Occupational Biomonitoring Guidance Document

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IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among **FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD**

Foreword

Biomonitoring is used to measure internal exposures or effects in exposed individuals or groups and accounts for all routes of potential exposure (i.e., inhalation, oral, and dermal) pathways, and thus interpretation of biomonitoring values requires an understanding of the toxicokinetics of the parent chemical. Biomonitoring guidance values and/or limit values are typically determined by national/international agencies and various terms, definitions, and approaches are used to set limit values, which in turn, may lead to different protection levels between different countries & organisations.

The goal of this document is to present examples and experiences of national approaches used to derive biomonitoring values and provide recommendations for deriving occupational biomonitoring assessment values and their practical use. The primary objective was to provide guidance on the derivation of health-based human biomarker assessment (referred to as Occupational Biomonitoring Level (OBL)) values, the use of OBL* in exposure assessment, screening health related risks with provisional OBL* and combining these approaches in risk management in a regulatory context. The procedures and specifications described in the guidance document can be followed to derive a high-quality OBL* value. Consequently, this guidance document is relevant for regulatory authorities, chemical industries, researchers and different stakeholders interested in addressing occupational and general population biomonitoring.

Development of an occupational biomonitoring guidance document was elaborated as a joint activity of the OECD Working Party on Exposure Assessment & OECD Working Party on Hazard Assessment (WPEA & WPHA) in collaboration with more than 40 institutes/ organisations (https://www.oecd.org/env/ehs/risk-assessment/occupational-biomonitoring.htm). The activity was started in September 2019 and the development of this guidance document was co-led by Robert Pasanen-Kase (SECO, CH) as coordinator, Nancy B. Hopf (Unisanté, CH), Tiina Santonen (FIOH, FI), Peter Kujath (BAuA, DE), Jos Bessems (VITO, BE), and the OECD secretariat. The guidance document was drafted in close collaboration with experts providing input on different aspects of biomonitoring and including Susana Viegas (ENSP/UNL, PT), Ludwine Casteleyn (KU Leuven, BE), Devika Poddalgoda (Health Canada, CAN), Farida Lamkarkach (ANSES, FR), and Thomas Göen (University of Erlangen, DE).

The initial draft guidance document was reviewed in October 2021 by experts from 14 different organisations/ institutes/ companies. Comments were discussed in a meeting held virtually in December 2021 with all involved experts as well as experts from WPEA & WPHA and the document was revised accordingly. The guidance document was circulated to the WPEA & WPHA in 2022 and finalized. This adopted biomonitoring guidance document is published under the responsibility of the Chemical and Biotechnology Committee of the OECD.

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Disclaimer: During the preparation and finalisation time of the guidance some affiliations and working fields changed.

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Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Adsorption, Distribution, Metabolism, Excretion
ANSES	French Agency for Food, Occupational and Environmental Health & Safety
AOP	Adverse Outcome Pathways
AOP-KB	Adverse Outcome Pathway Knowledge Base
Assessment value	Can be a health, risk, statistically or technically derived assessment value to be used biomonitoring, see OBL, POBL, ROBL or TOBL
ATSDR	Agency for Toxic Substances and Disease Registry
BAR	Biological Reference values, Biologische Arbeitsstoff Referenzwerte
BAT	Biological tolerance values in blood and urine, Biologische Arbeitsstoff-Toleranzwerte
BBLV	Binding Biological Limit Value
BE	Biomonitoring Equivalent
BEI	Biological Exposure Indices
BGV	Biological Guidance Value
BLV*	Biological limit value
BLW	Biological guidance value, Biologische Leitwerte
BM	Biomonitoring
BME	Biomarker of Exposure
BMDL	Benchmark Dose Lower Confidence Limit
BMGV	Biomonitoring Guidance Value
BOELV	Binding Occupational Exposure Limit Value
BRV	Biological Reference Value
CAD	Chemical Agents Directive
CMD	Carcinogenic and Mutagenic Directive
DEHP	Bis(2-ethylhexyl) phthalate or di(2-ethylhexyl) phthalate
DNEL	Derived No-Effect Level
$DNEL_{biomarker}$	Derived No Effect Levels expressed as internal concentrations
DNT	Developmental Neurotoxicity
EC	European Commission
ECHA	European Chemicals Agency
EGMAST	Extended Advisory Group on Molecular Screening and Toxicogenomics
EKA	Exposure equivalents for carcinogenic agents, Expositionsäquivalente für krebserzeugende Arbeitsstoffe
EQ*	Equivalent concentration
ESFA	European Food Safety Authority
EU	European Union
F_{UE}	a steady-state concentration factor for urine measured after 24h or 48h exposure
HBM GV	Human Biomonitoring Guidance Values
HBM4EU	European Human Biomonitoring Initiative

IOELV	Indicative Occupational Exposure Limit Value
HDA	Hexamethylendiamine
HDI	Hexamethylendiisocyanat
ISES	International Society for Exposure Science
ISO	International Organization for Standardization
IUCLID	International Uniform Chemical Information Database
KE	Key Event
KER	Key Event Relationship
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LoC	Level of Confidence
MAK*	Maximum workplace concentration or Maximale Arbeitsplatz Konzentration
MIE	Molecular Initiating Event
MoA	Mode of Action
NCO group	functional group of isocyanates
NIOSH	National Institute for Occupational Safety & Health
NOAEL	No-Observed-Adverse-Effect-Level
OECD	Organisation for Economic Co-operation and Development
OBL	Occupational Biomonitoring Level
OBEL	Occupational Biomonitoring Effect Level
OEL	Occupational Exposure Limit
OELV	Occupational Exposure Limit Value
OHP	Occupational Health or Hygiene Professionals
OSH	Occupational Safety and Health
PARC	European Partnership for the Assessment of Risks from Chemicals
PBD modelling	Physiologically Based Dynamic modelling
PBK modelling	Physiologically Based Kinetic modelling
POBL	Provisional Occupational Biomonitoring Level
POBEL	Provisional Occupational Biomonitoring Effect Level
PoD	Point of Departure
PPE	Personal Protective Equipment
RAC	Risk Assessment Committee, European Chemicals Agency
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	Reference Dose
ROBL	Reference Occupational Biomonitoring Level
ROBEL	Reference Occupational Biomonitoring Effect Level
RMM	Risk Management Measure
SCOEL	Scientific Committee on Occupational Exposure Limits
SEG	Similar Exposure Group
SUVA	Swiss National Accident Insurance Fund
TDI	Total Daily Intake
TLV®	Threshold Limit Value, level to which a worker can be exposed day after day for a working lifetime without adverse effects
TOBL	Technical Occupational Biomonitoring Level
TOBEL	Technical Occupational Biomonitoring Effect Level
TRV	Toxicity Reference Value
TWA	Time Weighted Average
WHO	World Health Organisation
WPEA	Working Party on Exposure Assessment
WPHA	Working Party on Hazard Assessment

