official guidance for HBM use
- No legal enforcement
- No guidance values or background/normal values

Related to the absence of health-based guidance values or population-based RVs, also an inability to interpret or use HBM data was raised rather high. Whereas in the OSH field (see next chapter) ethical aspects were raised, in risk assessment under other frameworks risk for public arousal/anxiety when real internal exposure becomes evident was ranked higher.

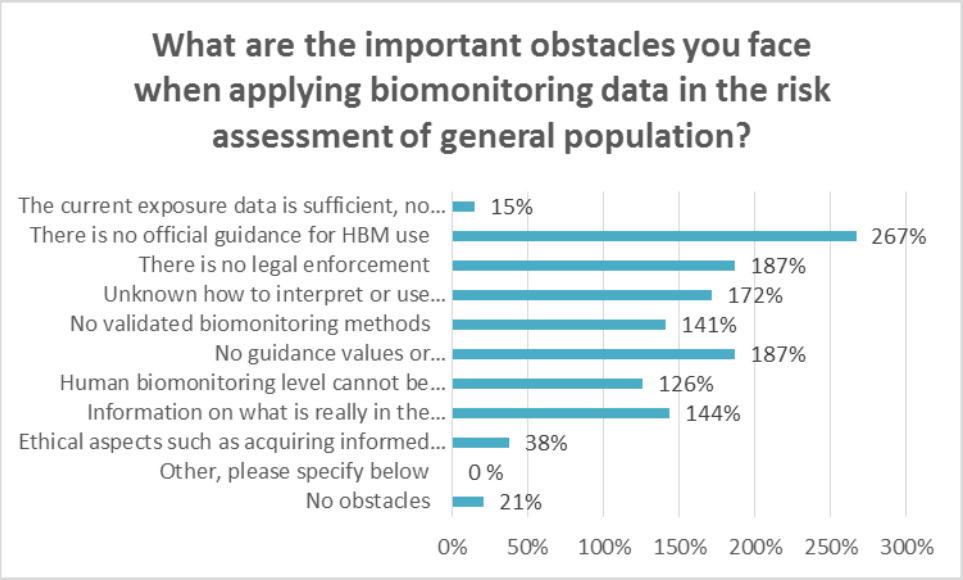

Figure 13: Obstacles faced when applying biomonitoring data in the risk assessment of general population (N=39). Question was asked on the following specific substance groups: Chemicals (in general), Phthalates/DINCH, Bisphenols, Per-/Polyfluorinated compounds, Flame Retardants, Cd/Cr, PAHs and air pollutants, Anilin family, e.g. MOCA, Chemical mixtures (pesticide mixtures), Emerging chemicals

The answers were given HBM4EU priority substance group specific and subsequently cumulated per obstacle. So no quantitative data interpretation is feasible, nevertheless, the above mentioned obstacles seem to be the most important general ones.

Except one, all 34 respondents confirmed that when it is possible to perform a HIA based on HBM data, it could be of additional value to assess certain policy goals prospectively and retrospectively. Many examples are given: phthalates, PFAS, Pb, arsenic, hexachlorobenzene.

According to the respondents, communication of HBM data in the general population is best done to the participants personally as well as within the health care system and obviously, to the national authorities involved in health programs.

4.4.4 Results: Use of HBM under occupational health and safety legislation

There were 28 respondents who responded in the second part of the questionnaire focused on occupational health and safety. Five of them were from non-EU countries and two without background information.

HBM is regularly done in different countries within the occupational safety and health interventions (56%, n=27). However, 44% responded that it is either not used or it is used only in a limited extent. In this case the answer was justified due to the fact that biomonitoring is legally required only when monitoring exposure to lead. Thus, regulation clearly facilitates the HBM appliance. Most of the respondents (73%, n= 26) indicate that there is guidance (regulatory, institutional) for the use of human biomonitoring in the risk assessment at workplaces (Figure 14). Only three of them (all representing different countries) said that there is no guidance in their country.

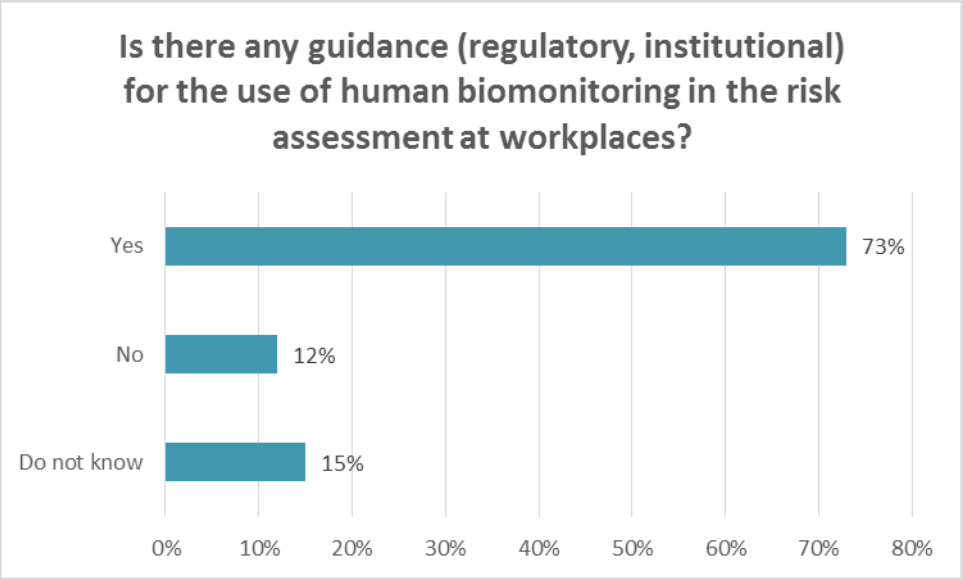

Figure 14: Existence of guidance (regulatory, institutional) for the use of human biomonitoring in the risk assessment at workplaces (N=26)

The main drivers to perform human biomonitoring at occupational settings were Health Surveillance performed by occupational health care and the existence of Regulations (e.g. B-Pb measurements required by law)" (67%, n=27), followed by the assessing the magnitude of internal exposure to a substance (52%) and confirming exposure to a specific substance (48%) (Figure 15). However, although the main driver to perform biomonitoring at workplaces is health surveillance made by occupational health care, only 37% of the respondents (n=24) indicate that the biomonitoring data is available for use in exposure assessment and management at the workplace (Figure 16).

Thus, the results of the biomonitoring in many cases are used only for individual health risk assessment and not for the workplace risk assessment and management, which is the responsibility of the employer. A reason for this, as mentioned by several participants, is the privacy concern. But, although personal data is often protected, group/ aggregated results could be used in many cases to review the risk assessment (e.g. identify high exposure situations).

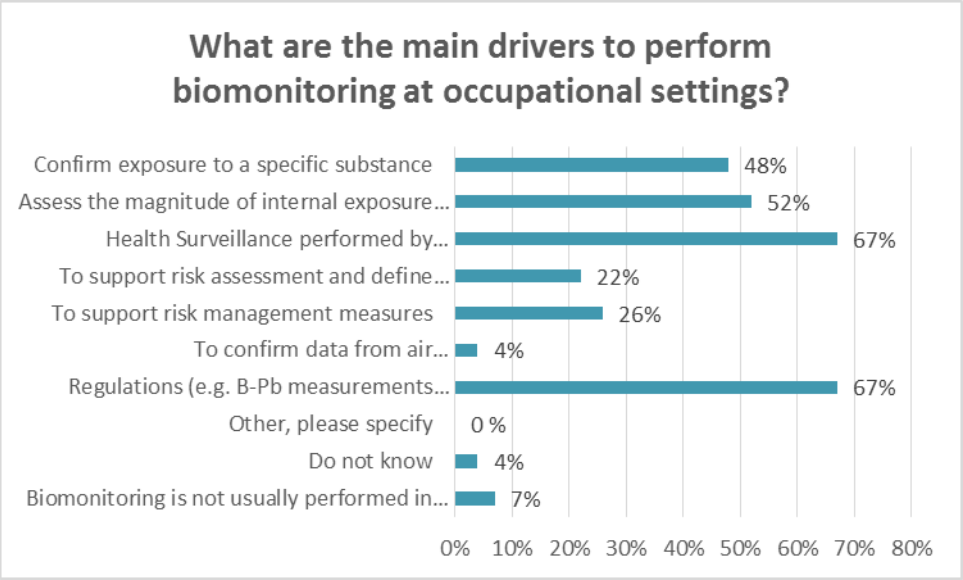

Figure 15: The main drivers to perform biomonitoring at occupational settings (N=27)

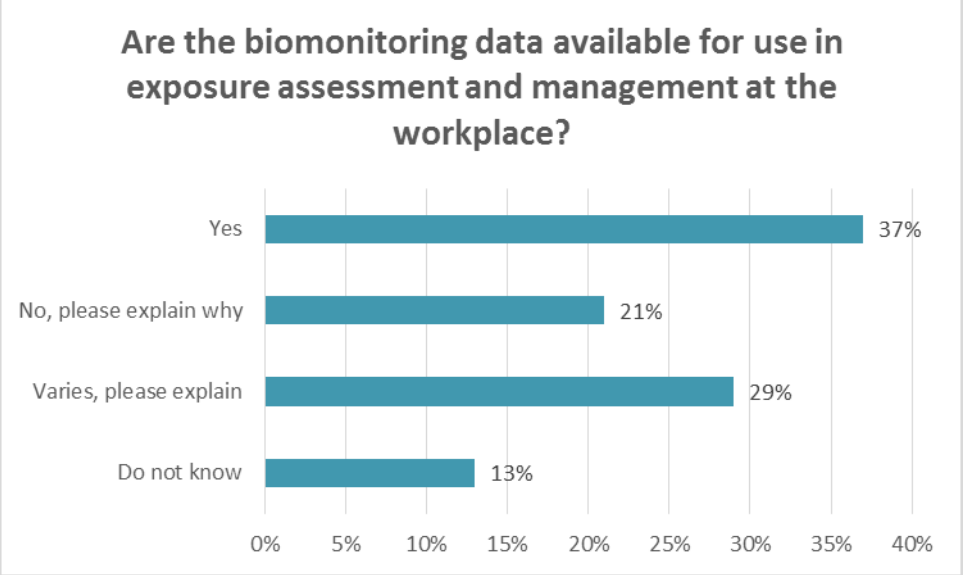

Figure 16: The availability of the biomonitoring data for use in exposure assessment and management at the workplaces (N=24)

Most of the respondents (77%, n=26) stated that there is guidance for the application of human biomonitoring in workplaces/occupational health care (Figure 17). However, when asked about the most important obstacles when using biomonitoring in risk assessment, lack of official guidance were the second important obstacle, just after the lack of legal enforcement (Figure 19). To the question on the effectivity of the regulations, most of respondents (69%, n=26) answered that the regulation is not effective enough to support the use of human biomonitoring in occupational health and safety (Figure 18).

Lead was again mentioned by several respondents as an exception since there is a specific regulation that supports HBM in case of occupational exposures to lead. Still related with this issue, for 17 respondents, lead was the substance mentioned more frequently for which there is a BLV or a BGV and most of the respondents (59%, n=22) stated that the values are binding limits given by the law. Ethical aspects like acquiring informed consent were surprisingly raised rather high when the data on the obstacles related to the chemicals in general were analysed separately

(data not shown). This is surprising when taking into account that human biomonitoring has long traditions in occupational health.

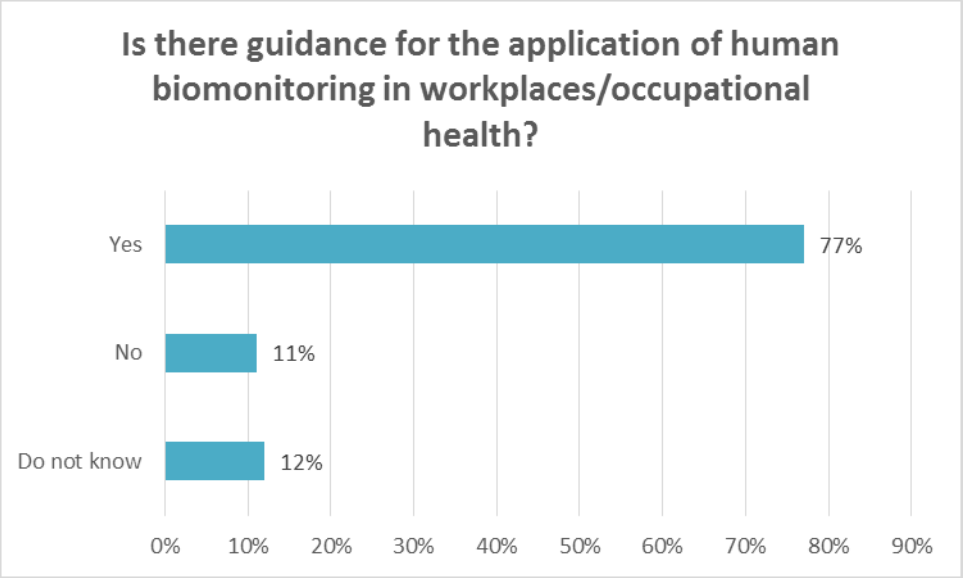

Figure 17: Existence of guidance for the application of human biomonitoring in workplaces/occupational health (N=26)

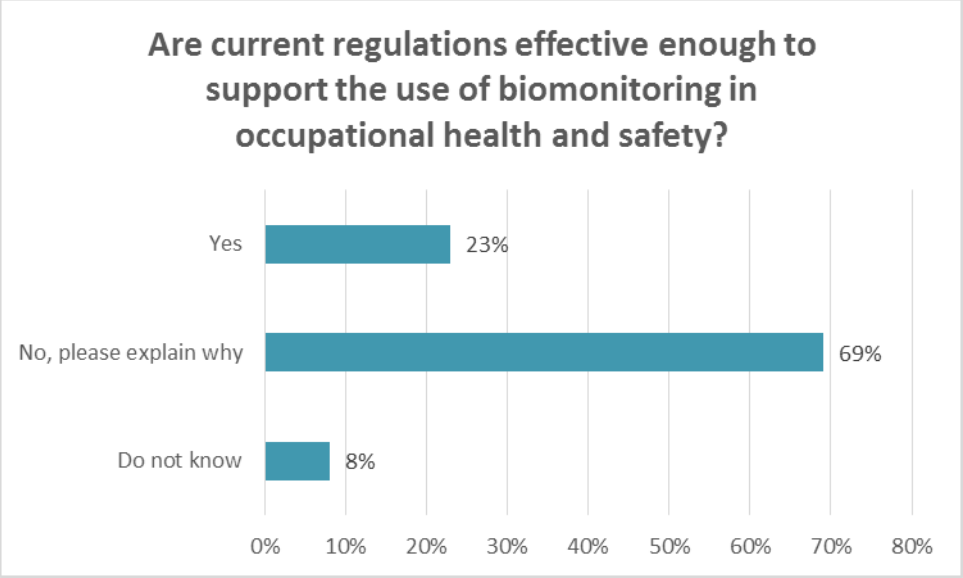

Figure 18: Effectivity of regulations to support the use of biomonitoring in occupational health and safety (N=26)

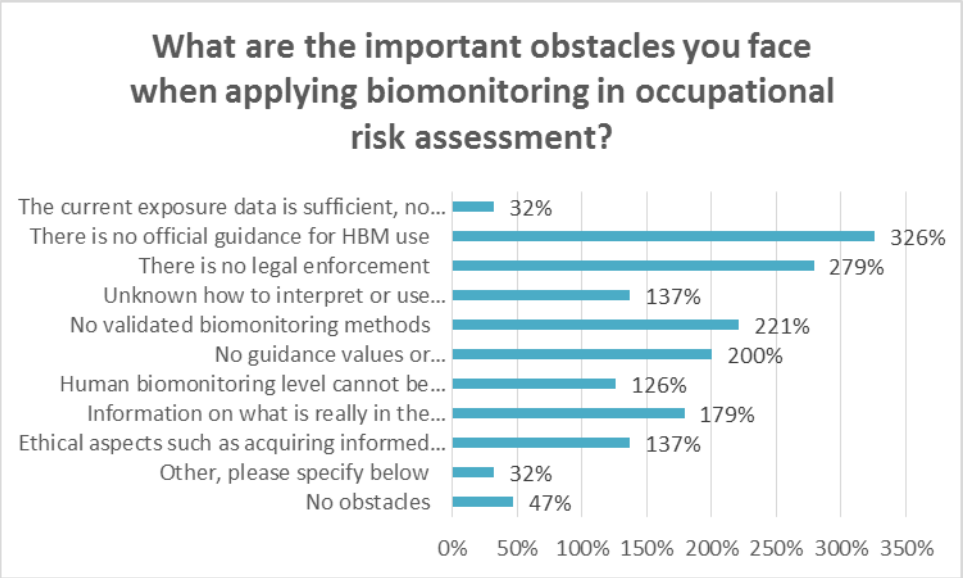

Figure 19: Obstacles faced when applying biomonitoring in occupational risk assessment (N=19). Question was asked on the following specific substance groups: Chemicals (in general), Phthalates/DINCH, Bisphenols, Per-/Polyfluorinated compounds, Flame Retardants, Cd/Cr, PAHs and air pollutants, Anilin family, e.g. MOCA, Chemical mixtures (pesticide mixtures), Emerging chemicals

More than half of the respondents (58%, n= 26) do not recommend the use of DNA or protein adduct analyses as a marker of exposure in occupational biomonitoring. Furthermore, only about one third of the respondents (35%, n=26) recommend the use of a biomarkers of effect (including e.g. “omics”- based biomarkers) in occupational biomonitoring. However, also 15% of the respondents mentioned “I don’t know”, which most probably reflects the fact that there are currently only few relevant, validated effect markers available.

Regarding the criteria for using human biomonitoring data in risk assessment, most of respondents answered that the existence of health based biological limit/guidance values (BLVs/BGVs) (96%, n=26) is the main criteria, together with the existence of validated method for human biomonitoring (92%). These were followed by the information on that HBM level can be related to the exposure source (85%) (Figure 19). Approximately half of the respondents (54%, n= 26) stated that biomonitoring results of workers are compared to occupational BLVs or BGVs.

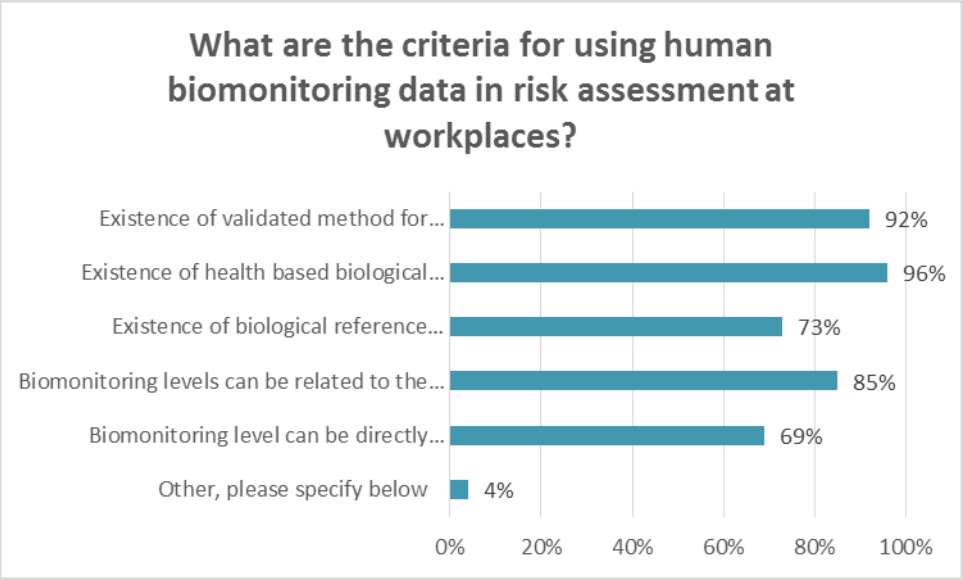

Figure 19: Criteria for using human biomonitoring data in risk assessment at workplaces (N=26)

44% of the respondents (n=25) stated that there is work going on to elaborate health based limit values for workers. However, 24% do not know if there is any action being developed concerning this issue.

Majority of the participants (68%, n=25) stated that occupational biomonitoring data is usually communicated to the Occupational Health Service, to the worker (60%) and also an overview of the results is communicated directly to the employer (44%) (Figure 20). Regarding this last aspect, 50% of the respondents (n=18) stated that the occupational health service have an obligation to give an overview of the biomonitoring results to the employer (Figure 21). However, 22% do 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.