Executive Summary

This occupational biomonitoring guidance document was elaborated in a joint activity including more than 40 institutes/ organisations in collaboration with the OECD* Working Party on Exposure Assessment and the OECD* Working Party on Hazard Assessment. The goal was dual. First, the guidance document presents current approaches used to derive biomonitoring values; and second, it provides globally harmonized recommendations on how-to derive and apply occupational biomonitoring assessment values. The derived health-based human biomarker assessment values are referred to as Occupational Biomonitoring Levels (OBL*s). OBLs* are suitable for the use in exposure assessment and screening a level of health-risk and finally, workplace risk management. Moreover, we strengthen the option of deriving Provisional Occupational Biomonitoring Levels (POBLs*) for chemical substances with limited human toxicity data availability, which can be used for identifying and managing possible occupational health-risks.

The guidance document draws mainly upon exposure- and partially on effect-biomonitoring approaches and gained experiences from the regulatory context. The procedures and specifications described in the guidance document aim to facilitate a high quality and sound occupational biomonitoring programmes. Furthermore, this guidance provides practical guidance on obtaining, evaluating and communicating BM* results following ethical and regulatory requirements. Using harmonised approaches in conducting and evaluating BM* campaigns will also facilitate the usability and interpretation of BM* data in an international context. Harmonised guidance will also help in interpreting levels found in exposed workers across countries. Consequently, this guidance document is relevant for Occupational Health Professionals (OHP*) and occupational safety and health (OSH*) specialists, regulatory authorities, chemical industries, researchers as well as stakeholders interested in addressing occupational and general population biomonitoring. The occupational biomonitoring guidance should increase the derivation and acceptance of OBLs* and implementation of these in biomonitoring programmes to reduce workers' exposures and ultimately, prevent occupational diseases.

1. Introduction

1.1. Introduction of Biomonitoring

1.1.1. Biomonitoring

In the area of occupational medicine or occupational hygiene, biomonitoring (also referred to as 'biological monitoring') is a tool to assess exposures by collecting biological materials from workers/persons and quantify the hazardous substances, their metabolites or their biochemical and/or biological effect parameters in the obtained biological materials. Chemical substances, substance groups or their metabolites in biological matrixes are called biomarkers of exposure. Biochemical, physiological or other alteration that is associated with an established or potential health impairment is called biomarker of effect.

Biomarkers of effect quantify effect responses in biological materials from workers/persons exposed to chemical substances. A more detailed definition is available in chapter 1.3.1.

Biological materials (biological matrices) are tissues, body fluids, excretions and secretions of the human body. In biomonitoring, urine and blood are commonly used but other matrices such as hair or exhaled breath condensate are also possible.

Exposure assessment is the estimated or measured magnitude, frequency and duration of exposure to chemical substances. Quantitative measurements are often included such as air concentrations of the chemical substance monitored during a task or a job as well as emissions of the chemical substance from exposure sources, and surface contamination of external boundaries (skin and workplace surfaces e.g., benchtops). In addition to these external exposure assessments (air monitoring and surface sampling), exposures are assessed with biomonitoring. Exposure assessments can be for work-related tasks, and would then include, in addition to the task itself, descriptions on materials used, processes, and installed controls.

Exposure profiles give an overall exposure assessment taking into account the exposures generated for each task performed within the job. Similar exposure groups (SEGs) are groupings of workers/persons with similar exposure profiles, meaning similarity and frequency of the tasks performed, the materials and processes with which they work, and the similarity of how they perform the tasks.

1.1.2. Biomonitoring measurement value

The biomonitoring measurement value is the concentration of a biomarker or a set of biomonitoring values in a single biological sample. Each measurement value must be accompanied by information on the uncertainty of the analytical method (JCGM, 2008). Data describing the identity of the sample (e.g., sample code) can be used to link biomonitoring measurement values with other exposure assessment data, person-related data such as age, gender, smoking habits, etc., if required for the assessment, and sample-related data, e.g., creatinine concentration and time of sampling.

1.1.3. Biomonitoring (BM) parameter*

A biomonitoring parameter is a specific analyte in a human biological material. The analyte represents either a hazardous compound or one of its metabolites, whose concentration corresponds with possible health hazards (exposure biomonitoring), or a marker of biochemical, physiological, or behavioural effects, which can indicate an adverse outcome (effect biomonitoring). The suitability of a BM* parameter is characterized by:

- The biomarker is specific and sensitive for the occupational chemical exposure in question.
- The biomarker elimination kinetics, e.g. biological half life time, enables a convenient sampling method.
- The biomarker concentration reflects a defined exposure interval.
- The biological matrix is easily available and sampling is compliant with ethical standards.
- An (bio)analytical method with appropriate reliability criteria, offered by at least one laboratory.
- The biomarker has an established Occupational Biomonitoring Level (OBL*), which can be used to evaluate the result.

1.1.4. Health surveillance

Occupational health surveillance is the monitoring of the health status of workers exposed to specific agents by means of periodic medico-physiological examination. Special consideration is given to diseases or clinical symptoms that may be the result of exposure, signs of excessive absorption of the respective chemical agent, and individual characteristics (e.g., pre-existing medical problems) that might increase an individual's disposition for an exposure-related disease or health disorder. The examinations can also include biomonitoring.

1.1.5. Occupational biomonitoring programme

To ensure that chemical exposures are prevented, employers need to develop comprehensive plan to assess exposures. An occupational biomonitoring programme is such a comprehensive planning of an in-company biomonitoring campaign. Biomonitoring programme needs to have a defined purpose and a defined sampling strategy. It determines, among other things, if the biomonitoring programme is part of health surveillance or of occupational hygiene measurements within the context of exposure assessment (more information is available in chapter 4.2 and 4.3).

Ethical considerations such as confidentiality and workers' rights to know their results need to be addressed to ensure that workers' individual rights in participating in the occupational biomonitoring programmes are respected. A competent Occupational Health or Hygiene Professional (OHP*) shall manage the biomonitoring programme, and consult with employees or their representatives regularly. Competence refers to both technical and organizational aspects including confidentiality and communication. The biomonitoring programmes use established biomonitoring methods and give instructions on the interpretation of results and actions needed from the results obtained. It also describes the coding of samples.

1.1.6. Occupational anamnesis

An occupational anamnesis is recorded information on the technical, organizational and collective protection measures as well as the worker's use of personal protective equipment, individual behaviour regarding occupational hygiene measures, and personal hygiene (e.g., washing hands before eating), and is usually obtained by a health professional through an interview with a worker participating in the occupational health surveillance programme.