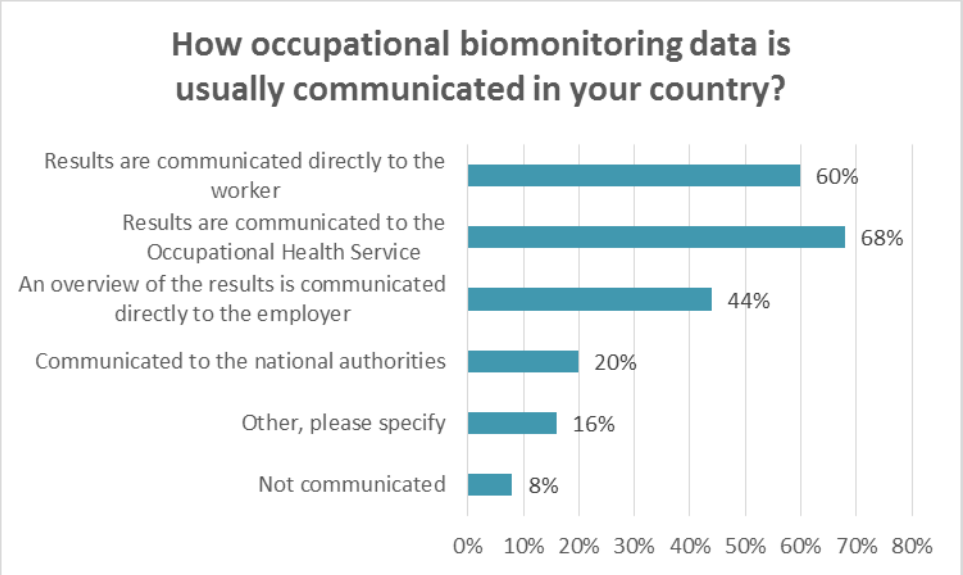

Figure 20: Communicating biomonitoring data of workers (N=25)

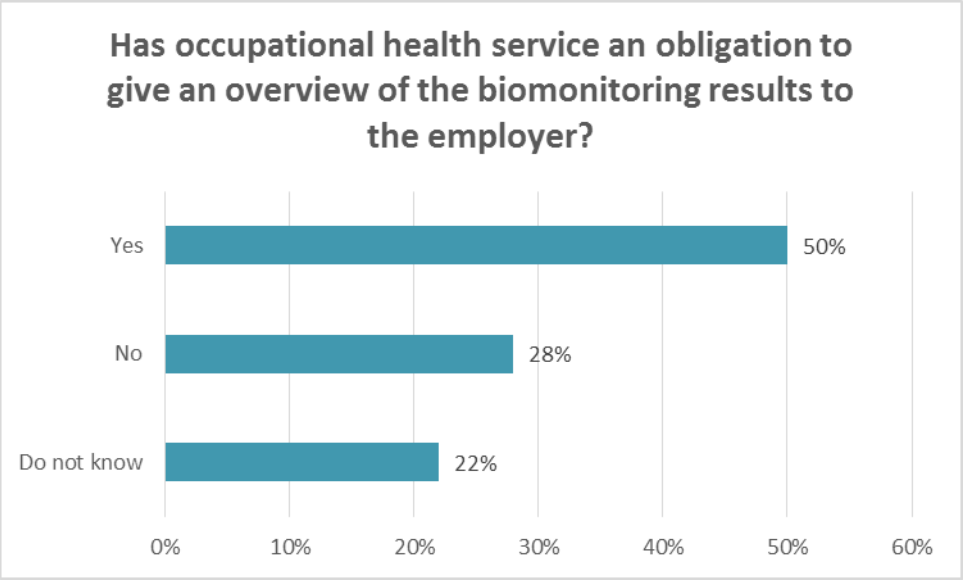

Figure 21: Obligation of occupational health service to give an overview of the biomonitoring results to the employer (N=18)

4.4.5 Discussion and general findings

Most participants were from EU countries. Nevertheless, 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, in some cases results as obtained from the survey were traced back to individual countries in order to ensure that some specific results do not only represent a situation in single country.

Taking the uncertainties around the representativeness of the respondents for the whole of Europe taking into account, the following more general findings can be taken forward within HBM4EU:

- HBM is mostly used under OSH framework, less under other risk assessment frameworks. However, also under OSH, the use of human biomonitoring is sometimes limited only to B-Pb which is legally binding.
- Outside the OSH domain, HBM is often incident driven (regulatory framework independent).
- Key obstacle for using the HBM instrument is the lack of guidance. This pertains both to:
    - The more scientific part of HBM (what biomarker to measure (parent substance or a metabolite), relation between exposure biomarker and most relevant adverse health effect, sufficient sampling size including size of subpopulations)
    - The technical and organisational part (not specified in the survey but very likely relating to validated sampling and analytical methods, how and to whom to communicate the results of HBM).
- Although under OSH framework most of the respondents noted that there is guidance available, also in this case it was considered that lack of guidance is one of the key obstacles.
- Another key obstacle was the lack of legal enforcement followed by the lack of guidance/limit values. Under OSH, also ethical aspects were raised.
- Under OSH, main drivers to perform human biomonitoring are the regulations and health surveillance. Regulations were, however, not considered sufficient by most of the respondents. Since biomonitoring is commonly done by occupational physicians as part of health surveillance, the results of it are not necessarily effectively used for the exposure/risk assessment and management at workplace because of the privacy concerns.

Sometimes, open question responses are more or less clearly linked to the EU or even to a specific EU or non-EU country. Further elaboration would most probably benefit from further discussion of these findings with the National Hub Contact Points (NHCPs) and in some cases further elaboration in connection with the NHCPs. It is also noted that responses to open questions contained some seemingly important references that could be useful for further work within HBM4EU Task 5.3. The full statistics to the survey are attached as Annex to this deliverable report.

5 Use of HBM in risk assessment – 1st substance group specific risk assessments

5.1 REACH risk assessment scheme

5.2 Phthalates

5.2.1 Restriction dossier

A restriction proposal was submitted by Denmark in 2011 to restrict the placing on the market of certain articles containing 4 phthalates (DEHP, BBP, DBP and DIBP).

ECHA's Risk Assessment Committee (RAC) and Socio-Economic Analysis Committee (SEAC) adopted opinions not supporting the proposal. A new proposal from ECHA and Denmark built on the previous restriction proposal was submitted in April 2016, presenting additional information and assessment covering the hazard, new information on exposure (especially DEMOCOPHES biomonitoring data), additional data on costs and trends in substitution, and a review of new information on benefits (ECHA, 2017c).

The exposure assessment has been based especially on DEMOCOPHES urinary biomonitoring samples taken in 2011-12 given that it is recent, consists of a large sample size, and is more representative for EU28 than all other human biomonitoring studies available, which are the criteria that determine the relevance of using HBM data. Morning urine samples were collected from mother-child pairs in 16 EU Member States and Switzerland from September 2011 until February 2012.

- Some observations could be drawn from the DEMOCOPHES biomonitoring exposure estimates, also from information available from Austria, France and Spain and from many other studies reporting urinary metabolite levels of the 4 phthalates, as the GerES IV (Koch et al., 2007; Becker et al. 2009), a retrospective study on 24h-urine samples from the German Environmental Specimen Bank (ESB) (Göen et al., 2009) and a Danish mother-child pairs study (Frederiksen et al., 2013),exposure of children is higher than that of mothers
- exposure to phthalates has declined over time when older biomonitoring studies are compared to the DEMOCOPHES data.
- based on several studies which measured urinary levels of phthalates together with diet change (fasting or low-phthalate diet) or measurement of the content of phthalates in the diet, it is assumed that 75% of the intake of DEHP is attributable to food (incl. drinks), whereas for DBP, DIBP and BBP it is assumed that 25% is attributable to food.
- Participants of DEMOCOPHES who reported to have PVC flooring or walls in their homes showed significantly higher BBP and DIBP metabolites in children as well as mothers and significantly higher DBP metabolite concentrations in children

One source of uncertainty in the estimates is the use of morning spot samples. This might underestimate exposure to the phthalates, as observations have shown that DEHP metabolite concentrations are higher in the evening than in the morning. It was also shown that within day variability was greater than between day variability, as was within person variability compared to between person variability.

The overall conclusion of the risk assessment based on the biomonitoring data (together with exposure modelling) points out that the identified risk to the general population is not adequately controlled and needs to be addressed. Indeed, based on the 95th percentile of combined exposure

to the 4 phthalates measured from human biomonitoring data, a risk were identified for children in 13 out of 15 Member States and for women in 6 out of 15 Member States. Overall, in 14 out of 15 Member States more than 5 percent of the children were at risk. Approximately 5% of new born boys (130 000) were at risk through in utero exposure in 2014 and about 16% boys (400 000) were at risk from direct exposure in 2014 (ECHA, 2017c).

Therefore, the proposed restriction targets the risks from exposure to the 4 phthalates by restricting their concentration in articles which have the highest contribution to exposure. Further follow-up of phthalate levels in general population will bring valuable information on the effectiveness of this restriction for the whole of Europe. Further assessment could take into account also the levels of other, less regulated phthalates.

Regarding the human HIA, Denmark considered that there was a lack of sufficient scientific evidence from the available human biomonitoring and epidemiological data for the development of dose-response relationships. Therefore, the benefits associated with reduced exposure to the four phthalates are not quantified in the dossier. Nevertheless, to illustrate the magnitude of these impacts Denmark evaluated and monetised the impacts based on all evidence available on exposure and observed effects (male infertility, cryptorchidism, and hypospadias) i.e. from animal studies, epidemiological data and evaluations from recent published reports on the disease burden of EDCs as well. The dossier submitter thus monetised benefits using the aetiological (attributable) fraction approach as an indication of the magnitude of the human health benefits expected, mentioning that considerable human benefits remain not monetised.

5.2.2 Opinion on the Application for Authorisation for DEHP used in formulation in compounds, dry-blends and Plastisol formulations (ECHA, 2015e)

Human biomonitoring data used by the applicants were judged of limited informative value, because they were not recent and because of their limited geographical coverage. Also, none of the HBM studies were reporting specific RMM, thus limited information concerning the level of risk management measures and operational conditions at the monitored workplaces were available.

5.2.3 Opinion on an Application for Authorisation for DBP used as an absorption solvent in a closed system in the manufacture of maleic anhydride (ECHA, 2014b)

Regarding the exposure assessment, an oral intake of DBP was calculated by RAC based on the 90th percentile of exposure estimates from urinary biomonitoring data of the applicant's workers.

Regarding the risk assessment, RAC calculated an RCR for workers using HBM data. RAC concluded that for this specific use of DBP, the health risk to workers (specifically reproductive toxicity) is adequately controlled.

5.3 Bisphenol A

5.3.1 Restriction dossier for BPA

A proposal to restrict BPA because of health risks for pregnant workers and consumers exposed to it in thermal paper - for example when they handle cash register receipts was submitted by the French authorities in May 2014.

France based its hazard assessment of BPA on the effects on several human health endpoints (the female reproductive system, the brain and behaviour, the mammary gland, metabolism and obesity). The effects on the mammary gland were considered the most critical endpoint, prevailing over the others. They were used to calculate the DNEL. At the time of the elaboration of the proposal, biomonitoring data evaluating specifically exposure through thermal paper were not

available (neither for workers nor for consumers). Thus the development of a BPA exposure scenario was proposed through the handling of thermo-printed receipts for workers (cashier) and the consumer and the human health assessment was based on the calculation of the disease burden for the effects of concern from modelled exposure data only.

RAC considered that the critical studies selected by France to calculate the DNEL did not allow quantification of the dose-response relationships and showed uncertainties. Therefore, for the purposes of calculating an oral DNEL, RAC selected the effects on the kidney and, as the available data indicated that kidney effects are not the most critical effects of BPA, applied an additional assessment factor of 6 to take account of the other endpoints in the overall hazard assessment. Since the restriction proposal was concerning the dermal route of exposure due to handling thermal paper, a DNEL for the dermal exposure route was also calculated for workers and the general population.

As regards exposure, RAC refined the assessment and complemented it with new biomonitoring information on cashiers' exposure to BPA. The analyses of biomonitoring studies performed by ANSES and by EFSA (EFSA, 2015) were included into an updated version of the restriction dossier. It appears however that the conclusions were different, mainly due to differences in assumptions and methods used as for example on the limit of detection of the unconjugated form of BPA in the plasma or on the credibility of studies considering lack of information with respect to sample collection and handling (ECHA 2015f). But, the HBM studies were indicating that "the cutaneous route of exposure from thermal paper sources was not negligible, based on the significant increase of urinary concentrations measured after testing cashiers during exposure scenarios". Applying this methodology, RAC concluded that the risk for consumers is adequately controlled but confirmed the risk for workers.

Regarding the uncertainties in the risk characterisation, RAC indicated that the exposure estimates for consumers carry relatively few uncertainties, in part, because HBM data are confirming that exposure does not exceed the DNEL. The confidence about a correct conclusion is thus relatively high. RAC concluded that the risks from BPA in thermal paper to human health were adequately controlled for consumers across the EU (ECHA 2015b). Regarding workers, RAC indicated that the available HBM data were scarce and of limited nature, thus providing a lower confidence level to the modelling results when compared to consumer exposure. However, as the integrated assessment of worker exposure performed is based on both modelling data and available human biomonitoring data, reasonable consistency is given since HBM data was largely supporting probabilistic modelling. RAC used the BE approach presented by Krishnan et al (2010) to convert urinary BPA levels as intakes. RAC concluded that the risks from BPA in thermal paper to human health were not adequately controlled for workers across the EU, and that measures to minimise exposure were to be implemented on an EU-wide basis (ECHA, 2015b).

Although human biomonitoring data were published, the dossier submitter and SEAC couldn't update the impact assessment on BPA, because in accordance with the conclusion of RAC, the available data did not allow a quantification of the dose-response relationship for the health effects of BPA. SEAC didn't use the benefit estimates presented in the French dossier but used instead expert judgment to determine the likelihood of observing an occurrence rate for each endpoint.

It has to be mentioned that interpretation of HBM data on BPA is not easy, as the biomonitoring studies are showing large fluctuations in urinary concentrations of BPA depending on the type of diet. Studies also clearly show that due to the rapid elimination of BPA from the body, the urinary concentration of BPA in the individuals is only representative of recent exposure (hours preceding the sample only). The urinary sampling also shows high variability, and while collection over 24 hours significantly represents the quantity of BPA excreted daily, it does not reflect the hourly excretion. One additional uncertainty was also related to the assumed higher proportion of BPA in

the blood after the dermal exposure when compared to oral exposure because of the by-passing of the first phase metabolism in liver. To account for this uncertainty a default assumption was used, which leaves room for refining the assessment when new information on the toxicokinetics of BPA after dermal exposure appears.

5.4 Perfluorooctanoic acid (PFOA) and PFOA-related compounds

5.4.1 Assessments on PFOA

REACH restriction dossier for PFOA

PFOA is a key compound within a larger group of substances, the per- and polyfluorinated substances (PFASs). Being a persistent, bioaccumulative and toxic (PBT) chemical, PFOA was recognised as a SVHC under REACH back in July 2013. There are also other PFASs that can degrade to PFOA in the environment, and are referred to as PFOA-related substances. These substances are therefore also included when determining the risk to human health posed by PFOA.

There are ongoing discussions on the appropriate POD for derivation of a $DNEL_{biomarker}$ for the general and the worker population respective HBM values for PFOA the current values differ among orders of magnitude. Below, the restriction proposal as prepared by Norway and Germany in 2016 as well as the subsequent opinion as published by ECHA's RAC are described.

Restriction proposal by Norway and Germany

A restriction proposal report was prepared by Norway and Germany in 2014 (Annex XV Proposal for a Restriction –PFOA, PFOA salts and PFOA-related substances; ECHA 2014c). Data from various research reports and studies alongside industry surveys by OECD were used to derive $DNEL_{biomarker}$–values for workers and the general population, to calculate external and internal exposures, and to assess risk to human health. In the restriction proposal, it was stated that human PFOA exposure has been shown to be linked to foetal transfer resulting in immunosuppression and reduced birth weight of children, as well as metabolic disturbances (T3, cholesterol) and increased time to pregnancy in adults. Various epidemiological studies that had suggested associations between PFOA exposure and various effects (e.g. reduced birth weight, elevated cholesterol levels) were used to calculate both internal and external DNELs for the general population as well as highly exposed workers. With available LOAEL data, DNELs were calculated for the different effects based on both animal external intake data but also on human exposure biomarker data. The restriction proposal contained $DNEL_{biomarker}$ values calculated on the basis of reduced birth weight or increased cholesterol levels observed in human population studies. The lowest $DNEL_{biomarker}$ values, 0.3 ng/ml serum and 0.6 ng/ml serum for the general and worker population, respectively, were based on reduced birth weights. Increased cholesterol levels resulted in slightly higher $DNEL_{biomarker}$ values of 0.74 ng/mL and 1.47 ng/mL, for general population and workers, respectively.

The risk characterisation suggested that the highest exposed among the general population is not protected towards the hazardous effects of PFOA. The RCRs for adults were 2-70 and for children even higher, 3-148. When evaluating these RCRs, the recent human data showing an impaired immune response associated to PFOA exposure were not taken into account, as these were not available at that time. These include the studies in the Faroese population by Grandjean and co-workers who have suggested an association between PFAS (including PFOA) exposure and impaired immune response in children. When childhood vaccination responses were used as a clinically relevant outcome, PFAS concentrations in maternal pregnancy serum showed a strong negative correlation with vaccine antibody concentrations in children at 5 years of age. This

occurred at dose levels which could result even lower DNELs (and thus higher RCRs). As humans are exposed to several PFAS compounds, possible mixture effects should ideally also be taken into account in risk assessment if the same target organs and MoAs can be assumed.

In general, the human studies resulted in lower DNELs than the rodent studies, suggesting that humans are more sensitive to the hazardous effects of fluorinated chemicals than rodents. Under physiological conditions PFOA is readily dissociated to the conjugate base perfluorooctanoate (PFO), which is the form actually measured in HBM. In the literature, however, it is referred to as PFOA. The use of HBM data has been invaluable in the risk assessment of PFOA due to the marked species differences in kinetics between animals and humans, bioaccumulative properties of PFOA and due to the availability of epidemiological human health and exposure data.

ECHA RAC opinion on PFOA restriction proposal

Following the restriction proposal described above, ECHA's risk assessment committee discussed this and subsequently published their opinion (ECHA, 2015g). The RAC opinion was mainly based on PBT properties of PFOA, which were alone sufficient for restriction. However, PFOA internal DNELs were also derived based on animal and human studies. The RAC did not agree with some proposals in the restriction dossier submitted by Germany and Norway. RAC derived a $DNEL_{biomarker}$ of 800 ng/ml and 1600 ng/ml for the general population and the worker population, respectively, arguing that a DNEL cannot be reliably derived from human data (ECHA, 2015g). Especially, dose-response related to the reduced birth weight were considered unreliable since the dose-response was seen only in general population studies with PFOA serum levels <10 ng/mL, but not in studies among highly exposed populations (populations living nearby contaminated sites with serum levels >50 ng/mL and occupationally exposed populations). The reasons for this discrepancy were not discussed in RAC opinion but may include confounders like co-exposure to other PFAS compounds among general population and reduced plasma volume expansion and therefore reduced clearance of PFOA through glomerular filtration as described Annex XV Proposal for a Restriction –PFOA, PFOA salts and PFOA-related substances (ECHA, 2014c).

German Human Biomonitoring Commission

The German Human Biomonitoring Commission has published a reassessment of the HBM values of PFOS and PFOA in 2016 (UBA, 2016). The HBM I value represents the concentration of a substance in human biological material below which no risk for adverse health effects over life time is expected (HBM Commission 2014). The respective HBM I values are 2 ng PFOA/ml and 5 ng PFOS/ml blood plasma (HBM Commission 2016). The HBM Commission has decided to use the existing POD ranges of 1 to 10 ng/ml as a basis and selected 2 ng/ml comprising the HBM I value for PFOA, pointing to the consistency of results from animal and epidemiological studies.

EFSA's risk assessment of PFOA

The current risk assessment by EFSA of PFOA from 2008 is based on data from animal experiments; more specifically the TDI is based on liver toxicity in rats and mice with a BMDL10 of 0.3 mg/kg bw/day. This results in a TDI of 1.5 µg/kg bw/day.

This TDI gives rise to an acceptable intake of 90 µg PFOA/day for a 60 kg person (eating 1 kg food per day). This value does not take sufficiently into account that PFOA accumulate in humans and the environment causing exposure to increase over time. Ideally the risk assessment should be based on body burdens, as it is done for e.g. dioxins and PCBs.

In order to evaluate the contribution to human PFOA exposure from food contact materials, a study at DTU Food showed that migration from cake and popcorn packaging materials gave rise to a calculated human exposure that occupied 4-12% of the present TDI set by EFSA. In light of the

current high TDI that needs re-evaluation, this exposure from food contact materials is of concern. Currently EFSA is re-evaluating the PFOA risk assessment in the light of new data, especially human data that has appeared since 2008.

Biomonitoring of residents exposed to PFOA –Dutch case study

There are some populations in Europe such as the Ronneby population in Sweden and a population in the Netherlands, which have been exposed to high levels of PFOA due to the environmental contamination. In the Netherlands, the health effects of the persistent PFOA are currently under investigation. The trigger is the Chemours scandal, in which residents living in the vicinity of a Teflon factory in Dordrecht have been exposed for 25 years (1970-2012) to elevated concentrations of PFOA. In addition to measurements of PFOA in water and air, blood samples have been taken from 382 residents distributed over four exposure groups. The measured PFOA-levels in blood (Van Poll et al., 2017) for the highest exposed group (up to 750 m from the plant) were in the range of 1.3 (minimum) – 147 (maximum) ng/ml serum with a median of 10.2 ng/ml. In a control area levels were 0.9 – 14.1 ng/ml serum with a medium of 3.4 ng/ml. From the 382 residents, 18 had a serum level of PFOA higher than 21 ng/ml, which is the maximum average European background level (ECHA, 2015h). The measured serum levels of PFOA appear to be similar to values calculated in 2016 using a computer model and support the risk assessment carried out. Depending on the exposure scenario, the levels calculated for the highest exposed groups were 80 -130 ng/ml serum (Zeilmaker et al., 2016). The health limit derived was 89 ng/ml serum. This limit value is based on liver toxicity in rats with a NOAEL of 0.06 mg/kg bw/day extrapolated to chronic human inhalation exposure using kinetic modelling that takes into account accumulation of PFOA. The human biomonitoring data therefore underscore the conclusion from 2016 that the general population health limit value of PFOA was exceeded for long periods of time and may have caused adverse health impacts. The link to health effects will be made through literature research and additional interviews with residents with higher exposures leading to serum levels above 21 ng/ml. The results of this study will be published at the end of the year 2017.