1.1.7. Similar Exposure Group (SEG) approach*

The Similar Exposure Group (SEG) approach is a sampling strategy where a group of workers have the same general exposure profile for a specific or several identified chemical agent(s) of interest. Exposure profiles are temporal exposure patterns related to specific types of jobs or tasks. The SEG concept (see chapter 4.3 and 4.4) is used for defining risk management measures (RMM) and for testing compliance with occupational exposure limit values (Technical Committee CEN 137, 2020).

1.2. Relevance of occupational biomonitoring

Biomonitoring, further called BM*, is widely used and of general relevance in occupational exposure-, risk assessment and workplace safety assessment and not only limited to countries and members participating in OECD Working Party of Exposure Assessment (WPEA) and Working Party on Hazard Assessment (WPHA).

BM* can address total exposure to dangerous substances handled at work and is a measure of internal exposure or effect (see chapter 1.1 introduction of terminologies). Depending on the used method BM* can be more invasive for workers than other monitoring methods. BM* accounts for all routes of exposures i.e., inhalation, oral, and skin exposure, and is especially beneficial when assessing exposures to chemical substances with skin notations or known skin uptake.

BM* requires little field equipment and can be a less costly alternative in monitoring workers' exposures. Consequently, more workers can be monitored simultaneously, which leads to an increased awareness of the effectiveness of the applied risk management measures (RMM*) as well as workers' health. Biomonitoring is complementary to other exposure assessment methods. The results of the monitoring can be used in implementing strategies to reduce exposures and ultimately, lower the risk for occupational diseases.Biomonitoring is especially indicated for assessing exposure scenarios to substances under the following situations (adapted from German Occupational Medical Rule (AMR) 6.2):

- Substances which may be absorbed through the skin in toxicological relevant amounts (skin notation)
- oral exposure may occur through contamination transfer (poor occupational hygiene)
- substances of high biological persistence (long half-life)
- carcinogens, mutagens or substances toxic to reproduction
- air monitoring may be impossible or impractical
- when exposure control relies largely on personal protective equipment (e.g., gloves or masks) where efficacy is difficult to demonstrate by other means.
- When exposure control relies on human behaviour i.e., doing a task in a particular way.
- internal exposure may be modified by physical stress (elevated minute volume)
- conditions, which may accelerate dermal resorption (high temperature, simultaneous exposure to penetration enhancers, etc.)
- accidental exposure

BM* can be used to assess the implemented RMM*s efficiency as it takes into account exposure from all sources of substances through all routes of exposures. More about the use of biomonitoring and sensoring at the workplace and practical and ethical considerations can be also found in a RIVM report (2018).

Currently, various national and international bodies are involved in deriving biomonitoring guidance values (BMGV*) or biological limit values (BLV*); however, there is no global harmonized approach to date. Furthermore, guidance for deriving BMGV*s or BLVs* is limited and detailed methods for deriving these values are lacking. Different approaches will result in different values for the same substance leading to different levels of risk management of the workers for the same substance. Consequently,

this will cause confusion amongst users of the BMGV such as exposure assessors. For this reason, initial efforts have already been made at the European level within the framework of the HBM4EU project to harmonize and agree upon so-called human biomonitoring guidance values for workers (HBM-$GV_{Workers}$) and the general population (HBM-GV_{GenPop}) (Apel et al., 2020). Further guidance in the occupational field may help in deriving and using health-based human biomarker values (BMGV*, BLV*, $DNEL_{biomarker}$*, HBM-GV_{Worker} etc.). In the following guidance, we use the neutral and overarching term Occupational Biomonitoring Level (OBL*) in accordance with Occupational Exposure Limits (OEL*) or Occupational Exposure Limit Values (OELV*) which are used for air monitoring.

1.3. Occupational Biomonitoring Level (OBL) introduction

OBL* values are often derived either as an equivalent to the (external) OEL* value (TLV®*, MAK*, worker-DNEL*) or based on a direct relationship between the biomarker and a related health effect. The ideal approach to setting an OBL* is to establish a direct association between biomarker level and a critical health effect. This is possible only in cases in which there are reliable research data on the correlations between biomarker levels and negative health effects. If this is not possible, then derivation of internal concentrations associated with an external dose or an external exposure limit value (OEL* value) is conducted. Routine biomonitoring surveillance will lead to more robust health effect correlation studies. Toxicokinetic knowledge together with measured/modelled data is needed to elucidate correlations between external exposure and biomarker levels. This correlation is key to establishing biomarker levels that correspond to OELs*. Establishing biomarker levels corresponding to external exposure levels is also known as forward dosimetry. Different forward dosimetry approaches have been applied to set health-based guidance values also for the general population. These may correspond to general population limit values for external exposure (TDI*, ADI*, RfD* etc) and include biomonitoring equivalents (BE*), described by (Hayes and Aylward, 2009), and the human biomonitoring values (HBM-I and HBM-II values) described by the German Human Biomonitoring Commission ((German HBM Commission, 1996; 2007); (Angerer et al., 2011)). Apel et al. (2017) have built on these two approaches (for general population) and on the ANSES approach (for worker limit value setting), and have established HBM-GVs of the current European project HBM4EU* (Apel et al., 2020). Different definitions for biological assessment values, here called OBLs*, are used interchangeably as well as various terms such as biological limit values or BLV* (previously by SCOEL*, ANSES*), biological exposure indices or BEI® (USA ACGIH* committee), BAT* values (DFG in Germany, SUVA* in Switzerland). Under REACH*, Biomarker DNELs* or "$DNEL_{biomarker}$*" are "Derived No Effect Levels" expressed as internal concentrations" (normally in urine or blood). DNELs are concentration levels below which a substance does not adversely affect human health (see: (ECHA* Guidance, 2012); (Boogaard et al., 2011)).

OBLs* are only derived when there are enough toxicological and kinetic data for a robust assessment see chapter 3.2. In the absence of an OBL*, alternatively a Provisional OBL (POBL*) (see chapter 3.3), a Reference OBL (ROBL*), or Technical achievable (TOBL*) can be derived (see chapter 3.4). ROBLs*, are not based on toxicological evaluation but are statistically derived values which are usually set as 95th percentile of the reference population levels (i.e., population not specifically exposed, not including populations exposed occupationally or via local industrial contamination). Once established, these can be used to distinguish highly exposed populations from those with typical background levels in the general population. Although these population reference values do not inform on health risks, but they may inform on potential occupational exposure and they need to be considered when deriving limit values for occupationally exposed populations (see chapter 3.4 and 5.5). Currently, on a global level, different approaches to derive occupational biomonitoring assessment values or kinds of OBLs* are described, but no detailed step-by-step guidance exists and only a few examples are given. A harmonized approach in deriving and applying OBLs* can lead to improved worker health and to increased availability and plausibility of biomonitoring assessment values. Because of the different functions of OBLs* every derivation which is dose dependent (OBL* & POBL*) is named in this guidance mainly health-based, because they can indicate a health risk. For the more risk based derivations for non-treshold substances we used health-risk based values. In contrast ROBL* and TOBL* are not health based and are set primary under technical considerations.

1.3.1. Introduction of terminologies for exposure and effect-biomonitoring

Proposed terminologies for exposure-biomonitoring:

- **OBL** or Occupational Biomonitoring Level
- **POBL** or Provisional Occupational Biomonitoring Level
- **ROBL** or Reference Occupational Biomonitoring Level
- **TOBL** or Technically achievable Occupational Biomonitoring Level

The derivation of an OBL*, ROBL*, TOBL* and POBL* is described in the chapters 3.2, 3.3, 3.4.

Other commonly used terminologies:

- **BLV®** or Biological Limit Value is the limit value for the relevant biomarkers (parent or one of its metabolites in biological media).
- **Point of departure or POD** is the lowest dose/concentration corresponding to a given adverse effect. PODs are often expressed as LOAEL(C), NOAEL(C), or BMDL*.

Proposed terminologies for effect-biomonitoring:

- **Effect biomarkers** are measurable biochemical, physiological, and behavioural effects or other alterations within an organism that, depending upon their magnitude, can be recognized as associated with an established or possible health impairment or disease ((WHO, 1993); (NRC, 2006)).
- **EQ** or **Equivalent concentration** is an integrative response of an effect biomarker translated into an effect concentration of a reference compound. Examples: The combined effect of estrogen receptor binding substances can be expressed in estradiol equivalents, the combined effects of dioxin like acting substances can be expressed as dioxin-equivalents.
- **OBEL** or refined **Occupational Biomonitoring Effect level (OBEL**) is a checked and refined POBEL* by application of existing Adverse Outcome Pathway (AOP) knowledge. Guiding principles for derivation of OBEL are intended to be developed in an OECD follow-up activity and were beyond the scope of and the allocated time for OECD Occupational Biomonitoring activity of Working Parties on Exposure and Hazard Assessment (WPEA/WPHA).
- **POBEL** or **Provisional Occupational Biomonitoring Effect Level** is an equivalent concentration of an OBL* for a relevant Mode of Action (MoA) or endpoint measured by an effect-biomarker. The response of an effect biomarker is expressed as an equivalent concentration. This level of effect-biomarker response is linked to adverse and accepted Points of Departure (PoDs) in risk assessments.
- **ROBEL** or **Reference Occupational Biomonitoring Effect Level** is a statistically defined effect value, which is not necessarily linked to any adverse health effect. It describes the background level of a relevant MoA /endpoint level which is present in a reference population of individuals of working age who are not occupationally exposed to substances inducing a relevant effect or MoA (e.g., 95th percentile).

1.4. Primary aims of guidance

This guidance aims to reflect the current state of knowledge in occupational biomonitoring and support a harmonized approach for:

- Deriving health-based human biomarker guidance or limit values, further called Occupational Biomonitoring Level (OBL*)
- Using biomonitoring in exposure assessment and risk management.

This occupational biomonitoring guidance document was elaborated in a joint activity including more than 40 institutes/ organisations in collaboration with the OECD* Working Party on Exposure Assessment and the OECD* Working Party on Hazard Assessment. The goal was dual. First, the guidance document presents current approaches used to derive biomonitoring values; and second, it provides globally harmonized recommendations on how-to derive and apply occupational biomonitoring assessment values. The derived health-based human biomarker assessment values are referred to as Occupational Biomonitoring Levels (OBLs*). OBLs* are suitable for the use in exposure assessment and screening a level of risk and finally, workplace risk management. Moreover, we strengthen the option of deriving Provisional Occupational Biomonitoring Levels (POBLs*) for chemical substances with limited human toxicity data availability, which can be used for identifying and managing possible occupational health-risks.

The guidance document draws mainly upon exposure- and partially on effect-biomonitoring approaches and gained experiences from the regulatory context. The procedures and specifications described in the guidance document aim to facilitate a high quality and sound occupational biomonitoring programmes. Furthermore, this guidance provides practical guidance on obtaining, evaluating and communicating BM results following ethical and regulatory requirements. Using harmonised approaches in conducting and evaluating BM campaigns will also facilitate the usability and interpretation of BM data in an international context. Harmonised guidance will also help in interpreting levels found in exposed workers across countries. Consequently, this guidance document is relevant for occupational safety and health (OSH*), Occupational Health Professionals (OHP*) specialists, regulatory authorities, chemical industries, researchers as well as stakeholders interested in addressing occupational and general population biomonitoring. The occupational biomonitoring guidance should increase the derivation and acceptance of OBLs and implementation of these in biomonitoring programmes to reduce workers' exposures and ultimately, prevent occupational diseases. Harmonized guidance will help in interpreting levels found in exposed workers and is complementary to other ongoing or upcoming international activities (e.g., HBM4EU*, ISES*, PARC*). It will increase the acceptance of health-based human biomarker values and OBL*, and their use in biomonitoring programs* to reduce workers' exposures and ultimately, occupational diseases.

In order to achieve these primary aims, seven tasks were defined by participating institutes and are partially reflected in the structure of the guidance (see chapter 6.1):

1. *Compare existing methods in deriving OBL* (Occupational Biomonitoring Levels)* for selected substances of high concern, including European Substances of High Concern (SVHC) candidate substances.
2. *Identify data gaps and future research* needs with regard to the regulatory use of biomarkers of exposure data.
3. *Propose quality criteria and minimum requirements* for the setting of OBLs* and Provisional OBLs and monitoring, including toxicokinetic data, providing a discussion of variance and uncertainty and procedural aspects of quality management.
4. Build upon the case studies as well as available current guidance, and elaborate concrete *general tiered guidance* on the derivation of OBL* with respect to accepted points of departure in risk assessment.
5. *Propose different OBL* derivation methods* for screening purposes and for more advanced regulatory risk assessment contexts.
6. *Recommend general biomonitoring options* in occupational settings taking into account cost-effectiveness and various risk management options.
7. *Provide a characterization and outlook for the use of effect-based biomarker monitoring* for substances or substance groups with a relevant mode of action for addressing co-exposures and relevant mixture effects.