5.4.2 Summary of different PFOA assessments

Within the various regulatory communities discussions on the most sensitive health endpoints are still ongoing. Recently, Fletcher and Stayner, presented a $BMDL_{01}$ (1% BMDL) of 2.8 ng/mL based on increased cholesterol levels, which was considered to represent the best characterised health effect in humans seen in a wide range of serum PFOA levels (Fletcher and Stayner, 2017). Results of the ongoing EFSA assessment are expected in autumn 2017.

The ‘orders of magnitude’ difference (e.g. a factor of 400 between the RAC proposed DNEL of 800 ng/ml and the German HBM-I of 2 ng/ml) highlights the need for alignment or at least communication of the various risk assessment bodies throughout Europe when it comes to hazard assessment, be it based on animal studies of human epidemiology and the subsequent derivation of a health based guidance value. Overall, however, human studies suggest that humans may be more sensitive to the hazardous effects of fluorinated chemicals than rodents. In addition, when taking into account the bioaccumulative properties of PFOA, human biomonitoring is the best way to assess the exposure to PFOA.

5.5 Anilines

5.5.1 Use of biomonitoring in the authorisation of MOCA

MOCA is an aniline derivative, which is used primarily as a curing agent in polyurethane production. It is a genotoxic carcinogen to which a threshold for carcinogenic effects cannot be assigned. In animal studies it has caused increased incidence of lung, liver, mammary gland and urinary bladder cancers. Because of its carcinogenic properties, it was added to Annex XIV of REACH and it is currently authorised under REACH. MOCA has a low volatility and it is easily absorbed via the skin. Therefore, human biomonitoring is very valuable tool for the assessment of exposure to it in occupational settings. In occupational studies in polyurethane industry, urinary MOCA levels has correlated best with the MOCA surface contamination, whereas air levels have been often low (Cocker et al., 2009; Keen et al., 2012).

ECHA has performed a dose-response analysis for the carcinogenicity of MOCA and calculated cancer risk levels for different MOCA intakes (ECHA, 2015c). In its dose-response documentation ECHA also presents estimated cancer risks for different urinary MOCA levels measured as total urinary MOCA in the end of the work-shift in the end of the work week (ECHA, 2015c). Since urinary MOCA levels do not correlate with MOCA air concentrations, it is not possible to directly calculate urinary levels which correspond to occupational exposure to specific air levels. Neither there are any PBTK/PBPK models for MOCA. Therefore, in ECHA's document an open one-compartment model based approach was used to roughly estimate the daily doses corresponding to urinary MOCA level of 5 µmol/mol creatinine in the Friday afternoon (end of shift) sample (ECHA, 2015c). This was provided to the applicants of authorisation to facilitate the use of biomonitoring in the exposure assessment of MOCA in its industrial uses. General population is usually not exposed to MOCA, and the levels of MOCA and its metabolites in the urine of the non-occupationally exposed population are below the detection limits.

There is one application for authorisation for MOCA available at ECHA website (application by ReachLaw, 2016). It covers up to 89 sites in EU using MOCA as a curing agent in polyurethane production. Estimated number of exposed workers in EU is about 200. The authorisation has been applied for 12 years, but the commission decision or the ECHA committees (RAC and SEAC) recommendation on the application is not available yet. The applicant has used HBM data to assess the workers' exposure to MOCA (Reachlaw, 2016). In addition, there are published studies, especially from UK, on the exposure to MOCA in polyurethane manufacturing (Cocker et al, 2009; Keen et al., 2012, Robert et al., 1999). These all show urinary MOCA levels in the manufacturing of polyurethane which are about 10 µmol/mol creatinine or below. Using RAC dose response, this can be calculated to correspond the excess cancer risk of 3.3×10^{-5}. Besides HBM data, in the CSR the applicant has used modelling to assess inhalation and dermal exposure. Dermal exposures up to 13 -14.5 µg/kg bw were predicted by the model for two worker's contributing scenarios resulting in highest exposure in manual polyurethane moulding process. These can be calculated to correspond to a daily intake of up to about 450-500 µg/day and urinary levels up to 130-150 µmol/mol creatinine when assuming 50% bioavailability via dermal route (50% bioavailability via dermal route was assumed by RAC in its dose-response analysis. Thus, when comparing these values to available HBM data, it is evident that modelling of exposure results in a significant overestimation of exposure and risk. This example demonstrates how human biomonitoring can be used for more accurate exposure and risk assessment. Benefits of human biomonitoring in occupational exposure assessment include also that it takes into account also hand-to-mouth exposure, which cannot currently be assessed by any modelling tool. In this case, it is of particular relevance since MOCA has low volatility and can be present for a long period on workplaces surfaces facilitating this exposure route.

5.6 Polybrominated diphenylethers (PBDEs) assessment group

A good example on the use of HBM data under the mixtures framework is given in the publication by M.E. Meek et al. / Regulatory Toxicology and Pharmacology 60 (2011) S1–S14, (Annex A). This concerns PBDEs. 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. These upper-bounding estimates of exposure were considered conservative, in that they were based on summed estimates for all congeners for which data were available and highest measured concentrations for many media. Comparison of the critical effect level (i.e. 0.8 mg/kg bw per day for neurobehavioural effects in mice following neonatal exposure) with the upper-bounding deterministic estimate of exposure for the intake of total PBDEs (2.6 µg/kg bw per day in breastfed infants) resulted in a margin of exposure of approximately 300. Margins based on available HBM data were approximately 10-fold less. These were estimated through back-calculation of intakes by first-order kinetic modelling of limited data on levels in blood of the general population and comparison of estimated body burden for the critical study in animals with that for breastfed infants. However, confidence in these estimates was considered to be less, owing to the considerable limitations of the relevant data on biological half-lives of PBDEs in humans and their seeming inconsistency with what would be expected based on relevant physical/chemical properties. The degree of conservatism in this margin is relevant to its interpretation. One critical aspect is the large inter-individual variability in levels of PBDEs in breast milk within the general population. It should be noted that mean and median values for levels in breast milk were as much as 400- and 200-fold less, respectively, than the maximum values on which the estimates of exposure were based.

In comparison, effect levels in chronic studies for the same congener were approximately 100 times higher than that used in the margin of exposure. The margin of exposure does not, however, take into account the potential continuing increase in body burden of PBDEs (based on data for breast milk), should similar use patterns continue. Based on limited data, levels of PBDEs in human breast milk in Canada appear to be increasing with time (e.g. there was a 9-fold increase in mean concentration between 1992 and 2001). Prediction of trends in body burdens is precluded by the limited information on the toxicokinetics of PBDEs in humans and animals and transfer from human breast milk to infants, as well as the uncertainty in half-lives for removal processes for PBDEs in environmental media.

On the basis of this example, it can be concluded that HBM supported by PBPK/PBTK modelling is a pivotal tool in the domain of mixture exposure (cumulative exposure).

6 Overall summary and conclusions

In this report we have evaluated several international (WHO, UN FAO) and EU risk assessment schemes and the role of human biomonitoring in these schemes. Summary of the findings of this evaluation are presented in Table 7.

Table 7: International and EU risk assessment schemes

Risk Assessment Scheme	Biomonitoring recognised as an exposure assessment tool	Biomarkers of effect recognised as possible tools for e.g. hazard characterisation	Specific guidance available for the use of biomonitoring in risk assessment	Examples on the use of HBM exists. If these include HBM4EU priority chemicals, these are given in brackets	Remarks
WHO risk assessment scheme	yes	yes	yes	yes (toxic metals e.g. Hg/MethyltHg, Cd, Cr), toluene, nitrobenzene, etc.)	GEMS; IPCS/INCHEM
FAO risk assessment scheme	yes	yes	no	no	
REACH	yes (occupational /consumer /humans-via-the-environment exposure assessment)	no	+/-*	yes, HBM data were used for the needs of authorisation & restriction dossier (phthalates, BPA, MOCA, chromates, MDA)	*REACH guidance R8 mentions the possibility to derive DNELs based on biomarker levels
EFSA	Yes	Yes	Yes	Yes (cadmium and lead)	Guideline for risk assessment of contaminants in food and feed
EFSA review	Yes	Yes	No	Yes (Metals; PCBs; cotinine; mycotoxins; perchlorate; nitrosamine; alkaloids; dioxins; phthalates; PAHs; furans; fluorocarbons; organochlorines; phenols; PFCs; PBDEs; organophosphates; pyrethroids; chlorinated phenols; acrylamide; carbamates)	WHO risk assessment guidance is followed
EFSA review	Yes	Yes	No	Yes (PCBs, PBDEs, PFASs, PAHs, Parabens, Perchlorate, BPA, Phytoestrogen, VOCs)	Document focused on vulnerable groups

Risk Assessment Scheme	Biomonitoring recognised as an exposure assessment tool	Biomarkers of effect recognised as possible tools for e.g. hazard characterisation	Specific guidance available for the use of biomonitoring in risk assessment	Examples on the use of HBM exists. If these include HBM4EU priority chemicals, these are given in brackets	Remarks
EU Pesticides	yes	yes	no	HBM has been used for monitoring worker exposure. Most studied pesticides: Herbicides (in order): 2,4-D > atrazine > metolochlor = MCPA > alachlor = glyphosate. Insecticides (in order) were: chlorpyrifos > permethrin > cypermethrin = deltamethrin > malathion, Fungicides were: captan > mancozeb > folpet	Data from: Human biomonitoring data collection from occupational exposure to pesticides –EFSA supporting publication 2017:EN-1185. 207 pp.
EU Biocides	yes	no	no	no	
EU Cosmetics	no	no	no	yes	HBM data considered as support and complementary information only
EU OSH	yes	no (legislation, however, SCOEL methodology recognises this possibility)	no	only B-Pb taken into the legislation, however, SCOEL recommendations available for several HBM4EU priority chemicals, see table 6	Biomonitoring considered as part of health surveillance. Under CAD or CMD no BLVs given except for P-Pb)
WHO HIA scheme	Yes	?	No	Yes, lead, dioxins, EDCs in general	Current status: Dose-response relationships mainly based on external exposure

As can be seen from table 7, in most risk assessment schemes some reference to human biomonitoring has been made. Human biomonitoring is generally considered as a useful tool, which can be used as a 3rd tier method for the refinement of exposure assessment. Only few risk assessment schemes recognise, however, the possibilities of the effect markers in the hazard and dose-response analysis possibly due to uncertainties associated with HBM dosimetry for the setting the relevant dose descriptor. In addition, lack of guidance and lack of knowledge on the meaning of different effect markers may have an impact on this.

Although examples of the use of HBM data in the risk assessment can be found from almost all regulatory areas, the guidance on the use of HBM in risk assessment is generally either limited or missing. This was noted both in the evaluation of the risk assessment guidance and in the survey made to risk assessors. In food safety area, EFSA has, however, made recently good work to evaluate the use of HBM data in food safety and pesticide assessment. Additionally, guidance on the new possibilities to use human biomonitoring data could be useful; as the reduction in animal testing (3Rs) is reality and experimental information on e.g. toxicokinetics may be in many cases lacking, the existing HBM data could be integrated with data using non-animal methods (in vitro, in silico and HTP screening) in combination with computational modelling (PBTK) to generate more reliable information on toxicokinetics and to provide linkages between AOPs and human internal levels.

It seems that in some regulatory areas (e.g. REACH) the data requirements for registration do not in practise support the use of human biomonitoring although in principle human biomonitoring is given as an option for exposure assessment. This is mainly because there is no incentive to understand the relationship between internal exposure and health effects, and also toxicokinetics data, which is essential for the use of HBM data, does not belong to the basic data requirements under REACH. In addition, IUCLID database, meant for the registration of chemicals does not currently include a place for biomarker based DNELs.

In some regulative areas (pesticides, biocides) use of volunteer studies in the approval of new substances is not allowed. This may also limit the use of HBM data in those areas.

Under EU OSH legislation human biomonitoring is considered as health surveillance, and no clear distinction between exposure assessment using human biomonitoring as part of workplace risk assessment and management, and health surveillance (or assessment of individual health risks) of workers is made. The results of the human biomonitoring surveys are not always communicated to the employers due to the privacy concerns (even as summarised results of the group of workers), which limits their use in the risk assessment and management at workplace. Health based limit/guidance values (or biological equivalents) are considered important for the use of HBM not only in OSH field but also in other risk assessment fields. In OSH, also regulations seem to be important drivers to conduct human biomonitoring. Thus, following main conclusions can be made on the basis of the survey and the evaluation of risk assessment schemes:

- There is a general need for 1) having a reliable human biomonitoring methods using a specific marker for the substance of concern and 2) better guidance for the use of human biomonitoring in risk assessment under different risk assessment schemes. Examples of the successful use of human biomonitoring in risk assessment should be gathered and used in the development of such a guidance.
- Scientifically sound health based limit/guidance values (such as derived via the biological equivalents approach), preferably with at least some regulatory status are essential for chemical risk assessors to use measured HBM data in the risk assessment process. These should be developed at EU level. The lack or paucity of toxicokinetic data may, however, hamper the derivation of HBGVs. Fortunately, PBTK/PBPK modelling may be helpful[9].
- In OSH, legal enforcement seems essential – therefore, there is a need for inclusion of more BLVs in CAD/CMD. There is also a need for distinction between worker's health surveillance and human biomonitoring as part of workplace exposure and risk assessment and guidance for the use and communication of HBM data.

[9] The publication of Boogard et al. (2011) is providing pragmatic guidance on how HBM can be applied in risk characterisation under REACH using DNELs based on the concept of deriving BE. It concludes that coupling HBM data with a dose-response assessment based on internal and/or absorbed dose via use of BE provides a very powerful and scientifically robust approach to conduct RA.

In addition to the evaluation of the different risk assessment schemes we have presented 5 examples on the use of HBM in risk assessment. These include risk assessments of four phthalates (DEHP, BBP, DBP, DiBP), BPA, PFOA, MOCA and flame retardants. First three examples are based on the risk assessments under REACH restriction process, MOCA case is based on the authorisation application made for its use under REACH and flame retardants example is based on the publication by Meek et al (2011), which represents the use of human biomonitoring under WHO mixtures framework. These risk assessment cases describe the advantages of the HBM in the risk assessment; especially related to the refinement of exposure assessment. In addition, like in the case of occupational BPA exposure of cashiers, it can be used to support modelling data, giving a stronger basis for the assessment. In the PFOA case, human epidemiological studies based on the exposure biomonitoring suggest that humans may be more sensitive to the hazardous effects of fluorinated chemicals than rodents. In addition, it also shows challenges related to the interpretation of human epidemiological data, which have, by this far, resulted in the highly variable conclusions on the dose-responses of the hazards of PFOA to humans. In many of these cases there are still room for the refinement of the risk assessment; in PFOA case the need is obvious but also e.g. in the case of BPA the HBM based risk assessment included some uncertainties related for example on the fraction of free BPA available for systemic distribution after dermal exposure. In the case of phthalates, further follow-up of phthalate levels in general population will bring valuable information on the effectiveness of phthalate restriction. Further assessment could take into account also the levels of other, less regulated phthalates.

7 Proposals/recommendations for the better inclusion of HBM in risk assessment and health impact assessment

For the better inclusion of HBM in risk assessment and HIA, the first priority is to develop harmonised guidance for the various phases of HBM (recruiting, sampling, analysis, quality assurance, data management, data assessment, communication, follow-up strategy) in order to ensure the quality of the data collected. In addition, there is a need to:

- Create awareness on the capabilities of HBM and start discussions with regulators at EU and national level on better anchoring of HBM as tool in the various horizontal and vertical EU legislative risk assessment frameworks. This is critical to increase the frequency of use of the HBM tool as well as to create a level playing field for industry in Europe.
- It is important to build further on important existing knowledge. Thus groups of chemicals where the existing knowledge might be sufficient to derive robust health based biomonitoring limit/guidance levels or biological equivalents, should be considered first (this is already on-going under HBM4EU). Successful examples on the use of HBM should be created and collected (also on-going activity under HBM4EU) and used as a basis for the guidance on the use of HBM in RA/HIA.
- The existing HBM data should be integrated with data to be delivered using non-animal testing methods (*in vitro*, *in silico* and HTP screening) in combination with computational modelling (PBTK) to generate more reliable information on toxicokinetic and to provide linkages between AOPs and human internal levels. Well-designed HBM studies should be considered for this development with selection of priority groups of chemicals (e.g. CMR and EDCs).
- HBM has to be incorporated almost by default in European studies addressing exposure to mixtures, since HMB is probably the only way to obtain realistic exposure data regarding mixtures and aggregate exposure to chemicals from different sources. The collection of human biomonitoring data for pesticide workers should be considered to be added as routine component of existing occupational health surveillance programs in Europe.
- HBM data should be used to validate integrated and aggregated external and internal exposure models. 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.

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Annex A

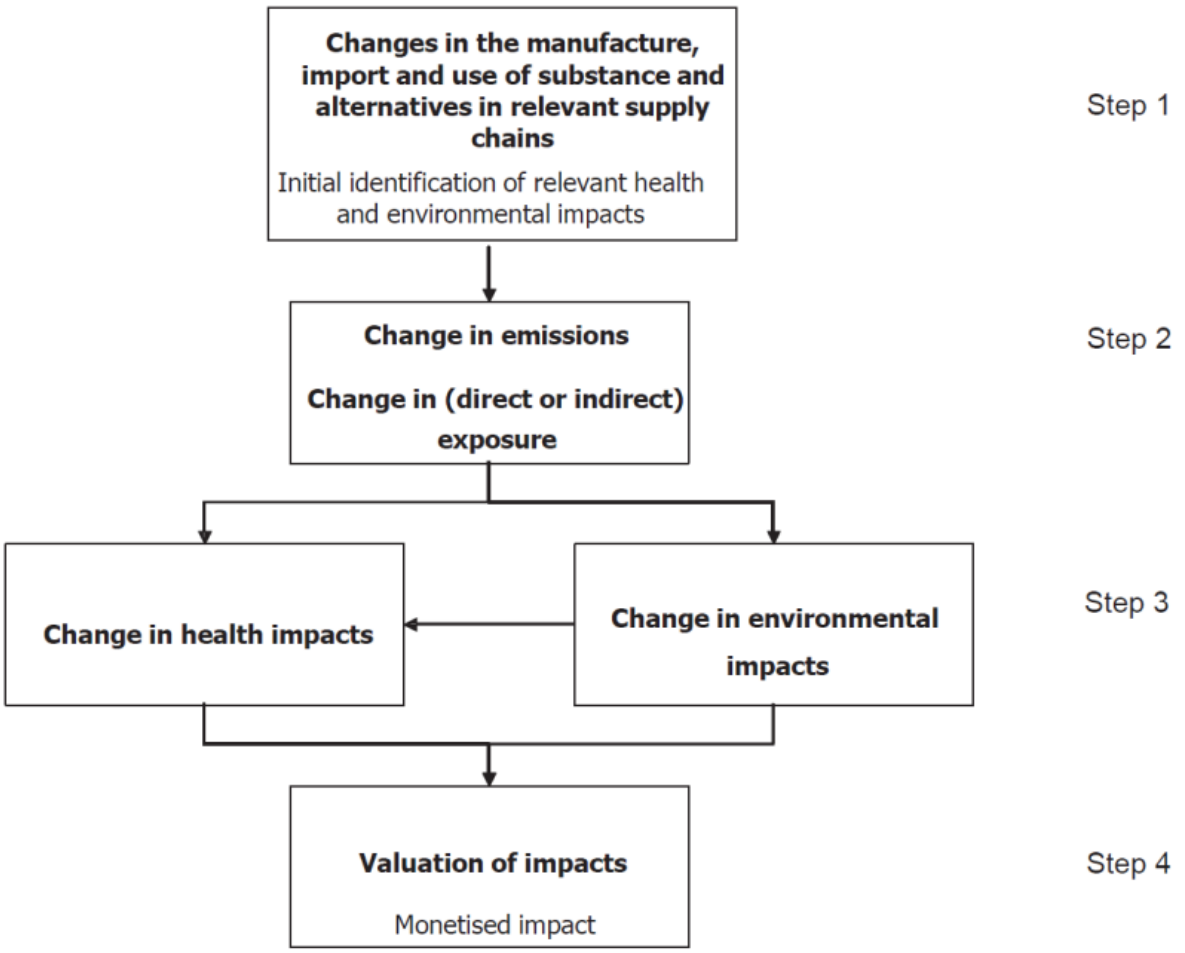


Figure A1: Scheme for assessment of health and environmental impacts. Figure 18 from (ECHA, 2008b)

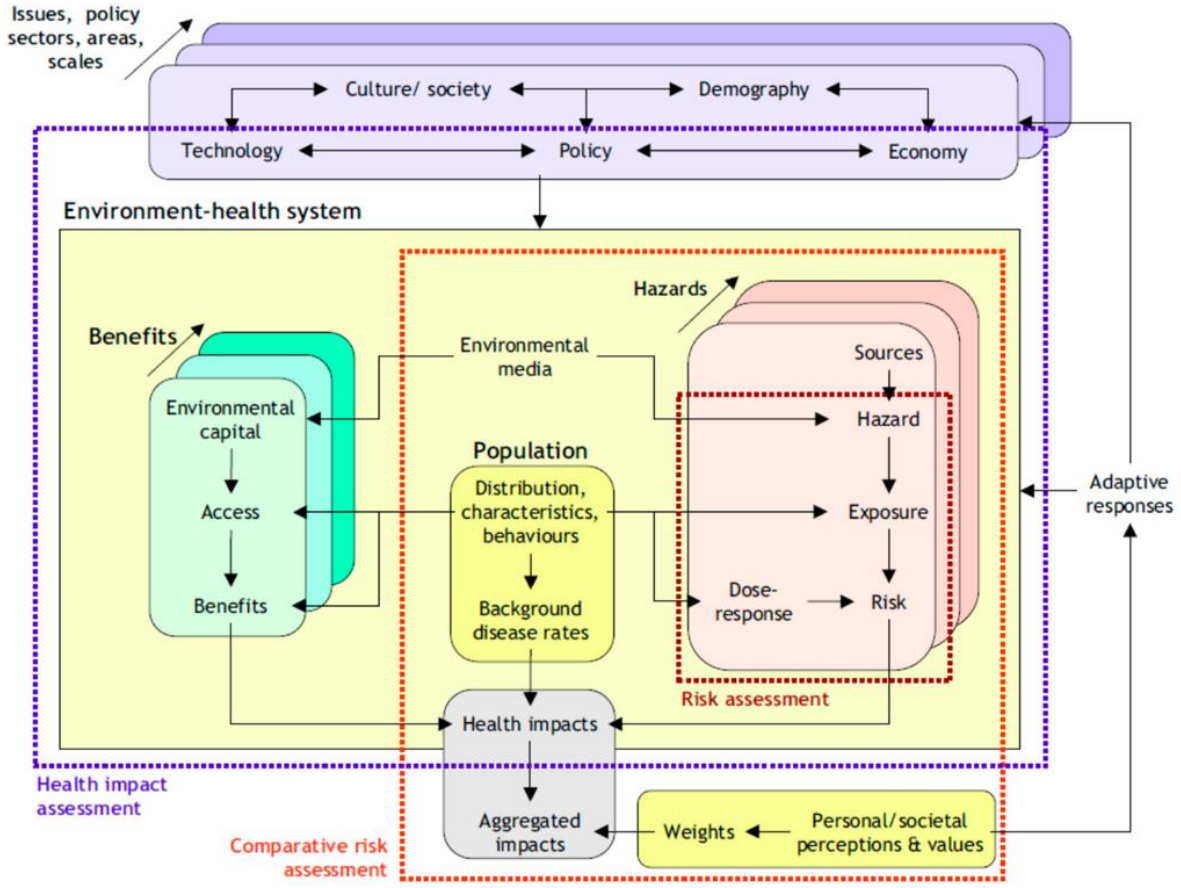


Figure A2: Integrated environmental HIA in relation to other forms of risk and impact assessment (Briggs, 2008)

Annex B

Questionnaire on human biomonitoring (HBM) for risk assessment purposes

Human Biomonitoring (HBM) is an important tool to survey the body burden of humans resulting from exposure to chemicals via different routes (lung, skin, digestive tract). Inclusion of HBM data could improve human health risk assessment of general people (exposure via air, drinking water and food) as well as workers, by providing more accurate data on exposures. In addition, by using HBM it could be possible to make direct linkage between internal exposure and AOPs (adverse outcome pathways) resulting in adverse health effects. Especially if the pollutant has a cumulative effect, and e.g. if the working conditions (personal protection equipment, inter-individual differences in respiratory ventilation, etc.) determine large differences in internal dose between individuals that are not taken into account by atmospheric metrology biomonitoring has proven its usefulness.

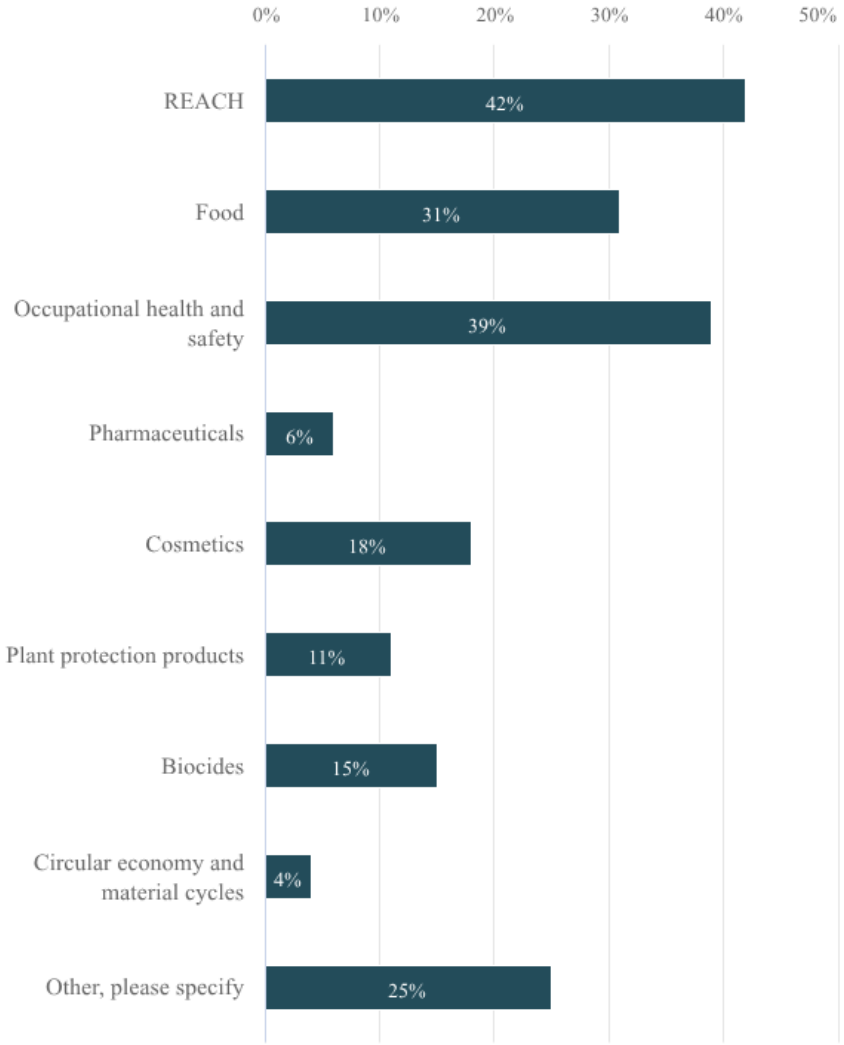
EU-funded project, HBM4EU, aims to develop new European wide biomonitoring based exposure data and exposure-health effect relationships based on internal exposure biomarkers and effect biomarkers for use in the risk assessment of chemicals. The ultimate goal is to improve human risk assessment of priority chemicals and mixtures by more efficient application of HBM. In order to achieve this goal, the current risk assessment practises in different countries and the current use of human biomonitoring in risk assessment of chemicals are evaluated. Therefore, we invite risk assessors, working under different regulatory contexts, to answer the short questionnaire on the use of HBM in risk assessment of chemicals.

You can exit the questionnaire at any time and return later to complete or revise the answers. To do so, please choose "Save & Continue later" and carefully record the address of the return link. After the last page you'll get to the summary page where you can review your answers. To submit the questionnaire click "Finish" at the bottom of the summary page.

Responses will be treated with confidentiality and sensitivity by the researchers. Gathered data will only be used for the purpose of research within HBM4EU and will be presented in an anonymised form.

1. 2. Under which regulatory frameworks are you working? Please select one or more options.

Number of respondents: 71, selected answers: 137



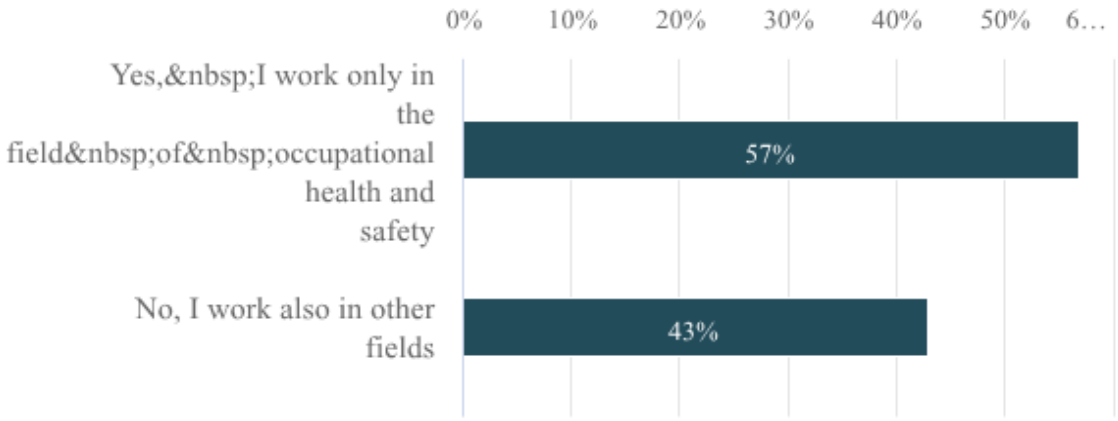
	N	Percent
REACH	30	42,25%
Food	22	30,99%
Occupational health and safety	28	39,44%
Pharmaceuticals	4	5,63%
Cosmetics	13	18,31%
Plant protection products	8	11,27%
Biocides	11	15,49%
Circular economy and material cycles	3	4,23%
Other, please specify	18	25,35%

Answers given into free text field

Option names	Text
Other, please specify	researcher
Other, please specify	Chemical safety
Other, please specify	Food Contact Materials
Other, please specify	CLP
Other, please specify	Specific regulations for pesticides in the public health sector
Other, please specify	Stockholm convention on POPs
Other, please specify	consumer products
Other, please specify	Environmental Health
Other, please specify	Contaminants in food
Other, please specify	BREFs
Other, please specify	POPs, Consumer and construction products, indoor air,
Other, please specify	Toys, Clothing, and other consumer products
Other, please specify	Nanotechnology
Other, please specify	Pharmaceutical veterinary medicines
Other, please specify	Water, air
Other, please specify	CLP
Other, please specify	CLP
Other, please specify	Public health

2. 2.1. If you are working only in the field of occupational health and safety, select "Yes" to move to the questions addressing only those aspects. If your work is divided to other fields as well, select "No" to continue to the questions on human biomonitoring on general population.

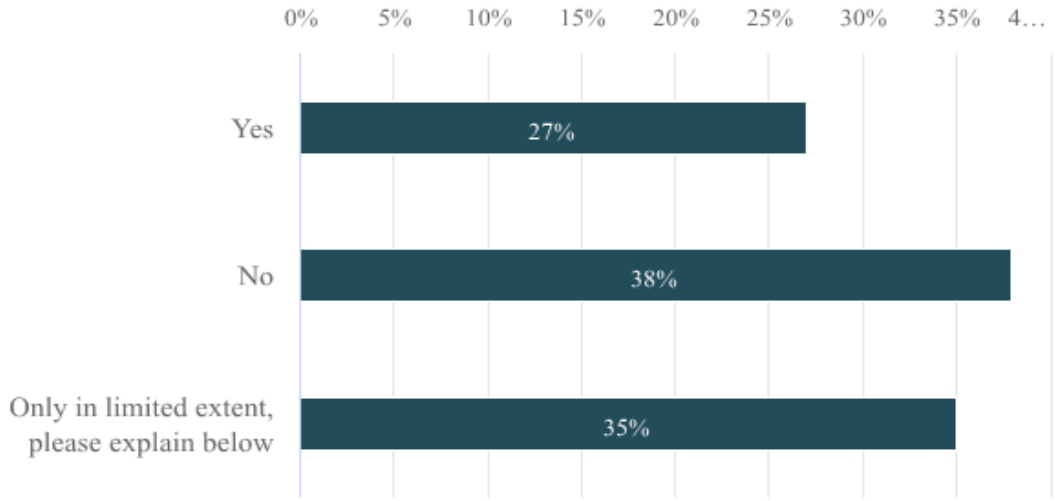
Number of respondents: 28



	N	Percent
Yes, I work only in the field of occupational health and safety	16	57,14%
No, I work also in other fields	12	42,86%

3. 3A. Considering the regulatory field you are working, is human biomonitoring regularly applied in your country?

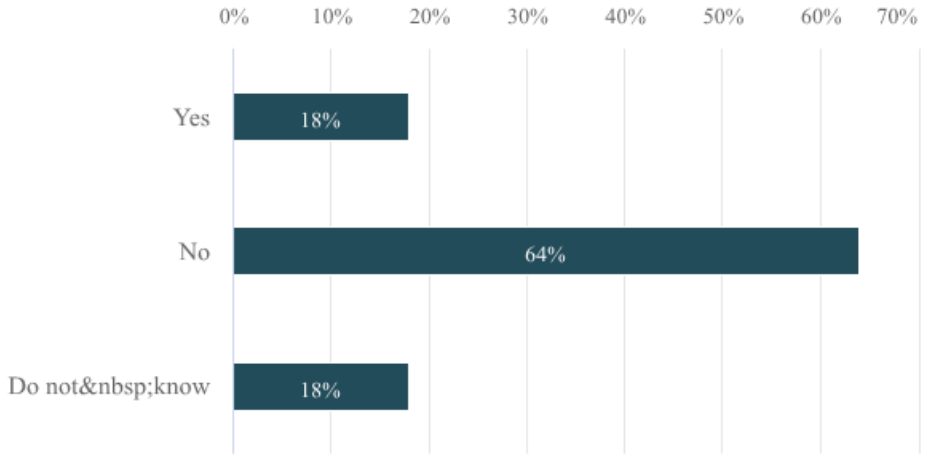
Number of respondents: 55



	N	Percent
Yes	15	27,27%
No	21	38,18%
Only in limited extent, please explain below	19	34,55%

4. 4A. Is there any guidance (regulatory, institutional) for the use of human biomonitoring data for risk assessment in your country?

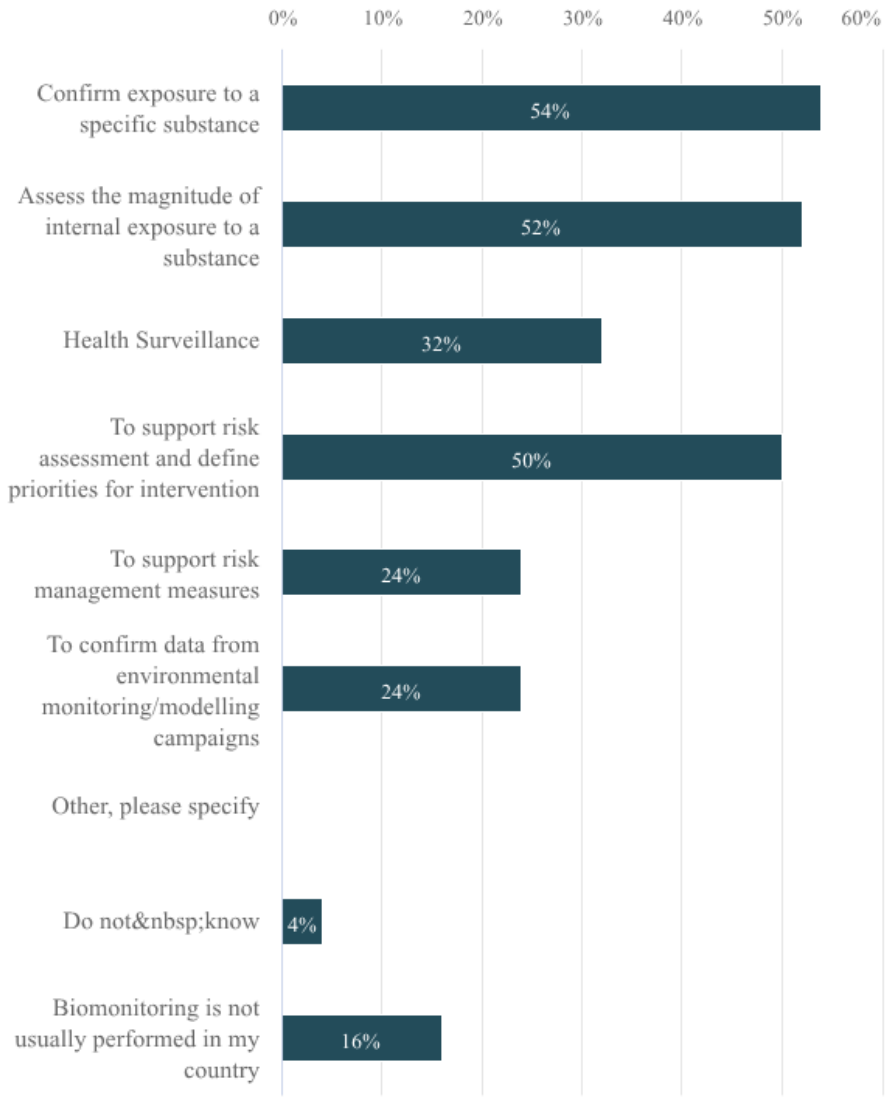
Number of respondents: 55



	N	Percent
Yes	10	18,18%
No	35	63,64%
Do not know	10	18,18%

5. 5A. If applicable in your country, what are the main drivers to start human biomonitoring campaign in general population? Select at maximum three main drivers.

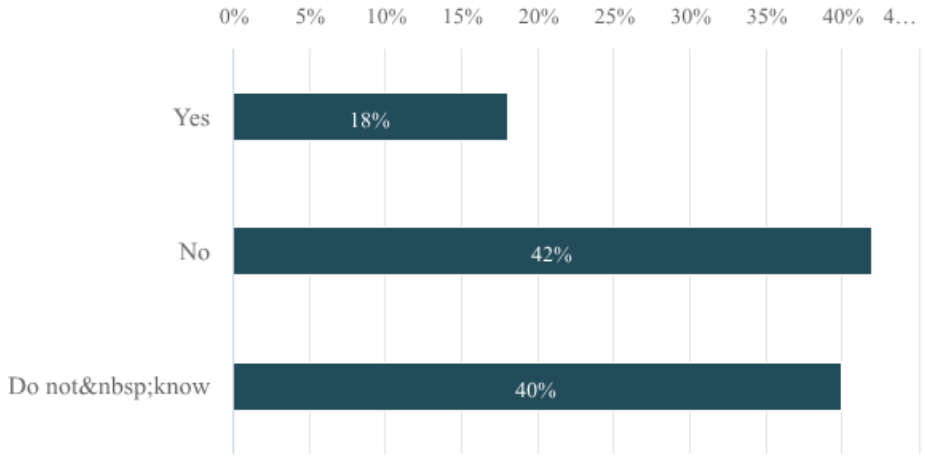
Number of respondents: 50, selected answers: 128



	N	Percent
Confirm exposure to a specific substance	27	54%
Assess the magnitude of internal exposure to a substance	26	52%
Health Surveillance	16	32%
To support risk assessment and define priorities for intervention	25	50%
To support risk management measures	12	24%
To confirm data from environmental monitoring/modelling campaigns	12	24%
Other, please specify	0	0%
Do not know	2	4%
Biomonitoring is not usually performed in my country	8	16%

6. 6A. In your country, is there any specific guidance for the technical and organisational application of HBM?