2. Review of widely applied BM* assessment schemes for OBL* derivation

2.1. Selected assessment schemes

Different widely applied methods for deriving health-based biological limit values for occupational exposure are available e.g., from EU Scientific committees SCOEL*/RAC*, MAK Commission*, ACGIH*, ANSES*, HBM4EU*. Below we describe the practices and data requirements for deriving health-based or health-risk based limit or guidance values for substances under these schemes. Tables 1 and 2 summarize the main similarities and differences between these schemes.

2.1.1. SCOEL/RAC**

SCOEL has given recommendations for biological limit values for more than 20 different substances. SCOEL* Biological Limit Values (BLV*s) are meant for the evaluation of potential health risks in the practice of occupational health. Exposure equivalent to the BLV* is considered not to affect the health of the employee adversely, when they are compiled regularly under workplace conditions (8 hours/day, 5 days/week), except in cases of hypersensitivity. In general, OELs* and BLVs* are reflecting similar internal exposure to the substance; in this case, the BLV* is related to a group average level. In addition, SCOEL* may give Biological Guidance Values (BGVs*), which are statistically derived values representing the upper concentration of the chemical agent or one of its metabolites in any appropriate biological medium corresponding to the 90th or 95th percentile in a defined reference population. Reference population is preferably an occupationally non-exposed group of people. SCOEL* BLVs* do not indicate a sharp distinction between hazardous and non-hazardous exposures. Due to biological variability, it is possible for an individual's measurement to exceed the BLV* without incurring an increased health risk. If, however, measurements persistently exceed the BLV*, or if the majority of measurements of specimens obtained from a group of workers exceed the BLV*, the cause of the excessive values must be investigated and action taken to reduce the exposure.

SCOEL* BLVs* may be derived in one of three ways:

When there are studies in humans (occupational field studies or experimental laboratory studies on volunteers), linking adverse effects with concentrations of the chemical or its metabolites in biological media, the no-observed-adverse-effect-level (NOAEL*) may directly be used to derive the BLV*.

If human studies can 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* or OELV*. Supporting evidence may be drawn from toxicokinetic modelling. The two exposure limits (OEL*, BLV*) are generally based on equivalent effects of substances on the exposed worker (exemption: substances for which the OEL*or OELV* is established on the basis of local effects e.g., local irritation, a BLV* may still be based on systemic adverse effects)

In case of biological effect monitoring, the BLV* is directly derived from suitable studies in humans.

BLVs* derived by the first and third methods can be regarded as directly health-based and these methods are, in principle, to be preferred. The first approach has been used in the case of highly cumulative substances, for example, in the case of SCOEL* recommendations on lead, cadmium, mercury and hexachlorobenzene. It should be noted, that in order to use this approach, there should be good quality human [usually epidemiological] data linking adverse health effects to biomarker levels.

BLVs* derived by the second method are measures of exposure, which, for substances with health-based OELs* or OELVs*, can be regarded as adequate to prevent adverse health effects. The second approach is the approach most commonly used by SCOEL*. It is important to note that for the use of this approach, measured human data (either experimental data from controlled volunteer studies or data from workplace settings) providing a link between airborne concentrations of the compound and concentrations of the compound or its metabolites in biological media is needed. If this was not available, SCOEL* did not usually derive a BLV*. Toxicokinetic modelling was rarely used for the setting of BLVs* (2-methoxyethanol and its acetate being the only case).

The documentation of a recommended BLV* needs to include a discussion of the toxicokinetic and toxicodynamic parameters that determine the sampling time, which is very important especially for substances with short biological half-lives (of several hours or less).

SCOEL* ceased in 2019 and its tasks were transferred to European Chemicals Agency's (ECHA) Risk Assessment Committee (RAC). RAC applies the same approach for the setting of BLVs* as applied by SCOEL*. ECHA document (ECHA, 2019) describes that health based BLV* can be either derived directly from human studies containing data on biomarker levels and (early) biological effects, or from the OEL* or OELV* on the basis of established correlations between air levels and biomarker level. Detailed guidance is not available but (ECHA, 2019) refers to the ANSES* and MAK* guidance on recognized methods for the derivation of BLVs*. The main SCOEL methodology can be found in (SCOEL, 2017).

*2.1.2. MAK Commission**

The Permanent Senate Commission of the German Research Foundation (Deutsche Forschungsgemeinschaft) for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission*) has established biomonitoring assessment values for more than 100 substances and substance groups, respectively. Assessment values in biological material were typically set in whole blood, serum or urine. The MAK commission* rated other matrices, namely saliva and hair analyses, as not suitable for occupational biomonitoring. The character of the assessment values varies from health-based limit values, which are called Biological Tolerance values (Biologische Arbeitsstoff-Toleranzwerte, BAT* values) and Biological Guidance Values (Biologische Leit-Werte, BLW*), to descriptive based values, like Biological Reference values (Biologische Arbeitsstoff-Referenzwerte, BAR*) and Exposure Equivalents for Carcinogenic Substances (Expositionsäquivalente für krebserzeugende Arbeitsstoffe, EKA). EKA are not specific limit values, but a set of data that describe the correlation between the concentration of a substance in air and a biomarker in biological material.

BAT* values are based on a relationship:

- between the systemic exposure and the resulting effect of the substance or
- between external and internal exposure

The derivation of a BAT* value can be based on various constellations of scientific data, which reveal a quantitative relationship between exposure concentration and body burden and therefore permit the linking of biomonitoring values with the maximum workplace concentration (MAK*). These include studies that reveal a direct relationship between concentrations of a substance and metabolite in biological material (body burden) and adverse effects on health or studies which reveal a relationship between a biological indicator (effect parameter) and adverse effects on health.

The derivation of the BAT* value is based on the average of the systemic exposure. The BAT* value is exceeded when the average concentration of several examinations in an individual is greater than the BAT* value. Average values greater than the BAT* value must be evaluated in relation to occupational-medical and toxicological data.

Adverse effects on health cannot be deduced from the exceedance by one single measurement. This is not valid for acute toxicity, which must not be permitted at any time. The individual evaluations of substances include evidence of acute toxic effects. Substances with a BAT* value that targets an acute toxic effect are marked with an appropriate footnote in the List of MAK* and BAT* Values ("derivation of the BAT* value as ceiling value because of acute toxic effects").

Adherence to the BAT* values does not always guarantee the safe protection of the unborn child, as there are no or insufficient studies available on the harmful effects of many harmful substances on the health of the child. The MAK Commission* examines all harmful working materials with MAK* or BAT* values to determine whether a harmful effect is unlikely to occur, these are indicated by specific pregnancy groups. In the case of carcinogenic substances, the internal exposure must be assessed on the basis of the exposure equivalents for carcinogenic agents (EKA). Carcinogen categories and grouping categories of the MAK commission; for details refer to (DFG, 2021).