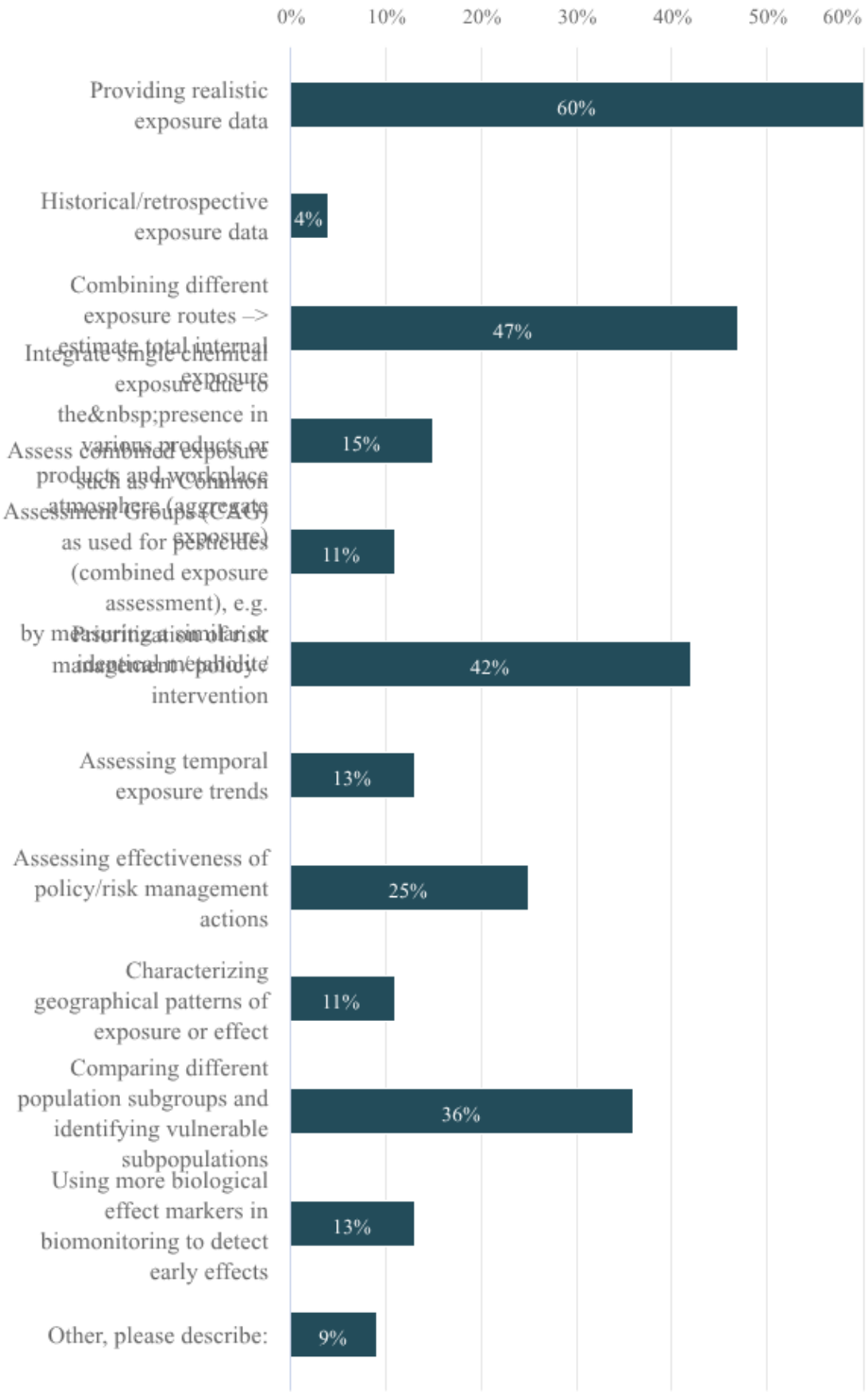
Number of respondents: 55



	N	Percent
Yes	10	18,18%
No	23	41,82%
Do not know	22	40%

7. 7A. In your opinion, how could human biomonitoring best contribute to risk assessment/management and possibly, in a few years from now, with new developments? Select three most important aspects

Number of respondents: 55, selected answers: 157



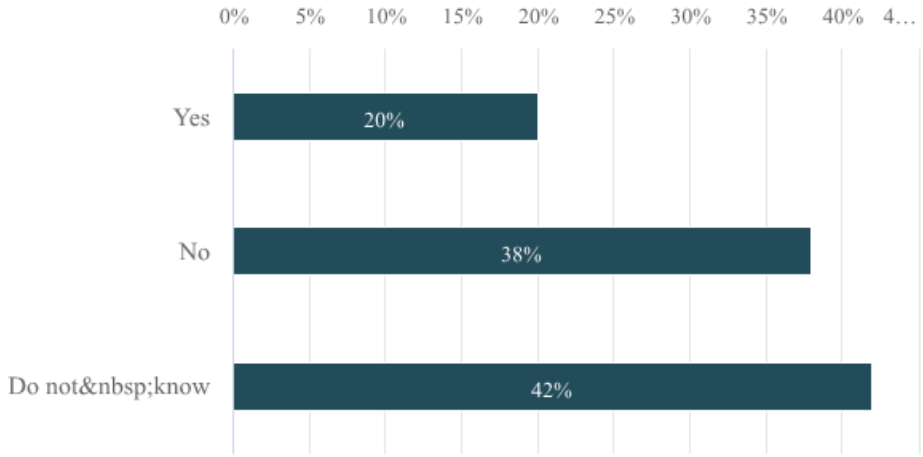
	N	Percent
Providing realistic exposure data	33	60%
Historical/retrospective exposure data	2	3,64%
Combining different exposure routes –> estimate total internal exposure	26	47,27%
Integrate single chemical exposure due to the presence in various products or products and workplace atmosphere (aggregate exposure)	8	14,55%
Assess combined exposure such as in Common Assessment Groups (CAG) as used for pesticides (combined exposure assessment), e.g. by measuring a similar or identical metabolite	6	10,91%
Prioritisation of risk management / policy / intervention	23	41,82%
Assessing temporal exposure trends	7	12,73%
Assessing effectiveness of policy/risk management actions	14	25,45%
Characterising geographical patterns of exposure or effect	6	10,91%
Comparing different population subgroups and identifying vulnerable subpopulations	20	36,36%
Using more biological effect markers in biomonitoring to detect early effects	7	12,73%
Other, please describe:	5	9,09%

Answers given into free text field

Option names	Text
Other, please describe:	Comparision of HBM data with health based guidance values
Other, please describe:	Surveillance of new emerging contaminants of concern
Other, please describe:	Support epidemilogical research
Other, please describe:	These are all very relevant aspects of HBM and all of them would be beneficial.
Other, please describe:	Integrating routes and sources, but with the remark that source contribution (often needed for policy makers) is very difficult!

8. 8A. In your country, do you use or have you used DNA or protein adducts as a marker of exposure in the risk assessment?

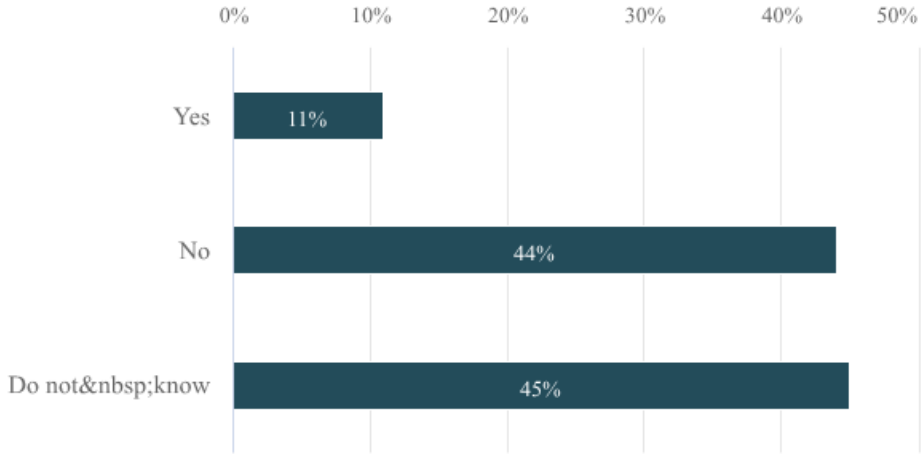
Number of respondents: 55



	N	Percent
Yes	11	20%
No	21	38,18%
Do not know	23	41,82%

9. 9A. In your country, do you use or have you used biomarkers of effect (including e.g. “omics”-based markers) in the risk assessment?

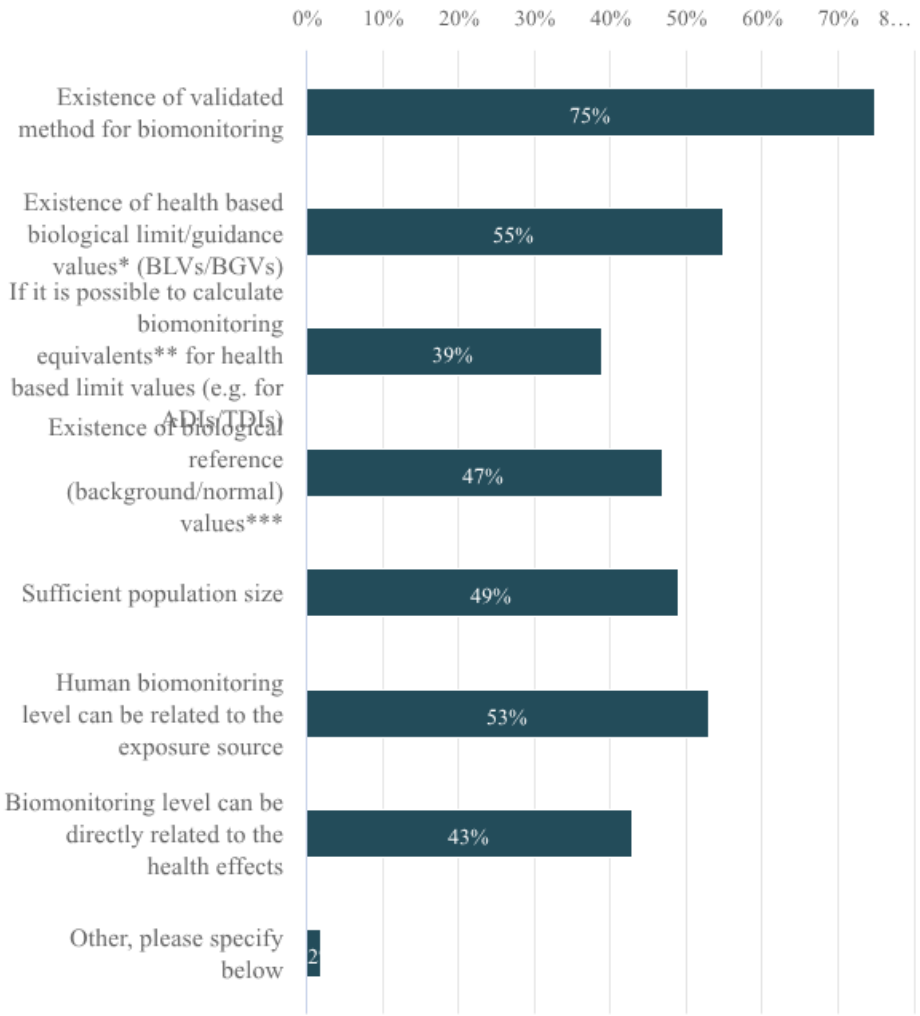
Number of respondents: 55



	N	Percent
Yes	6	10,91%
No	24	43,64%
Do not know	25	45,45%

10.10A. What are your criteria for using human biomonitoring data in risk assessment? Please tick all relevant options.

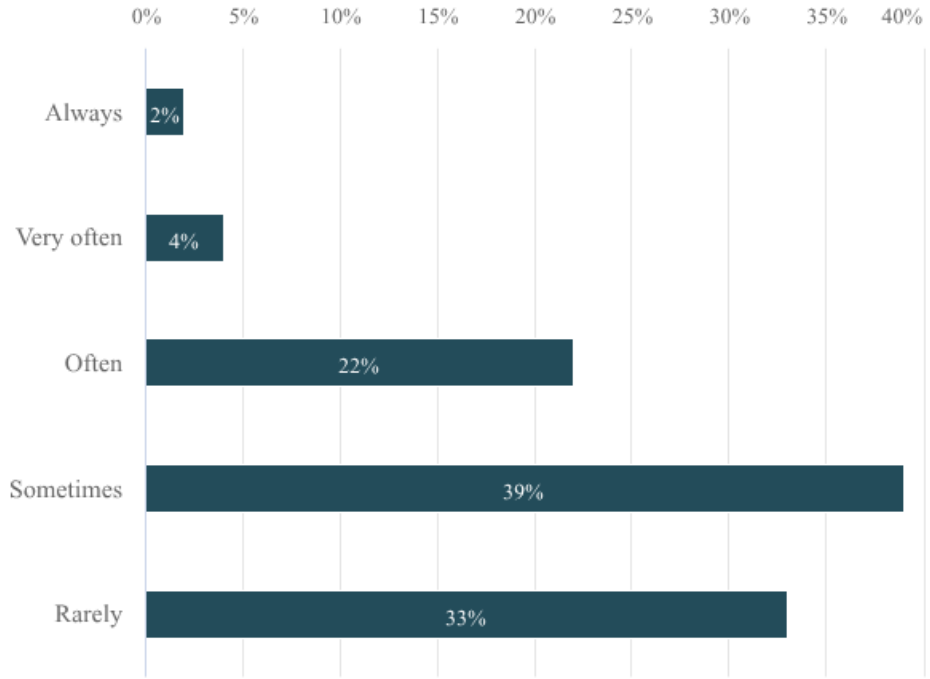
Number of respondents: 51, selected answers: 185



	N	Percent
Existence of validated method for biomonitoring	38	74,51%
Existence of health based biological limit/guidance values* (BLVs/BGVs)	28	54,9%
If it is possible to calculate biomonitoring equivalents** for health based limit values (e.g. for ADIs/TDIs)	20	39,22%
Existence of biological reference (background/normal) values***	24	47,06%
Sufficient population size	25	49,02%
Human biomonitoring level can be related to the exposure source	27	52,94%
Biomonitoring level can be directly related to the health effects	22	43,14%
Other, please specify below	1	1,96%

11.11A. According to your experience, how often can your criteria for using human biomonitoring data in risk assessment be fulfilled?

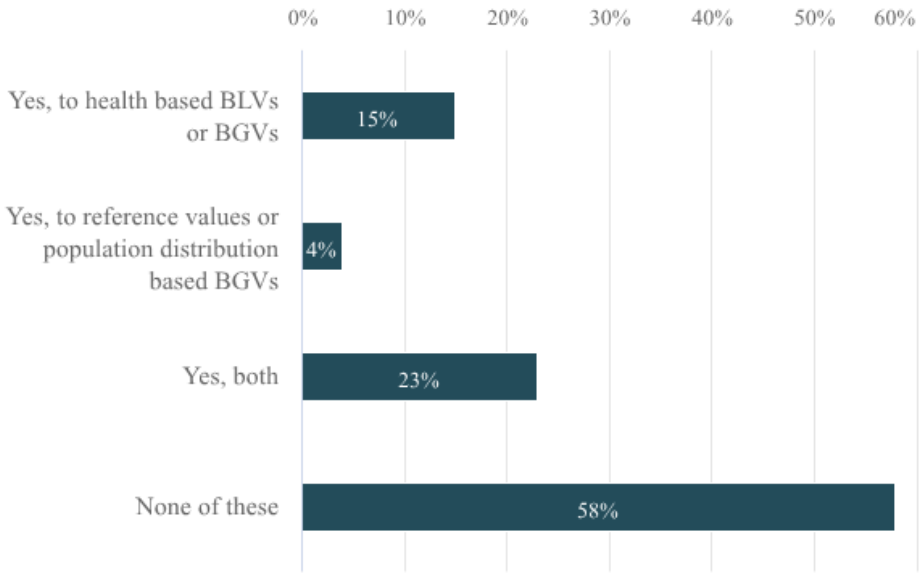
Number of respondents: 49



	N	Percent
Always	1	2,04%
Very often	2	4,08%
Often	11	22,45%
Sometimes	19	38,78%
Rarely	16	32,65%

12.12A. In your country, are HBM results of the general population usually compared to biological limit values (BLVs)/biological guidance values (BGVs) or reference values set for general population?

Number of respondents: 48



	N	Percent
Yes, to health based BLVs or BGVs	7	14,58%
Yes, to reference values or population distribution based BGVs	2	4,17%
Yes, both	11	22,92%
None of these	28	58,33%

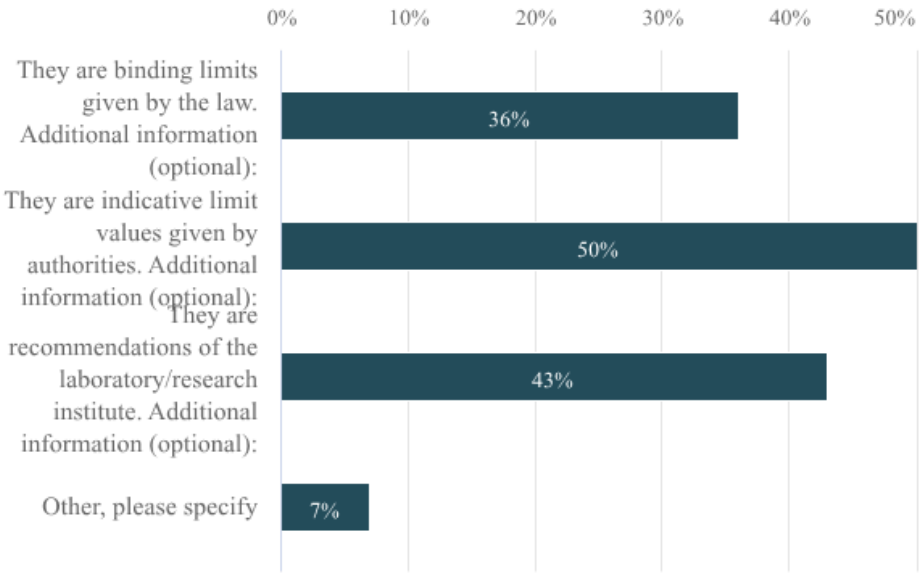
13.12A.1. Please specify the substances for which there is a BLV or a BGV in your country. You can also provide a link to the list of BLVs or attach a list as an attachment.

Number of respondents: 13

Responses
1) German HBMI values 2) Biomonitoringequivalents (summit toxicology) derived by different international organisations (EFSA, USEPA, etc.)
Please consult Tiina Santonen@ttl.fi
See SCOEL list
In case of need, reference and HBM values are taken from the German Umweltbundesamt; see the list there
Please address to the Austrian Umwelbundesamt
We refer to HBM values of the German HBM Commission and other health based HBM values; for Occupational Risk assessment some BAT values are listed in the respective Regulation
Use of internationally derives limit/guidance values
www.rivm.nl/bibliotheek/rapporten/609300023.pdf See appendix 7 for the Biological Limit Values
For contaminants in food, biomonitoring levels are compared with the levels used as basis for setting TDIs at EFSA. For instance: - The blood Pb concentration associated with 2% increase in blood pressure at population level or the one Associated with a 1% decreased IQ in children or with increased risk of kidney disease in the adult population. - The urinary Cd level considered safe by EFSA in relation to kidney disease - The blood Hg concentration not associated with adverse cognitive effects in children
https://www.ciop.pl
Toluène Styrène DEHP acrylamide BBP DBP hexavalent chromium and his compounds 2-butoxyéthanol & acetate
BLV (D.Lgs 106/09): Pb blood 60 µg/100 ml (40 µg/100 ml women<45 years) RVs from various sources: A. Alimonti, B. Bocca, D. Mattei, A. Pino. Programme for Biomonitoring the Italian Population Exposure (PROBE): Internal Dose of Metals. Istituto superiore di sanità. Rapporti Istisan 11/9 (2011) SIVR. Terza lista dei valori di riferimento per elementi, composti organici e loro metaboliti. Edizione 2011. Società Italiana Valori di Riferimento, 2011 Aprea C., Catenacci G. Valori di riferimento degli Antiparassitari. G Ital Med Lav Erg. 2003, 25(1):37-60

14. 12A.2. What is the legal status of these values?

Number of respondents: 14, selected answers: 19



	N	Percent
They are binding limits given by the law. Additional information (optional):	5	35,71%
They are indicative limit values given by authorities. Additional information (optional):	7	50%
They are recommendations of the laboratory/research institute. Additional information (optional):	6	42,86%
Other, please specify	1	7,14%

Answers given into free text field

Option names	Text
They are binding limits given by the law. Additional information (optional):	This is true for occupational limit values. They do not directly apply to environmental exposures, but can be used for comparison
They are binding limits given by the law. Additional information (optional):	https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=10009034
They are binding limits given by the law. Additional information (optional):	Only for lead in blood
They are binding limits given by the law. Additional information (optional):	only for blood lead
They are binding limits given by the law. Additional information (optional):	D.Lgs 106/09
Other, please specify	Not aware

Option names	Text
They are recommendations of the laboratory/research institute. Additional information (optional):	Yes, in Biotox a database produce by INRS. http://www.inrs.fr/publications/bdd/biotox.html
They are recommendations of the laboratory/research institute. Additional information (optional):	A. Alimonti, B. Bocca, D. Mattei, A. Pino. Programme for Biomonitoring the Italian Population Exposure (PROBE): Internal Dose of Metals. Istituto superiore di sanità (2011)
They are indicative limit values given by authorities. Additional information (optional):	German HBM values widely accepted in Austria
They are indicative limit values given by authorities. Additional information (optional):	SIVR

15. 13A. For the substances for which no BLV or BGV exists, what references do you use to interpret data (e.g. BLV or BGV from other countries)?

Number of respondents: 33

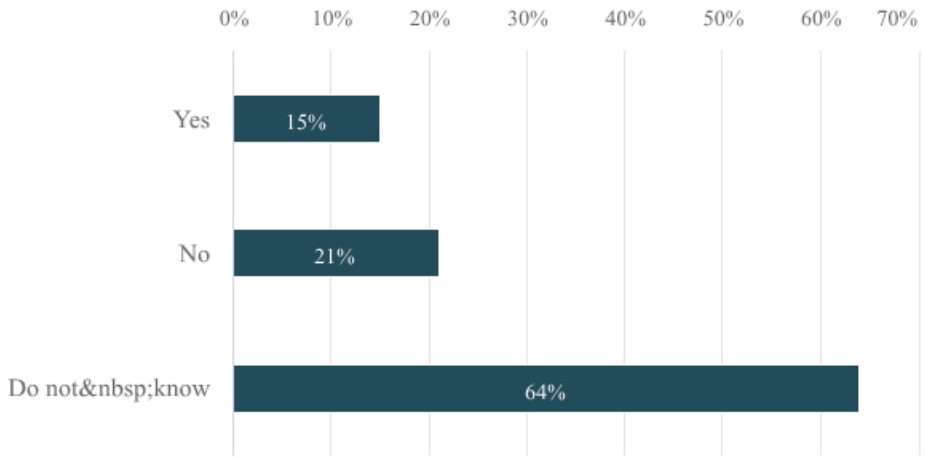
Responses
Comparison references values other countries
Reference values from other countries
No experience.
We do not have much experience of using HBM data under REACH. DNELs and DMELs are used in REACH.
We use international results
Do not know (POPs?)
Calculate biomonitoring equivalents for health based limit values
All available data can in principle be used case by case. I am not aware of any "official" Swedish BLV/BGVs for the general population
Exposure reference values (e.g. for food health based guidance values), Clinical reference values (i.e. GFR)
BLV or BGV from other countries, or described in the literature.
Non
See answer to 12A
BLV or BGV from other countries
Levels at which effects were reported in epidemiological and/or toxicological studies. Reference values, expert opinion
Probably such values would be used from other countries if available.
HBM is rarely used in the general population. Only after incidents (eg PFOA - Du Pont) In that case RIVM derived a reference value.
Rarely BE values from other countries

Responses
HBM values of the German HBM-Commission, Values derived by ECHA, EFSA, WHO, ATSDR, Health Canada and others
ACGIH, BAT, WHO, CDC, NAHES
Question 12A should be answered by the Federal Environmental Agency (UBA). HBM data (e.g., urinary concentrations of metabolites of phthalates and BPA) can be used for back-calculating internal exposure, which in turn can be compared to TDI values.
Use of internationally derives limit/guidance values
Measurements in control populations
Yes, or back calculate (if data allow) to (external) exposure estimates
We don´t have experience of using HBM under REACH and Biocides
BLV or BGV from other countries Literature data about dose-response
I do not know.
In France, INRS has a website (Biotox) in which reference values from other countries or institutions are listed (e.g. SCOEL, ACGIH, DFG, FIOH etc.)
BLV or BGV from other countries
No experience.
RVs from Other Countries: C. Schulz, M. Wilhelm, U. Heudorf, M. Kolossa-Gehring. Update of the reference and HBM values derived by the German Human Biomonitoring Commission. Int. J. Hyg. Environ. Health, 215 (2011), pp. 26-35 CDC (Centers for Disease Control and Prevention). National Report on Human Exposure to Environmental Chemicals. Department of Health and Human Services Atlanta, GA (2001) U. Ewers, C. Krause, C. Schulz, M. Wilhelm. Reference values and human biological monitoring values for environmental toxins. Int. Arch. Occup. Environ. Health, 72 (1999), pp. 255-260 D. Haines, G. Saravanabhavan, K. Werry, C. Khoury. An overview of human biomonitoring of environmental chemicals in the Canadian Health Measures Survey: 2007 to 2019. Int. J. Hyg. Environ. Health, 220 (2017), pp. 13-28. A. Batáriová, V. Spěváčková, B. Beneš, M. Čejchanová, J. Šmíd, M. Černá. Blood and urine levels of Pb, Cd and Hg in the general population of the Czech Republic and proposed reference values. Int. J. Hyg. Environ. Health, 209 (2006), pp. 359-366. C. Freire, R.J. Koifman, D. Fujimoto, F. de Oliveira Souza Vanessa Cristina Barbosa, S. Koifman. Reference values of cadmium, arsenic and manganese in blood and factors associated with exposure levels among adult population of Rio Branco, Acre, Brazil. Chemosphere, 128 (2015), pp. 70-78. Schoeters G, Den Hond E, Colles A, Loots I, Morrens B, Bruckers L et al. (2012). The Flemish Environment and Health Study (FLEHS) – Second Survey (2007–2011): Establishing Reference Values for Biomarkers of Exposure in the Flemish Population. In: Knudsen E, Merlo DF, editors. Biomarkers and human biomonitoring. Volume 1. London: Royal Society of Chemistry, 135–165 (Issues in Toxicology, No.1). Fréry N, Vandentorren S, Etchevers A, Fillol C (2012). Highlights of recent studies and future plans for the French human biomonitoring (HBM) programme. Int J Hyg Environ Health, 215(2):127–32. Castaño A, Sánchez-Rodríguez JE, Cañas A, Esteban M, Navarro C, Rodríguez-García AC et al. (2012). Mercury, lead and cadmium levels in the urine of 170 Spanish adults: a pilot human biomonitoring study. Int J Hygiene Environ Health, 215(2):191–5. Snoj Tratnik J, Mazej D, Horvat M (2012). Human biomonitoirng studies in Slovenia – toxic metals, arsenic and essential elements. In: Human Biomonitoring (HBM) – Linking Environment to Health and Supporting

Responses
Policy. Proceedings of the Conference, Larnaca, Cyprus, 22–25 October 2012. Nicosia: Ministry of Health, 88. Smolders R, Den Hond E, Koppen G, Govarts E, Willems H, Casteleyn L et al. (2014). Interpreting biomarker data from the COPHES/DEMOCOPHES twin projects: Using external exposure data to understand biomarker differences among countries. Environ Res. doi: 10.1016/j.envres.2014.08.016 [Epub ahead of print]. Wookhee Choi, Suejin Kim, Yong-Wook Baek, Kyungho Choi, Keejae Lee, Sungkyoon Kim, Seung Do Yu, Kyunghee Choi. Exposure to environmental chemicals among Korean adults-updatesfrom the second Korean National Environmental Health Survey (2012–2014). International Journal of Hygiene and Environmental Health 220 (2017) 29–35 Biolomonitoring equivalents (BEs): Cd in urine (Hays et al., 2008); As inorganic in urine (Hays et al., 2010)
No experience

16. 14A. Is there work going on to elaborate health based limit values for general population in your country?

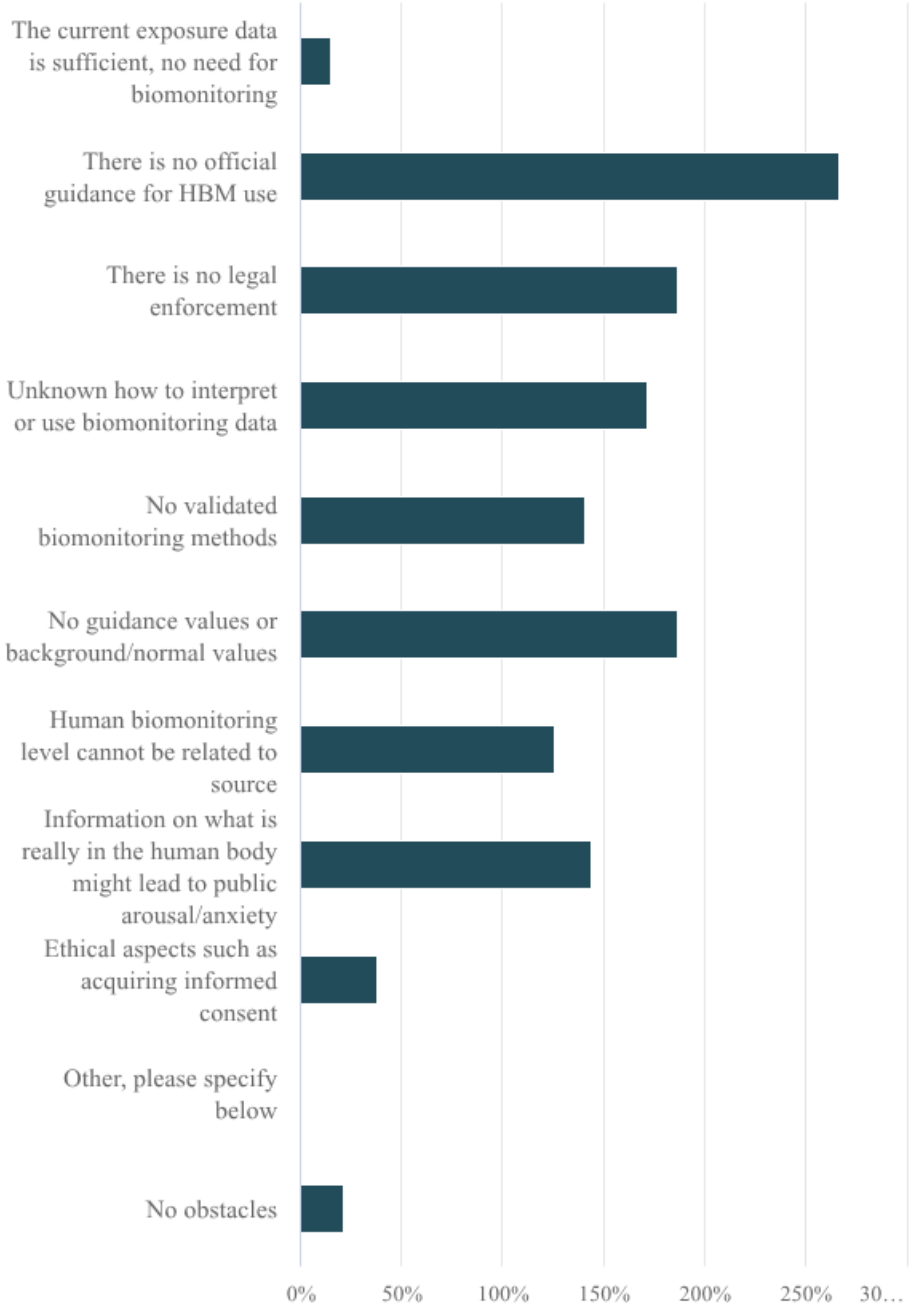
Number of respondents: 53



	N	Percent
Yes	8	15,09%
No	11	20,76%
Do not know	34	64,15%

17. 15A. What are the important obstacles you face when applying biomonitoring data in the risk assessment of general population? Please fill in matrix for the chemicals in general and for the following priority compounds. Notice that the table needs to be scrolled to the right to see the rest of the columns!

Number of respondents: 39, selected answers: 506



	Chemicals (in general)	Phthalates/DINCH	Bisphenols	Per-/Polyfluorinated compounds	Flame Retardants	Cd, Cr	PAHs and air pollutants	Anilin family, e.g. MOCA	Chemical mixtures (pesticide mixtures)	Emerging chemicals	Total	Average	Median
The current exposure data is sufficient, no need for biomonitoring	1	2	0	0	0	1	1	0	1	0	6	4,5	4
	16,66%	33,33%	0%	0%	0%	16,67%	16,67%	0%	16,67%	0%			
There is no official guidance for HBM use	17	8	8	11	9	11	10	7	12	11	104	5,35	5
	16,35%	7,69%	7,69%	10,58%	8,65%	10,58%	9,61%	6,73%	11,54%	10,58%			
There is no legal enforcement	17	6	6	8	6	6	8	5	6	5	73	4,73	4
	23,28%	8,22%	8,22%	10,96%	8,22%	8,22%	10,96%	6,85%	8,22%	6,85%			
Unknown how to interpret or use biomonitoring data	14	6	6	5	6	4	4	5	10	7	67	5,16	5
	20,9%	8,95%	8,95%	7,46%	8,96%	5,97%	5,97%	7,46%	14,93%	10,45%			
No validated biomonitoring methods	12	4	4	6	5	5	5	2	6	6	55	5,02	5
	21,82%	7,27%	7,27%	10,91%	9,09%	9,09%	9,09%	3,64%	10,91%	10,91%			
No guidanc	16	5	4	9	8	6	7	3	6	9	73	5,03	5

	Chemicals (in general)	Phthalates/DINCH	Bisphenols	Per-/Polyfluorinated compounds	Flame Retardants	Cd, Cr	PAHs and air pollutants	Anilin family, e.g. MOCA	Chemical mixtures (pesticide mixtures)	Emerging chemicals	Total	Average	Median
e values or background/normal values	21,91%	6,85%	5,48%	12,33%	10,96%	8,22%	9,59%	4,11%	8,22%	12,33%			
Human biomonitoring level cannot be related to source	10	5	5	6	4	5	4	2	4	4	49	4,67	4
	20,41%	10,21%	10,21%	12,25%	8,16%	10,2%	8,16%	4,08%	8,16%	8,16%			
Information on what is really in the human body might lead to public arousal/ anxiety	14	4	4	5	4	4	4	4	7	6	56	5,02	5
	25%	7,15%	7,14%	8,93%	7,14%	7,14%	7,14%	7,14%	12,5%	10,72%			
Ethical aspects such as acquiring informed consent	6	1	1	1	1	1	1	1	1	1	15	4	3
	40%	6,66%	6,66%	6,66%	6,67%	6,67%	6,67%	6,67%	6,67%	6,67%			
Other, please	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	-			

	Chemicals (in general)	Phthalates/DINCH	Bisphenols	Per-/Polyfluorinated compounds	Flame Retardants	Cd, Cr	PAHs and air pollutants	Anilin family, e.g. MOCA	Chemical mixtures (pesticide mixtures)	Emerging chemicals	Total	Average	Median
specify below													
No obstacles	2	2	1	2	1	0	0	0	0	0	8	2,75	2,5
	25%	25%	12,5 %	25%	12,5 %	0%	0%	0%	0%	0%			
Total	109	43	39	53	44	43	44	29	53	49	506	4,96	5

18. 16A. In case it is possible to perform a health impact assessment based on HBM data, do you think this could be of additional value to assess certain policy goals (prospective and retrospective)? If yes, can you give an example?

Number of respondents: 34

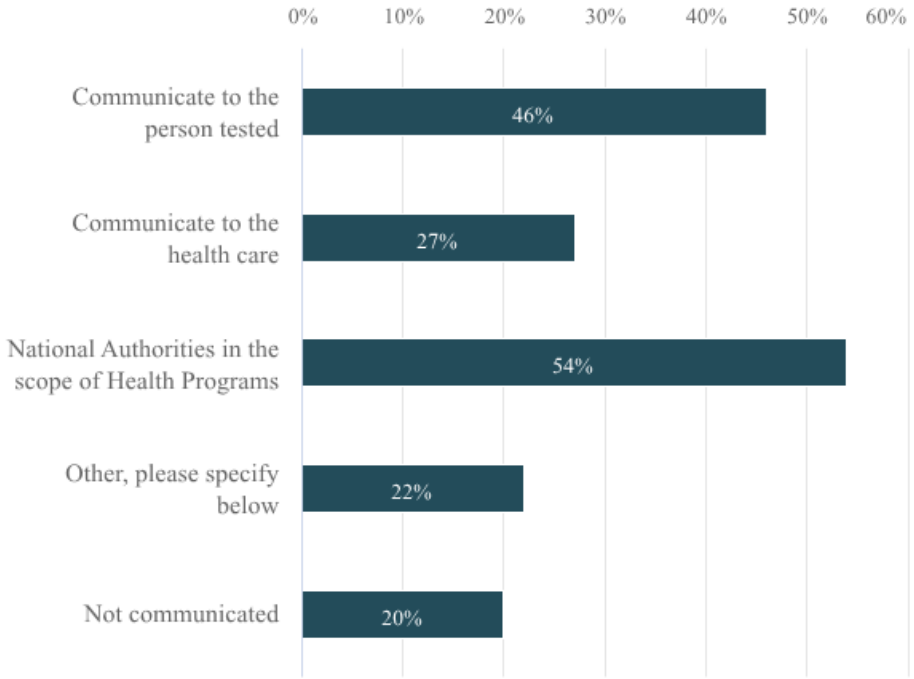
Responses
Yes, it's more convincing for policymakers. e.g. lead reduction in blood and avoidance of IQ loss in children
-
Yes, it is of additional value to assess certain policy goals
Yes. We are using HBM data to monitor exposure of the general population to organophosphate pesticides, following a regulatory intervention.
Evidence of exposure of certain chemicals
HBM can be used to prioritise management of chemicals, if it is posible to rank the chemicals according to the risk.
Yes -It can help for risk assessment, to identify emerging health concern and to protect vulnerable population. -To support regulatory measures (e.g. restriction) and assess their effectiveness -To assess application for authorisation

Responses
-Identification of bioaccumulative substances
Yes, in order to prioritise policy actions (e.g. DALYs determination regarding toxic compounds)
Yes. mainly because the results would possibly be less speculative. It might also be reassuring if no or low exposures can be confirmed by HBM
At this moment it is difficult to assess the risk for example acrylamide. Biomonitoring could be a way forward to assess the current and furture (after certain policy options) risk. HBM data could be of additional value to assess policy goals.
Validation of dietary exposure assessement. Corrolation between HBM data and health effects.
Yes. An important example of using HBM data in Brazil would be to access the real health protection impact provided by recent regulations imposed for mycotoxins in foods.
Good example may be phthalates, upon their risk assessment are already based numerous legal acts, e.g. in REACH, in cosmetics, food contact materials
Yes, we have applied this in the case of accidental exposure of a village to arsenic in drinking water.
I do not understand the question. HBM measures exposure. It does not directly inform about health impact. It might help establishing a causal association between exposure and effect in a scientific study though. But how is it applied in impact assessment? HBM can inform about the success of policy measures (e.g. documenting downward trends in exposure)
Yes, e.g. like it has been done for the lates phthalates restriction proposal prepared by ECHA and Denmark
Yes. The main problem in epidemiology is exposure assessment. When a clear dose-respponse relationship between internal exposure and a health effect is found, measures to reduce the exposure can be taken, and incorporated in prospective policy goals.
Yes
at European Level (e.g. phthalate restricition based on HBM exposure data and risk assessment as well as calculating the magnitude of adverse effects and their costs) at International Level (UNEP: human biomonitoring data are an essential part of the risk profiles which are basis for listing substances under the convention. In Austria: reduction of residue Limits of HCB in food due to high Body burdens in a Population living in a contaminated area
Lead regulatory environment - lower values over years due to regulations and changed practices
Phthalates
HBM can show internal concentrations. Useful for validation of exposure models and better estimation of intake routs if these models are linked to the HBM values
Yes, but only dependent on the policy question, so only when relevant.
Possibly

Responses
Yes, health impact assessment based on HBM data is of additional value to assess certain policy goals. Example: phthalates
Yes, policy goal should be to prevent exposure exceeding safe levels
No
I think HBM data could be used to perform a health impact assessment.
Yes, lead free fuels
Yes, I think this could be of additional value to assess our certain policy goals. It could help to prioritise policy goals as well as it allow to estimate current situation for the chemicals in general and/or for the certain priority compounds like phthalates or heavy metals in the different matrices (blood, urine etc.)
YES We used data on lead level among children in certain polluted area (Mezica) as an indicator of efficiency of the measures
Yes Example: A PFAS water contamination occurred in Veneto (Italy), and local policy makers undertaken a series of measures (e.g. carbon filters on the water supply system) to limit exposure of people residing in the areas interested by contamination. In order to assess the extent of the human exposure they also asked ISS to perform a HBM study that evidenced high serum PFAS concentrations in exposed subjects. As a consequence of HBM results health protection measures were added to actions to limit exposure, in particular a special health surveillance plan for overexposed subjects.
yes
Of course. By measuring the concentration of chemicals in body, biomonitoring allows to define exposure of chemicals and this data can be directly linked to epidemiological surveys, in order to estimate exposure-response relationships and provide valuable information on potential health risks.

19. 17A. How do you communicate biomonitoring data in case of general population? Tick all options that apply

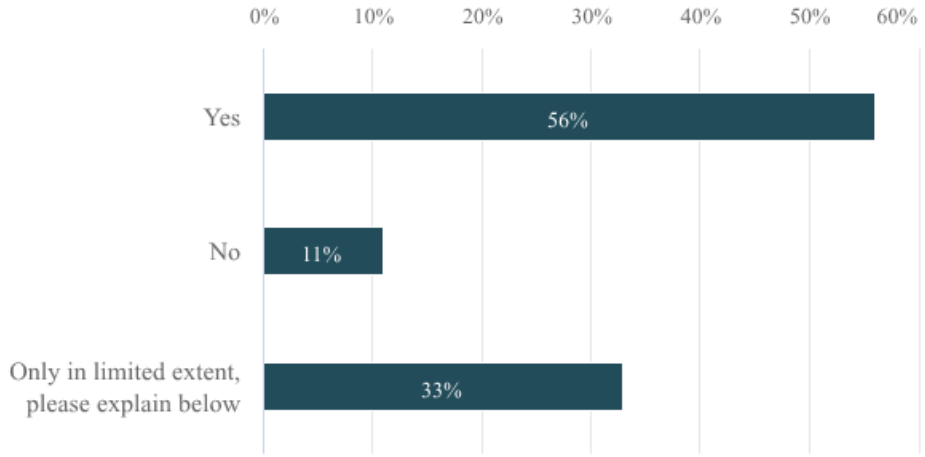
Number of respondents: 41, selected answers: 69



	N	Percent
Communicate to the person tested	19	46,34%
Communicate to the health care	11	26,83%
National Authorities in the scope of Health Programs	22	53,66%
Other, please specify below	9	21,95%
Not communicated	8	19,51%

20. 3B. Is human biomonitoring regularly applied in your country in occupational safety and health?