BLW*s are derived from non-carcinogenic effects of carcinogenic substances and for substances without sufficient data. They are likewise established as averages. If the BLW* is exceeded, the risk of health impairment cannot be excluded. Therefore, it is necessary to broaden the knowledge of the basics of the relationship between external and internal exposure and the resulting health risks in order to be able to derive BAT* values. In this context, BLW* are helpful in that they provide an important basis for the physician to be able to use biomonitoring at all. By continuous improvement of the technical conditions and the technical, hygienic and organizational protective measures, concentrations that are as far as possible below the BLW* should be aimed for. BAR* values describe the background level of a substance that is present concurrently at a particular time in a reference population of persons of working age who are not occupationally exposed to the substance. The BAR* values are based on the 95th percentile of the distribution function in a random sample from a defined population group. It must be taken into account that the reference level of the background exposure can be influenced by such factors as age, sex, social status, residential environment, lifestyle and geographical region. Occupational exposure in the individual or a group of workers can be identified by comparing the biomonitoring values with the BAR*.

*2.1.3. ACGIH®**

The American Conference of Governmental Industrial Hygienists is a not-for-profit corporation and a professional association of industrial hygienists and practitioners of related professions with headquarters in Cincinnati, Ohio, USA. One of its goals is to advance worker protection by providing timely, objective, scientific information to occupational and environmental health professionals.

ACGIH®* establishes Threshold Limit Values (TLV®*s) for chemical substances and physical agents and Biological Exposure Indices (BEI®s*). Today, the list of TLV®*s and BEI®s* includes over 600 chemical substances and physical agents, as well as over 30 BEI®s* for selected chemicals (ACGIH, 2021).

BEI®s* are developed by committee consensus through an analysis and evaluation process. The detailed scientific criteria and justification for each BEI®* can be found in the Documentation of the Threshold Limit Values and Biological Exposure Indices. The principal material evaluated by the

BEI®* Committee includes peer-reviewed published data taken from the workplace (i.e., field studies), data from controlled exposure studies, and from appropriate toxicokinetic modeling when available. The results of animal research are also considered when relevant. The Documentation provides essential background information and the scientific reasoning used in establishing each BEI®*. In recommending a BEI®*, ACGIH®* considers whether published data are of reasonable quality and may also consider unpublished data if a complete copy of the data/report is provided to ACGIH®*, although unpublished data are never used as the primary basis for a BEI®*.

BEI®s* generally represent the levels of determinants that are most likely to be observed in specimens collected from healthy workers who have been exposed to chemicals to the same extent as workers with inhalation exposure at the TLV®*–Time-Weighted Average (TLV®*–TWA*). However, there are BEI®s* for chemicals for which the TLV®s* are based on protection against non-systemic effects (e.g., irritation or respiratory impairment) where biological monitoring is desirable because of the potential for significant absorption via an additional route of entry (usually the skin). There are also BEI®s* that better predict health effects than air levels and finally, BEI®s* that are based on the levels in the environmentally exposed population. The BEI®* generally indicates a concentration below which nearly all workers should not experience adverse health effects. The BEI®s* have notations that indicate certain limitations. Notation "B" is given when the determinant may be present in biological specimens collected from subjects who have not been occupationally exposed, at a concentration that could affect an interpretation of the results. It is assigned when the observed 95th percentile value of a random sample from national population studies is more than 20% of the BEI®*. "Pop" indices are assigned when there are insufficient data to establish numerical BEI®* but where there are sufficient data on background levels in the general population to guide the health care professionals in the exposure assessment. Information given in the BEI documentation includes analytical methods, possible potential for confounding exposures, specimen collection recommendations, limitations, as well as other essential information, specific for each compound and analyte.

*2.1.4. ANSES**

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES*) was created on 1 July 2010. It is an administrative public establishment accountable to the French Ministries of Health, Agriculture, the Environment, Labour and Consumer Affairs. One of the main missions of the French Agency is the derivation of reference values (toxicological reference/limit values, occupational reference/limit values, DNEL*, and other related values). For workers, in addition to OEL* or OELV*, ANSES* derives, when it is relevant (if routes other than inhalation contribute largely to absorption, for cumulative pollutant, to take into account interindividual factors), biological limit values (BLV*). Since 2010, ANSES* has given recommendations for biological limit values for about 19 different substances, which are available on ANSES* OEL*/BLV* website (ANSES, 2021). The Biological limit value (BLV*) is the limit value for the relevant biomarkers (parent or one of its metabolites in a biological media). Depending on the available data and on the mode of action of the substance, the BLV* is derived according to different approaches:

1- <u>For substances with a threshold effect</u>

The options are similar to those of the former SCOEL*:

- As the 1st option of the SCOEL*, data based on epidemiological or volunteer studies are analyzed in order to quantify a dose-response relationship between biomarkers concentrations and the critical effect.
- As described by the SCOEL* above, if it is not possible to quantify the relationship between concentrations of biomarkers and health effects, the alternative approach is to quantify the relationship between concentrations of biomarkers and atmospheric concentrations, to establish a BLV* corresponding to exposure to the French 8h-OEL*(regulatory or recommended by ANSES*). In this case, however, extrapolations are based on strong correlation(s) between the internal concentrations and the atmospheric concentrations of the substance, giving regression equation(s) or kinetic modelling.

<u>2- For substances without a threshold effect</u>

- in some cases, BLVs* may be based on a risk assessment and expressed by a scale providing three individual excess risks: 10^{-4}, 10^{-5} and 10^{-6} (i.e., an excess risk of contracting an additional cancer for respectively 10000, 100000 and 1000000 exposed people). These relationships may be derived from kinetic modelling, or correlations from exposure data

- in the absence of sufficient quantitative data, the biological limit value is calculated on the basis of another effect; the BLV* is then called a "pragmatic BLV*". This latter value does not guarantee the absence of health effects, but aims to limit exposure to these substances in the workplace.

ANSES also recommends biological reference values (BRVs*), which correspond to concentrations found in a general population whose characteristics are similar to those of the French population. These BRV*s cannot be considered to offer protection from the onset of health effects, but allow a comparison with the concentrations of biomarkers assayed in exposed workers). More information about derivation methods can be found in (ANSES, 2014, 2017)

*2.1.5. HBM4EU**

HBM4EU* is a joint effort of 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020 (HBM4EU website, 2021), Within the framework of the HBM4EU five years project (from 2017 to 2021), human biomonitoring guidance values HBM-GV*for the general population and for workers have been derived. It should be noted that these values are recommendations from a research project and do not have any regulatory status. Values are published for Cadmium (Lamkarkach et al., 2021), Bisphenol A (Ougier et al., 2021), Phthalates and DINCH (Lange et al., 2021) and the Pyrrolidones NMP and NEP (David et al., 2021). Further information and values are available in the Deliverables D 5.2, D 5.6 and D 5.9 and D 5.12 on the HBM4EU website.

The methodology of HBM-GVs derivation is based on existing derivation schemes as used by the German Human Biomonitoring Commission (German HBM Commission 1996, 2007, 2014) regarding the general population and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES (2014)) regarding the occupational field. The data collection on the substances of concern is based as a priority on recently published reports, if available. These reports can be issued from established EU bodies, such as SCOEL*, EFSA*, EU* (risk assessment reports (RAR)), international organisations (e.g., WHO*, IARC), and relevant national scientific committees (e.g., DECOS, MAK*, US-EPA, ATSDR, US NIOSH, German HBM Commission, ANSES*). REACH registration dossiers and the recent peer- reviewed literature are also be considered for additional and/or new data, but an exhaustive review of the scientific literature is not performed (Apel et al., 2020).

*Options for deriving HBM-GVs**

Three options are available (for both HBM-GV*$_{GenPop}$ and HBM-GV*$_{Workers}$). The 1st and 2nd options correspond to options already described above by SCOEL* and ANSES*. However, there is a 3rd possible option, on the basis of the HBM-I value and BE$_{POD}$* approach. This approach consists of extrapolating a critical dose (POD*) identified in a key animal study into a human internal concentration of a selected biomarker. After applying assessment factors to convert the POD* to a 'toxicity reference value (TRV*)-like' value, the next step is to calculate the internal concentration of the substance/its biomarker(s) corresponding to the 'TRV-like' value (via PBK* modelling or a simple urinary mass balance approach) (for further details see Apel et al., 2020).

A global level of confidence (LoC) (high, medium or low) is attributed to each derived HBM-GV reflecting the uncertainties underlying its derivation. The LoC* is attributed regarding the selected option of derivation, nature and quality of toxicological and toxicokinetic data; choice of the critical effect and the mode of action; the selection of critical dose; and the selection of the key study. More information about derivation methods can be found in (Apel et al., 2020). Examples on the allocation of confidence levels are given in annex A).

2.2. Summary review of widely applied methodologies in OBL* derivation

The following tables summarize the existing schemes and methodologies for the derivation of OBL*, possible differences in the approaches and data requirements. It should be noted that there are also other national schemes available but these have been selected since their methodologies are published/described and available. It should be noted that HBM4EU values are only research project related values and have no regulatory status or any link to national or regional regulations.

Table 1. General prioritisation and review process for OBL* derivation schemes described above.

Step / organisation	SCOEL* / RAC* (Europe)	MAK* (Germany)	ACGIH* (USA)	ANSES* (France)	HBM4EU*
Working program Elaboration **(prioritisation)**	Mandated for different substances received from DG Empl	Requests from German authorities, occupational physicians and hygienists	Substances selected from requests sent to ACGIH* or from the TLV* committee	Request from the French ministry for Labour (DGT) or internal request (ANSES*)	Substances selected from the different HBM4EU* prioritization rounds
Appraisal process	SCOEL*: SCOEL* experts prepared the recommendation (until year 2019) RAC*: ECHA* prepares scientific report, which is evaluated by RAC* and RAC* opinion formed.	Two-step collective appraisal: (1st) Working group on Setting of BAT* values; (2nd) Plenum of MAK commission*	Two-step process: 1st a feasibility assessment, and if sufficient scientific evidence 2nd BEI* development	Collective appraisal: Working group on BME* Expert Committee on Reference Values	Elaboration of a document by UBA/ANSES *ANSES*: the working group on BME is contributing*
Validation process	SCOEL*: (1) Document send to consultation to national experts ((2) Comments taken into account and responses sent to commenting experts. RAC*: (1) Public consultation of the ECHA document. (2) RAC consultation of the RAC opinion, stakeholders can comment in the meeting.	(1) Two-step collective appraisal (see before); (2) public feedback period (6 months after announcement); (3) Re-evaluation in case of public feedback	Committee members vote for "Notification of intended changes" published in the booklet. A finalized approved document available for public comments. Document adapted by BEI* committee and approved.	1- Validation of a collective expertise report 2- Public consultation (comments taken into account in a final version) 3- Adoption of the conclusions	1- Document send to consultation to national experts and experts from European agencies 2- Comments taken into account and responses sent to contributing experts
Diffusion and endorsement process	1. SCOEL* recommendation published in EC* website. RAC* opinion/ECHA* scientific report published in	Annual publication of the HBM assessment values in the "List of MAK and BAT values" (issue and delivery to the German Ministry	Annual publication of the TLV-BEI booklet by ACGIH*.	1 – Publication of ANSES opinion 2- Social	Sending to the EU Commission and Publication in peer reviewed

Step / organisation	SCOEL* / RAC* (Europe)	MAK* (Germany)	ACGIH* (USA)	ANSES* (France)	HBM4EU*
	ECHA* website. 2. Both go to DG Empl and ACSH and legislative process to set limit values is initiated. 3. If binding limit value is set an impact assessment is performed and socio-economic and feasibility factors are taken into account. Note that although SCOEL*/RAC* has recommended >20 BLVs*, only blood lead has been included in legislation as a binding BLV*.	of Labor and Social Affairs on July 1st); the Committee of Hazardous Substances (advisory board of the German Ministry of Labor and Social Affairs) takes notice and discusses the values of the MAK commission* in general, but is free to set official values different.		concertation (for discussion on possible delays, technical and economic feasibility problems) 3- Publication of a decree (binding OEL*or BLV*) or an order (indicative OEL*or BLV*)	journals and on the HBM4EU website

Table 2. Brief characterisation for widely used OBL* derivation schemes

Step / organisation	SCOEL* /RAC* (Europe)	MAK (Germany)	ACGIH* (USA)	ANSES* (France)	HBM4EU*
Recommended Values	BLV*, BGV*	BAT*, BLW*, BAR*, EKA*	BEI*	BLV*, pragmatic BLV*, BRV*	HBM-GV*Workers
Method of derivation for substances with a threshold effect	Relationship between health effects and BME* levels or, Correlation between atmospheric value and BME levels Mass balance approach or PBK* modelling has not been used by this far without measured data on correlations.	2 options - Relationship between health effects and BME* levels - Correlation between atmospheric value and BME levels	2 options - Relationship between health effects and BEI* levels - Correlation between air and biological values to find the equivalent BEI* for the set TLV* value PBK* modelling used for support.	2 options - Relationship between health effects and BME* levels - Correlation between atmospheric value and BME* levels *Mass balance approach can be investigated* and PBK* modelling used as support	3 options - Relationship between health effects and BME* levels - Correlation between atmospheric value and BME levels - based on a POD*-experimental study on animal) *Tools used: Mass balance approach or PBK* modelling widely used*
Method of derivation for substances	No BLV* derived, only BGV*.	Yes, BAR* and EKA*	Yes, if other health effects occur.	Excess risk and if not possible recommendation of a	No

without a threshold effect				pragmatic value and/or BRV* (2 options above)	
Method of derivation for substances with limited data	No BLV* derived.	Yes, BLW*	If negative feasibility assessment then no BEI*	Recommendation of a BRV* if no data? No value	Where lack of data? Low level of confidence attributed if no data? No value