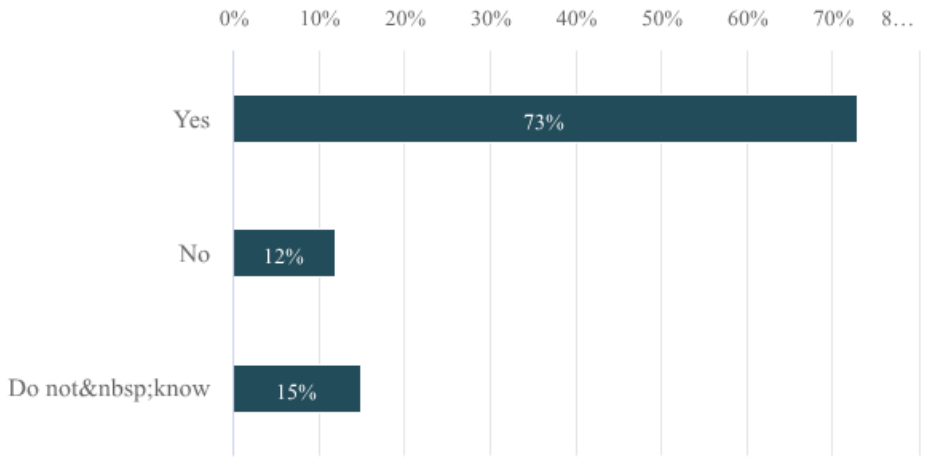
Number of respondents: 27



	N	Percent
Yes	15	55,56%
No	3	11,11%
Only in limited extent, please explain below	9	33,33%

21. 4B. Is there any guidance (regulatory, institutional) for the use of human biomonitoring in the risk assessment at workplaces in your country?

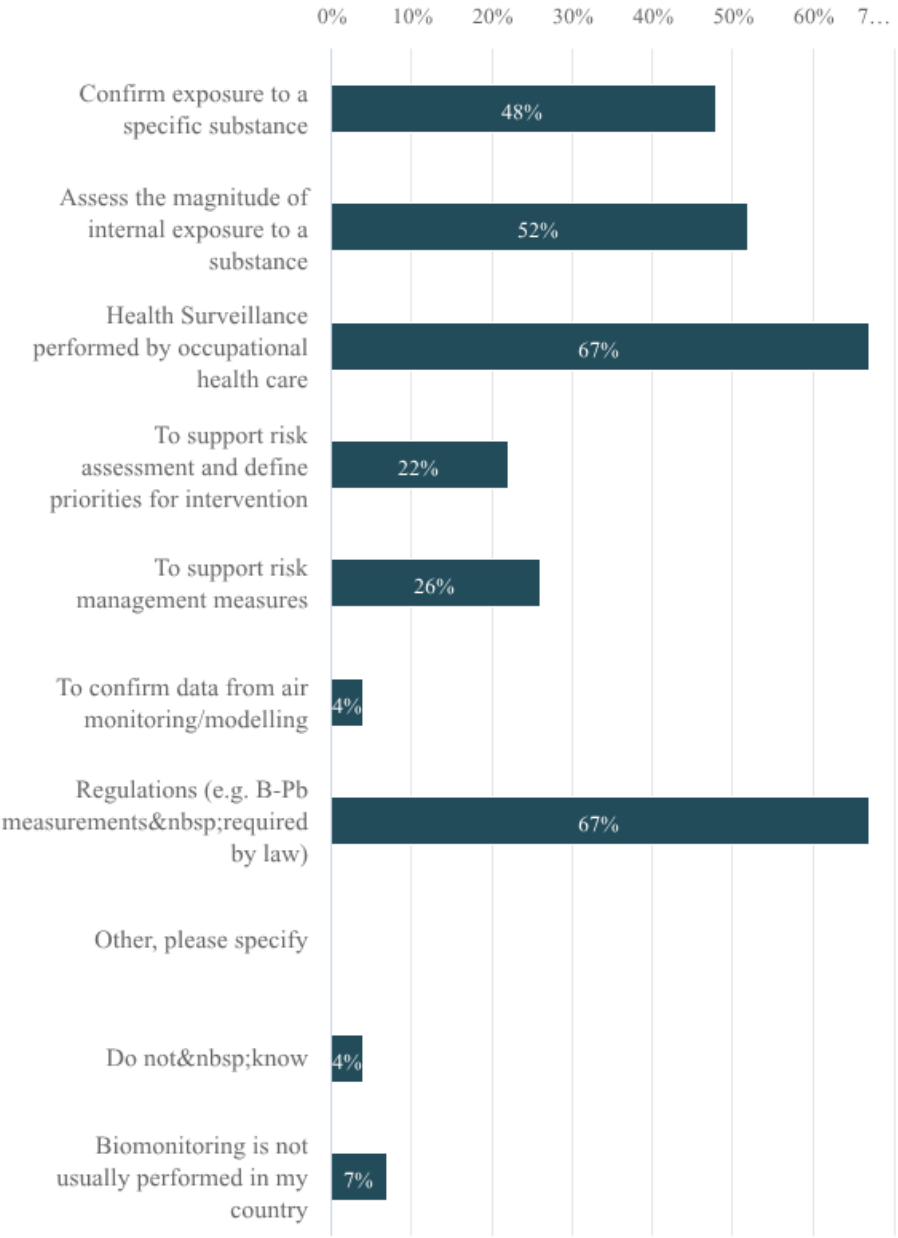
Number of respondents: 26



	N	Percent
Yes	19	73,08%
No	3	11,54%
Do not know	4	15,38%

22. 5B. If applicable in your country, what are the main drivers to perform biomonitoring at occupational settings? Select at maximum three main drivers

Number of respondents: 27, selected answers: 80

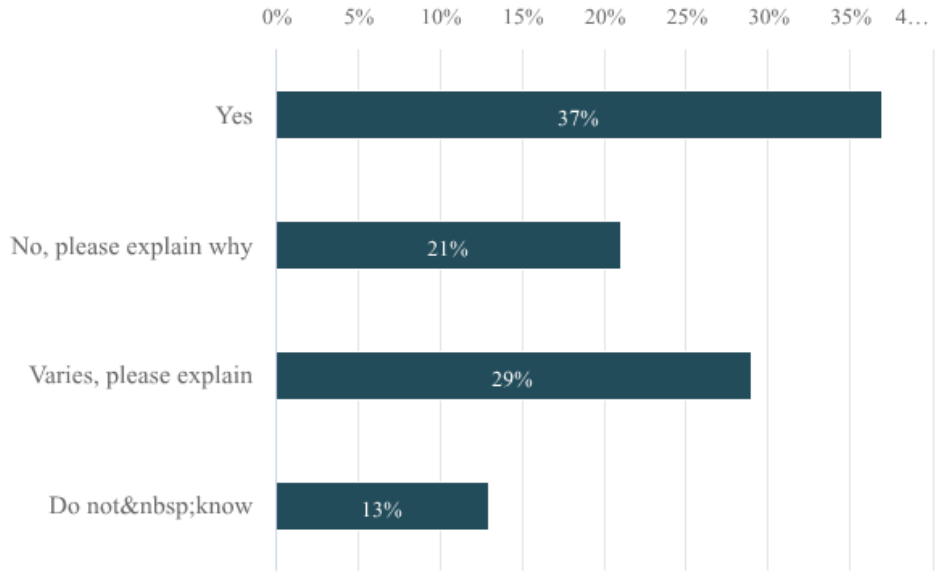


	N	Percent
Confirm exposure to a specific substance	13	48,15%
Assess the magnitude of internal exposure to a substance	14	51,85%
Health Surveillance performed by occupational health care	18	66,67%
To support risk assessment and define priorities for intervention	6	22,22%
To support risk management measures	7	25,93%

	N	Percent
To confirm data from air monitoring/modelling	1	3,7%
Regulations (e.g. B-Pb measurements required by law)	18	66,67%
Other, please specify	0	0%
Do not know	1	3,7%
Biomonitoring is not usually performed in my country	2	7,41%

23. 6B. If one of the main drivers to perform biomonitoring at workplaces is health surveillance made by occupational health care, are the biomonitoring data available for use in exposure assessment and management at the workplace?

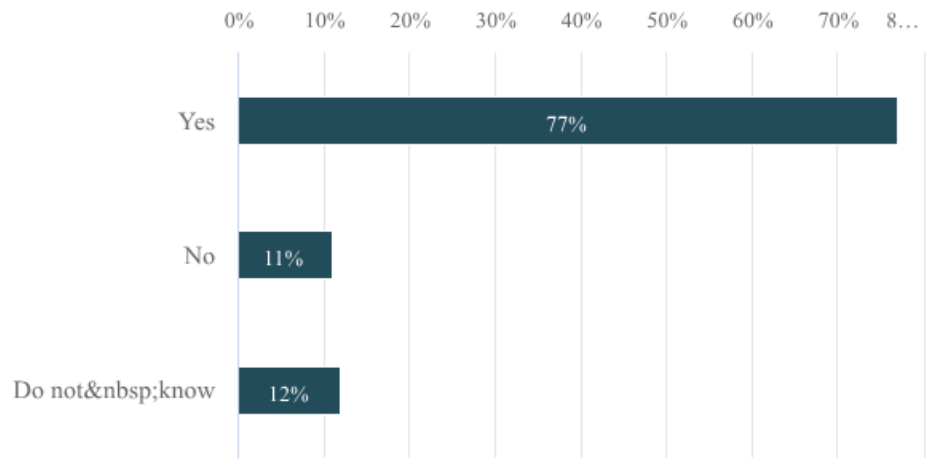
Number of respondents: 24



	N	Percent
Yes	9	37,5%
No, please explain why	5	20,83%
Varies, please explain	7	29,17%
Do not know	3	12,5%

24. 7B. In your country, is there guidance for the application of human biomonitoring in workplaces/occupational health care?

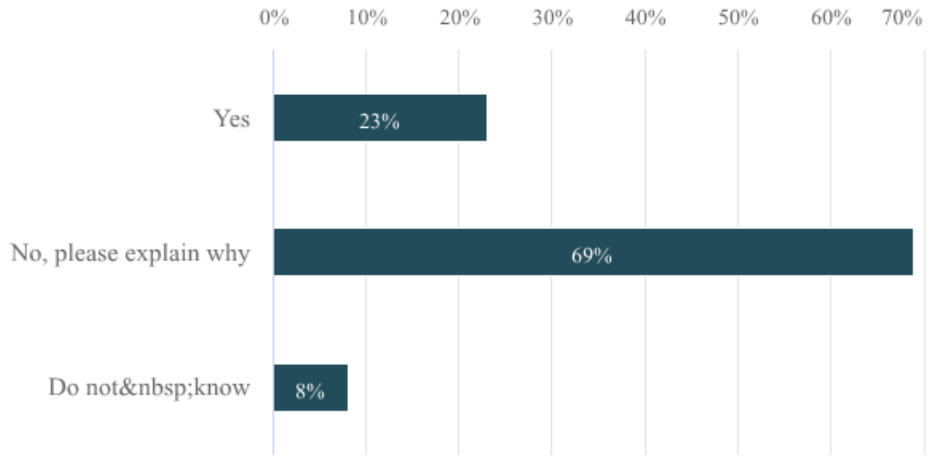
Number of respondents: 26



	N	Percent
Yes	20	76,92%
No	3	11,54%
Do not know	3	11,54%

25. 8B. According to your view, are current regulations in your country effective enough to support the use of biomonitoring in occupational health and safety?

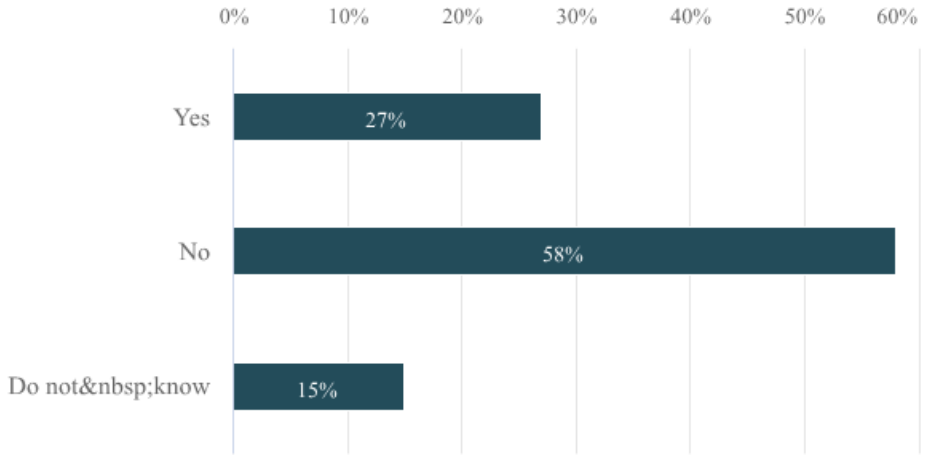
Number of respondents: 26



	N	Percent
Yes	6	23,08%
No, please explain why	18	69,23%
Do not know	2	7,69%

26. 9B. In your country, do you recommend the use of some DNA or protein adduct analyses as a marker of exposure in occupational biomonitoring?

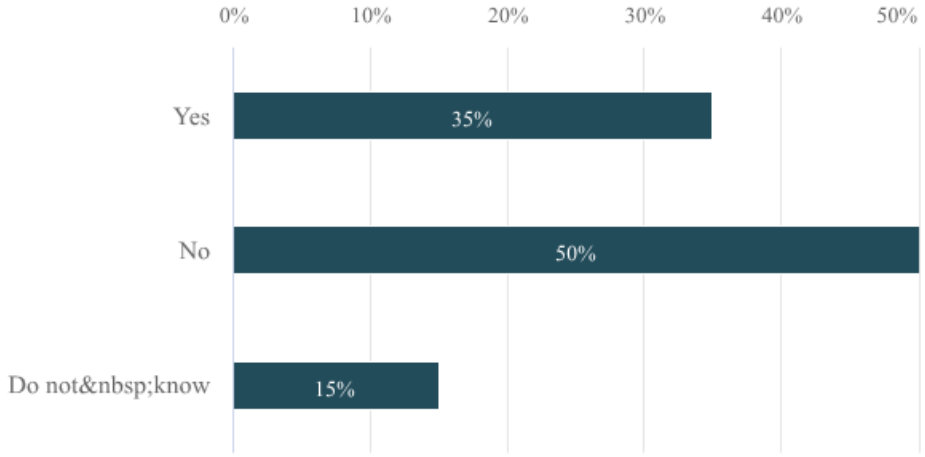
Number of respondents: 26



	N	Percent
Yes	7	26,92%
No	15	57,69%
Do not know	4	15,39%

27. 10B. In your country, do you recommend the use of some biomarkers of effects (including e.g. “omics”-based markers) in occupational biomonitoring?

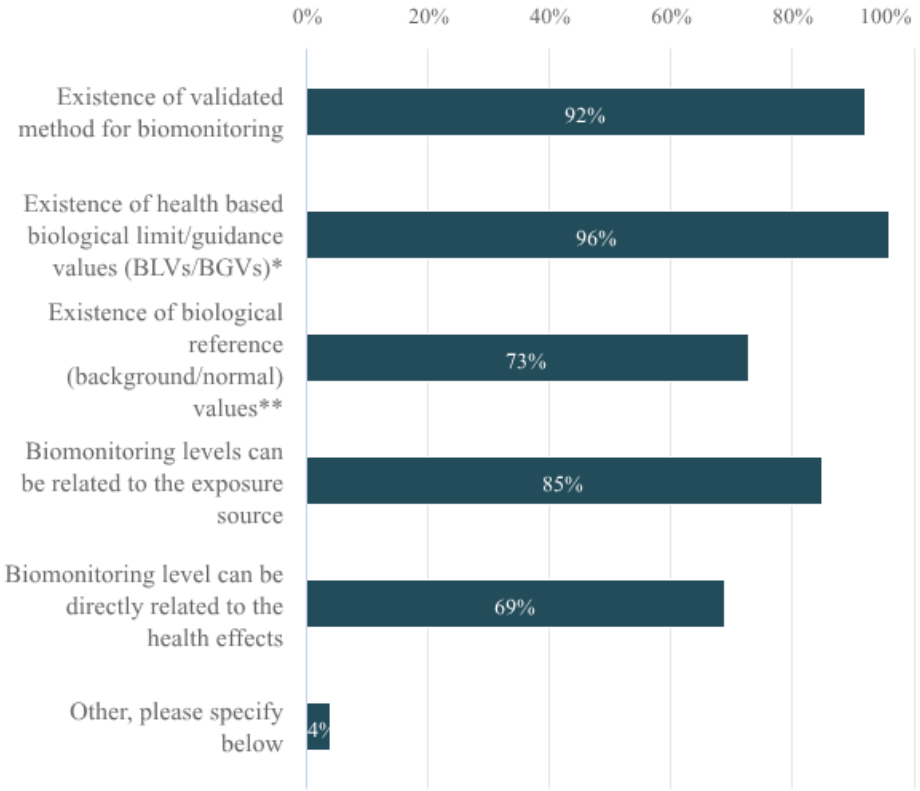
Number of respondents: 26



	N	Percent
Yes	9	34,62%
No	13	50%
Do not know	4	15,38%

28. 11B. In your opinion, what are the criteria for using human biomonitoring data in risk assessment at workplaces? Please tick all relevant options.

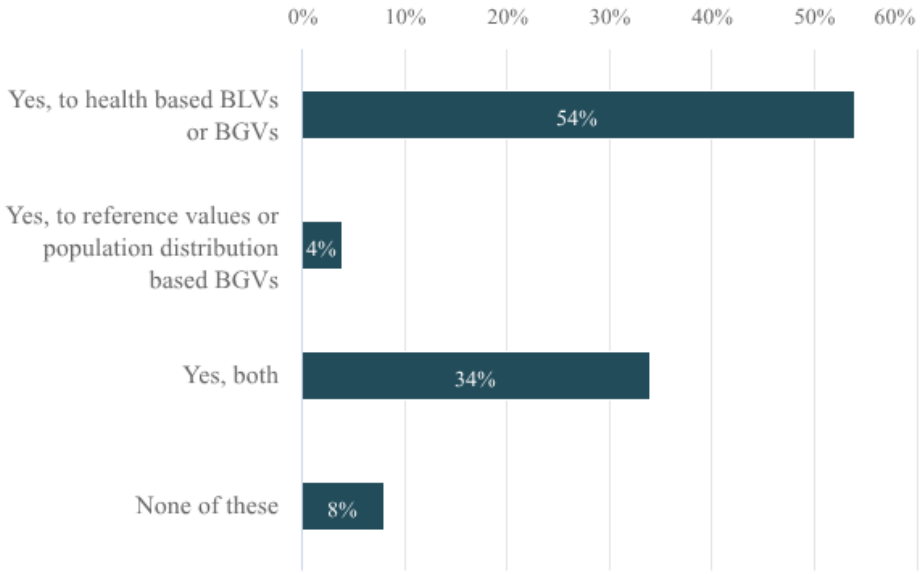
Number of respondents: 26, selected answers: 109



	N	Percent
Existence of validated method for biomonitoring	24	92,31%
Existence of health based biological limit/guidance values (BLVs/BGVs)*	25	96,15%
Existence of biological reference (background/normal) values**	19	73,08%
Biomonitoring levels can be related to the exposure source	22	84,62%
Biomonitoring level can be directly related to the health effects	18	69,23%
Other, please specify below	1	3,85%

29. 12B. Are biomonitoring results of workers compared to occupational biological limit values (BLVs)/biological guidance values (BGVs) or reference values?

Number of respondents: 26



	N	Percent
Yes, to health based BLVs or BGVs	14	53,85%
Yes, to reference values or population distribution based BGVs	1	3,85%
Yes, both	9	34,61%
None of these	2	7,69%

30. 12B.1. Please specify the substances for which there is a BLV or a BGV? You can also provide a link to the list of BLVs or attach a list as an attachment.

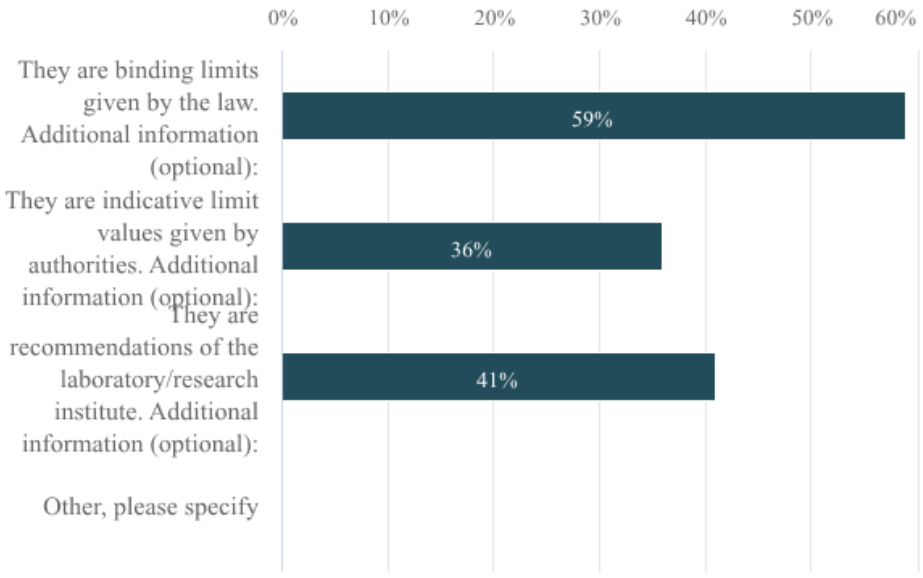
Number of respondents: 17

Responses
BLVs and BGV in occupational settings
http://www.irsst.qc.ca/media/documents/PubIRSST/T-03.pdf?v=2017-06-21
Arsenic, mercury, ethylbenzene, phenol, cadmium, cobalt, chromium(VI), xylene, lead, MOCA, nickel, carbon disulphide, styrene, tetrachlorethylene, toluene, trichlorethylene. See "Liite 2" at http://julkaisut.valtioneuvosto.fi/handle/10024/79109
http://www.acgih.org/tlv-bei-guidelines/biological-exposure-indices-introduction
http://www.acgih.org/tlv-bei-guidelines/biological-exposure-indices-introduction
See the SCOEL BLV's
Please follow the link to the law where you can find the information you are looking for: https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=10009034

Responses
Again a legal document. Sorry, this is not my domain! It could be an attachment to the "Grenzwerte-Verordnung". But I am not sure!
PbB
Binding value: only for lead (transposition of a european directive) - but this value is considered too high according to current scientific views
Pb and Cd are given in stipulations See https://www.av.se/arbetsmiljoarbete-och-inspektioner/publikationer/foreskrifter/medicinska-kontroller-i-arbetslivet-AFS-20056-foreskrifter/?hl=medicinska kontroller
ww.dol.gov.co.za - hazardous chemical substance - BEI schedule
BLV for lead only: Lead, 50 ug/dl, blood For BGVs see the attached list
See "Límites de exposición profesional a agentes químicos en España, 2017", page 127 and ff. http://www.insht.es/InshtWeb/Contenidos/Documentacion/LEP%20_VALORES%20LIMITE/Valores%20limite/LEP%202017.pdf
The document edited by the INSHT (National Institute of Safety and Hygiene at Work) "Occupational Exposure Limits for Chemical Agents in Spain" (http://www.insht.es/InshtWeb/Contenidos/Documentacion/LEP%20_VALORES%20LIMITE/Valores%20limite/LEP%202017.pdf).
https://www.ciop.pl MAC documentation (full text; PiMOSP)
BLV (D.Lgs 106/09): Pb blood: 60 µg/100 ml (40 µg/100 ml women<45 years)

31. 12B.2. What is the legal status of these values?

Number of respondents: 22, selected answers: 30



	N	Percent
They are binding limits given by the law. Additional information (optional):	13	59,09%
They are indicative limit values given by authorities. Additional information (optional):	8	36,36%
They are recommendations of the laboratory/research institute. Additional information (optional):	9	40,91%
Other, please specify	0	0%

Answers given into free text field

Option names	Text
They are recommendations of the laboratory/research institute. Additional information (optional):	Additional values are given by the Finnish Institute of Occupational Health. see www.ttl.fi/biomonitorointi -> Analyysit ja näytteenotto-ohjeet (in Finnish)
They are recommendations of the laboratory/research institute. Additional information (optional):	Finnish Institute of Occupational Health gives recommendations of the institute (list of these values not given here)
They are recommendations of the laboratory/research institute. Additional information (optional):	Yes, in Biotox a database produce by INRS. http://www.inrs.fr/publications/bdd/biotox.html
They are binding limits given by the law. Additional information (optional):	Only for lead
They are binding limits given by the law. Additional information (optional):	B-Pb 0,8 μmol/l blood for women below 50 years and 1,5 μmol/l fro women over 50 yrs. If B-Cd over 50 nmol/l employee must investigate why and take preventive measures, if B-Cd is over 75 nmol/l person is not allowed to continue work and exposure to Cd.
They are binding limits given by the law. Additional information (optional):	lead only
They are binding limits given by the law. Additional information (optional):	Only for Pb
They are binding limits given by the law. Additional information (optional):	lead
They are binding limits given by the law. Additional information (optional):	for lead (Pb) only
They are binding limits given by the law. Additional information (optional):	only for blood lead
They are binding limits given by the law. Additional information (optional):	D.Lgs 106/09
They are indicative limit values given by authorities. Additional information (optional):	Concerns the substances listed in question 12B.
They are indicative limit values given by authorities. Additional information (optional):	Biological guidance values listed in the attachment abobe are indicative values given by the Ministry of Social Affairs and Health
They are indicative limit values given by authorities. Additional information (optional):	In practice, they are applied as a criteria to identify the risk for individual workers

32. 13B. For the substances for which no BLV or BGV exists for workers, what references are used to interpret data (e.g. limit values from other countries)?

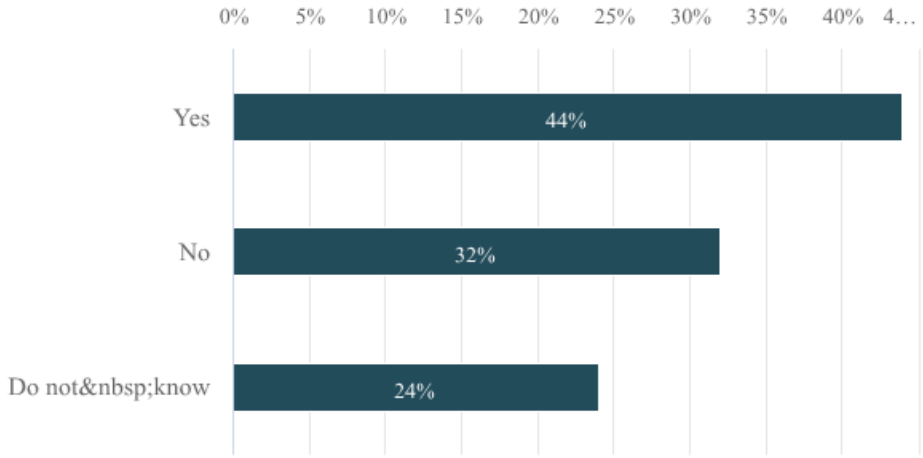
Number of respondents: 19

Responses
limit values from other countries
We usually refer to the booklet of ACGIH, the German DFA or the book Lauwerys.
No idea.
If there are no reference values, the biomarker is not used to follow workers
If there are no reference values, the biomarker is not used to follow workers
NHANES Canada Health Measure Survey ACGIH BEI DFG BAT
Do not know
usually they are not analysed in the occupational Setting (except in scientific studies)
When BM is performed, reference values from NIOSH of Germany are used. Laboratories may also give reference values, but one should be careful since these values are often for the general population. Another source is the Handbook of Lauwerys and Hoet.
http://www.toxi.ucl.ac.be/documents/mbi.htm: ACGIH, SCOEL,DFG, INRS, IRSST, FIOH, LTAP (Louvain centre for Toxicology & Applied Pharmacology, UCL)
ACGIH, BAT, cdc, who
Limit values from other countries, like USA, European Unión and its Member States
SCOEl (BLV), ACGIH (BEI), DFG (BAt, EKA, BLW, BAR), FIOH (BAL)
If there are no references values, the biomarker is not used to follow workers.
BLV or BGV from other countries Literature data about dose-response
In France, INRS has a website (Biotox) where reference values from other countries or institutions are listed (such as SCOEL, ACGIH, DFG, FIOH etc).
Metals: List of recommended health-based biological limit values (BLVs) and biological guidance values (BGVs) Scientific Committee on Occupational Exposure Limits (SCOEL) (last update: June 2014): BLV Cd in urine: 2 µg/g creatinine BLV Pb its inorganic compounds in blood: 30 µg/100 ml BLV Hg and inorganic Hg2+ compounds: 10 µg/l in blood, 30 µg/g creatinine in urine BGV Ni and Ni compounds in urine: 3 µg/l BAT values (DFG): Pb blood 40 µg/100 ml (10 µg/l women<45 years); As urine 50-130 µg/l; Cd urine 15 µg/l; Co urine 6-300 µg/l; Cr(VI) urine 12-40 µg/l; Ni urine 15-70 µg/l; V urine 35-140 µg/l. ACGIH BEIs (end of workweek): As urine 35 µg/g creatinine; Cd urine 5 µg/l; Co urine 15 µg/l and Co blood 1 µg/l; Cr(VI) urine 10-25 µg/l; Pb blood 30 µg/100 ml; V urine 50 µg/l.

United Kingdom biological monitoring guidance values: Hg urine 20 µmol/mol creatinine (sampling time random) Pesticides: BAT values (DFG): AchE, Lindano in blood and serum; p-nitrophenol in urine ACGIH BEIs: AchE, p-nitrophenol in urine, PCP in urine and plasma
In research projects (case studies) we use limit values from other countries.

33. 14B. Is there work going on to elaborate health based limit values for workers in your country?

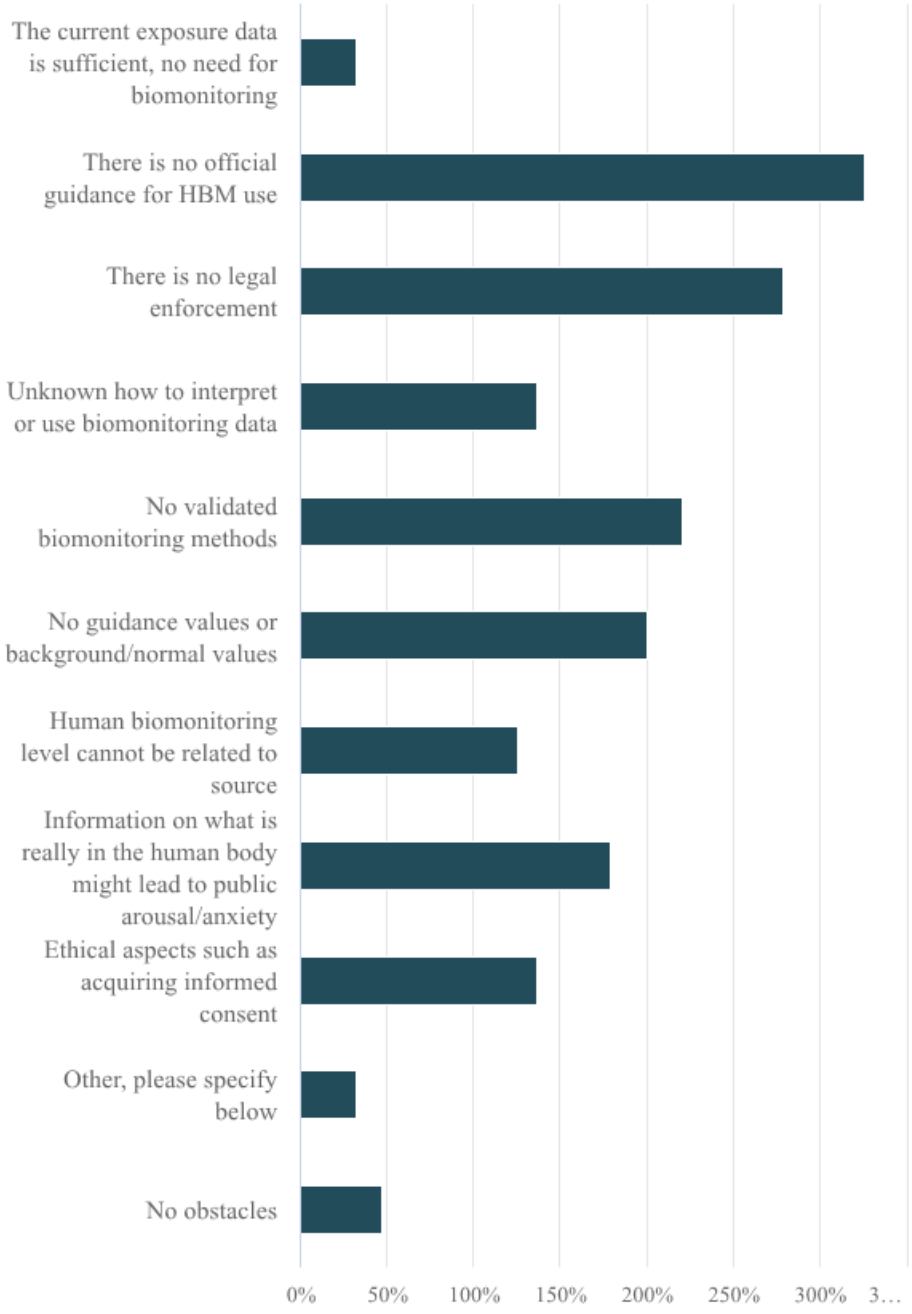
Number of respondents: 25



	N	Percent
Yes	11	44%
No	8	32%
Do not know	6	24%

34. 15B. What are the important obstacles you face when applying biomonitoring in occupational risk assessment? Please fill in matrix for chemicals in general and for the following priority compounds. Notice that the table needs to be scrolled to the right to see the rest of the columns!

Number of respondents: 19, selected answers: 326



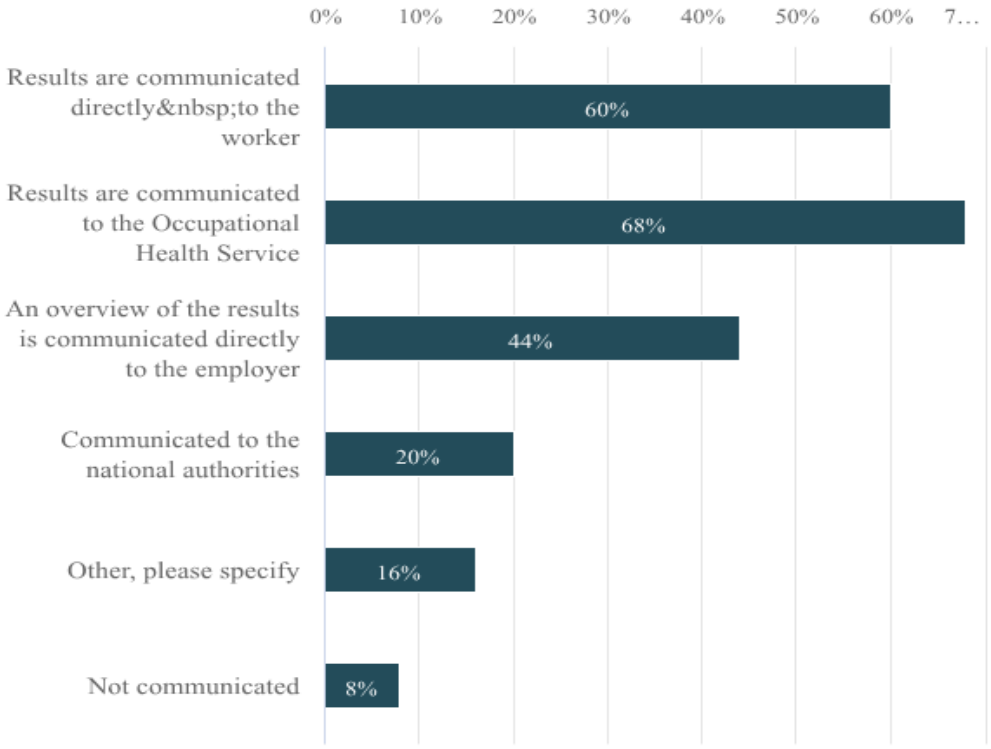
	Chemicals (in general)	Phthalates/DINCH	Bisphenols	Per-/Polyfluorinated compounds	Flame Retardants	Cd, Cr	PAHs and air pollutants	Anilin family, e.g. MOCA	Chemical mixtures (pesticide mixtures)	Emerging chemicals	Total	Average	Median
The current exposure data is sufficient, no need for biomonitoring	1	0	0	1	1	2	1	0	0	0	6	4,83	5,5
	16,66%	0%	0%	16,67%	16,67%	33,33%	16,67%	0%	0%	0%			
There is no official guidance for HBM use	9	8	8	8	8	3	5	3	5	5	62	4,73	4
	14,52%	12,9%	12,9%	12,9%	12,9%	4,84%	8,07%	4,84%	8,07%	8,06%			
There is no legal enforcement	10	6	6	6	6	4	6	2	4	3	53	4,57	4
	18,87%	11,32%	11,32%	11,32%	11,32%	7,55%	11,32%	3,77%	7,55%	5,66%			
Unknown how to interpret or use biomonitoring data	7	3	2	3	3	0	3	1	2	2	26	4,35	4
	26,92%	11,54%	7,69%	11,54%	11,54%	0%	11,54%	3,85%	7,69%	7,69%			
No validated biomonitoring methods	8	5	5	6	5	3	3	2	3	2	42	4,38	4
	19,05%	11,91%	11,91%	14,29%	11,9%	7,14%	7,14%	4,76%	7,14%	4,76%			
No guidanc	7	4	4	4	5	3	3	2	3	3	38	4,74	4,5

	Chemicals (in general)	Phthalates/DINCH	Bisphenols	Per-/Polyfluorinated compounds	Flame Retardants	Cd, Cr	PAHs and air pollutants	Anilin family, e.g. MOCA	Chemical mixtures (pesticide mixtures)	Emerging chemicals	Total	Average	Median
e values or background/normal values	18,42%	10,53%	10,53%	10,53%	13,16%	7,9%	7,89%	5,26%	7,89%	7,89%			
Human biomonitoring level cannot be related to source	4	4	3	4	4	1	1	1	1	1	24	4,04	4
	16,66%	16,66%	12,5%	16,66%	16,67%	4,17%	4,17%	4,17%	4,17%	4,17%			
Information on what is really in the human body might lead to public arousal/ anxiety	6	4	4	3	4	3	4	2	2	2	34	4,65	4,5
	17,65%	11,77%	11,77%	8,82%	11,77%	8,82%	11,76%	5,88%	5,88%	5,88%			
Ethical aspects such as acquiring informed consent	8	3	3	3	3	3	3	0	0	0	26	3,42	3
	30,77%	11,53%	11,54%	11,54%	11,54%	11,54%	11,54%	0%	0%	0%			
Other, please	1	1	1	1	1	0	0	1	0	0	6	3,83	3,5

	Chemicals (in general)	Phthalates/DINCH	Bisphenols	Per-/Polyfluorinated compounds	Flame Retardants	Cd, Cr	PAHs and air pollutants	Anilin family, e.g. MOCA	Chemical mixtures (pesticide mixtures)	Emerging chemicals	Total	Average	Median
specify below	16,66%	16,66%	16,67%	16,67%	16,67%	0%	0%	16,67%	0%	0%			
No obstacles	2	0	1	1	0	2	1	2	0	0	9	4,89	6
	22,23%	0%	11,11%	11,11%	0%	22,22%	11,11%	22,22%	0%	0%			
Total	63	38	37	40	40	24	30	16	20	18	326	4,45	4

35. 16B. How occupational biomonitoring data is usually communicated in your country? Tick all options that apply.

Number of respondents: 25, selected answers: 54



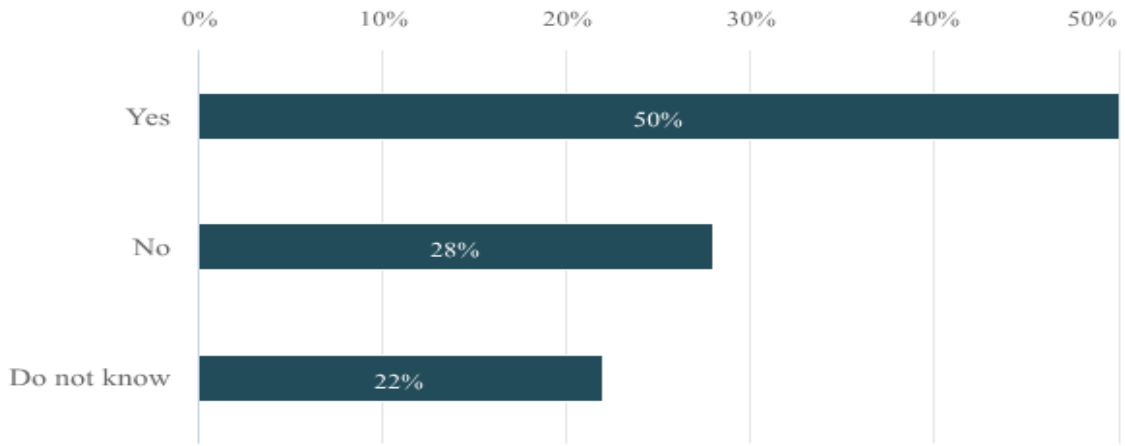
	N	Percent
Results are communicated directly to the worker	15	60%
Results are communicated to the Occupational Health Service	17	68%
An overview of the results is communicated directly to the employer	11	44%
Communicated to the national authorities	5	20%
Other, please specify	4	16%
Not communicated	2	8%

Answers given into free text field

Option names	Text
Other, please specify	Committee for prevention at work (in a way that medical secret is kept)
Other, please specify	An overview of the results is communicated to the employer, providing that confidentiality is preserved
Other, please specify	Publications
Other, please specify	The results have to be sent to the ministry of labour

36. 16B.1. Has occupational health service an obligation to give an overview of the biomonitoring results to the employer?

Number of respondents: 18



	N	Percent
Yes	9	50%
No	5	27,78%
Do not know	4	22,22%

37. 16B.2. Please, elaborate how the results are communicated to the employer (by company/plant, by task, are statistical data provided)

Number of respondents: 9

Responses
These is the responsibility of the responsible physician prescribing the analysis.
Results for the workplace are provided to the employer. Some general statistics are provided. Often because many workplaces are small, results are provided related to task or special exposure group or time spent near sources of exposures
The worker receives the result of the examination. The employer only is informed about the date of the examination, the ability of the worker to work further with an exposure to the substance in question and about the date the next examination has to follow.
Only statistical data that not can be related to individuals will be reported. But only if the employer pays for the report.
The results have to be used to review the risk assessment and the prevention measures. Care has to be taken to report data (to the employer, to the committee for prevention at work) in such a way that the medical secret is respected.
POST SURVEILLANCE AND ANNUAL REPORTS
I am not aware of the practices but the arrangements vary.
Individual data are provided directly to employer
By task with statistical data