2.3. Summary health-based OBL* derivation methods

Overall, four different methods were identified that can be used for the derivation of health-based Occupational Biomonitoring Levels (OBL*):

1. Derivation of health-based biomonitoring values directly based on the data on correlations between biomarker and health effects.
2. Derivation of biomonitoring values indirectly using established correlations between air and biomarker levels.
3. Use of PBK* modelling to derive biomarker levels from external intake
4. Use of simple approaches, like the urinary mass balance approach to calculate corresponding biomarker levels for POD*s (NOAELs* etc.), and applying assessment factors to account for the uncertainties.

These OBL* derivation methods are described and applied to selected case studies in the chapters 3.2 Derivation of OBL for human toxicity data rich substances, and in the chapter 3.3 Derivation of Provisional OBL for substances with limited human toxicity datasets. A general tiered approach for derivation of health and non-health based OBLs* is provided in chapter 5.

3. Derivation of different Occupational Biomonitoring Levels (OBL)

3.1. Selection criteria of biomarkers & recommended methods

3.1.1. Selection criteria of biomarkers

Before the derivation of OBL* it is necessary to consider the applicability of available exposure biomarkers for the assessment of occupational exposure. Selection criteria for biomarkers to be applied in exposure assessment are listed below in Table 3.

Table 3. Criteria for selection of biomarkers, adapted from (Vorkamp et al., 2021, SFMT, 2016)

Selection criterion for a biomarker	Brief explanation
Specificity	Specificity with respect to the chemicals, i.e., its capacity to demonstrate exposure to this chemical agent with the lowest risk of false positive assessments. The specificity requirements of biomarkers are more important, as the expected exposure levels are lower.
Sensitivity	The measured concentration of the biomarker needs to correlate with the substance intake dose. Sensitivity with respect to the chemicals, i.e., its capacity to demonstrate exposure to this chemical agent with the lowest risk of false negative. Biomarkers should be able to detect low exposures. Sensitivity can be assessed by comparing its limit of quantification (LOQ) with expected values in the general population and workers. An analytical method with an LOQ* at the level of an OBL* should be avoided. Preferably the LOQ* should be lower than 10% of an OBL* with a variability of less than 50%.
Appropriate half-time	The biomarker should preferably have a half-time sufficiently long (few hours) to avoid excessive intra-individual variability in BM* measurements
Stability after sample collection	The biomarker needs to be stable in the sample for many hours during (refrigerated) transportation to the laboratory or before storage in a biobank. Transport conditions can be optimized easily to ensure stability.
Stability during storage	The cryo-preservability needs to be sufficient to guarantee high stability during storage in the biobank, usually at -20 °C.
Matrix availability and sample collection	A biological matrix that is easily accessible; sampling is non-invasive as possible and is easy to implement, a validated sampling protocol is preferred
Measurement validity	The biomarker concentration in the sample is not likely to be altered by contamination with a ubiquitous parent substance from the environment preceding and during the analysis. Variations in matrix composition can be easily corrected for (e.g., creatinine in urine, lipids in serum).

3.1.2. Recommended methods based on review

After confirming the availability of the valid biomarker for occupational exposure assessment, different methods can be used for the derivation of health-based occupational biomonitoring levels (OBLs*) for chemicals. These are listed in the table 4 below with preference ranking. In case of non-threshold substances, biomarker levels corresponding to a specific cancer risk level can also be derived using

this approach. Later in this chapter these OBL* derivation methods are applied to selected case studies. A general tiered approach for derivation of health and non-health based OBLs* is provided in chapter IV.V.

Table 4. Recommended methods for refined OBL* derivation with preference ranking

Derivation method	Data need	General Preference Ranking
1) Correlated exposure-effect biomonitoring: health-based biomonitoring values directly based on the data on correlations between biomarker and health effects	high	1 (based on confidence assessment)
2) Correlated OEL* or OELV* biomarker level: biomonitoring values using measured data on correlations between external exposure levels and biomarker levels. The OBL is usually set to correspond to health-based OELs set for air levels. [1]	medium-high	2 (based on confidence assessment)[2]
3) Simulated PBK* level: PBK* needs to cover all relevant exposure pathways (inhalation, skin uptake, and ingestion) and should predict the urinary biomarker excretion concentrations as well as central compartment (blood) concentrations. PBK* models should as far as possible incorporate human parameters and be adjusted or calibrated with human data.	medium-high	2-3 (based on confidence assessment)
4) Health based mass balance approach: health-based biomonitoring values based on simple approaches e.g., urinary mass balance approach to calculate biomarker levels corresponding to existing OELs* or to health PODs* (NOAELs* etc), and applying AFs* to account for the uncertainties (see chapter 3.3).	low-medium	3 (based on confidence assessment)

[1] OBL*s derived indirectly using established correlations between air and biomarker levels are associated with the existing OEL's and OELV uncertainties. These are related to: 1) the underlining toxicological and epidemiological data used to derive dose-response, and 2) the interspecies extrapolation.

The methods 1 and 2 have traditionally been used in occupational health for setting limit/guidance values for biomarkers for substances with a rich database on health effects and toxicokinetics. These methods are based on measured data and thus, given the highest preference. Although method 2 is based on measured data and correlations between air and urinary concentrations, the quality may vary. In addition, the data might be old and not cover exposure ranges relevant of today. This will have an impact on the confidence assessment, as exemplified with case studies later in this guide. PBK* modelling (used as an integrative term for PBPK and PBTK modelling) can be used to support measured data for air-urine correlations for method 2. Although not widely used, one example is from SCOEL* and their recommendation of a BLV* for 2-methoxyethanol (SCOEL, 2006). This BLV* was derived using a one-compartment model assuming time-invariant linear kinetics to estimate urinary excretion after occupational exposure. The predicted urinary concentrations were compared to actual measured data obtained from occupationally exposed workers. In general, when an existing OEL*or OELV* is taken as a starting point, the biomarker value needs to be updated with the revision of the OEL* or OELV*. Indeed, all such values need to be updated on a regular basis because toxicological knowledge increases over time and can lead to outdated OELs*or OELV*, and consequently, outdated biomarker values. The revised OBL* needs to be derived based on the new data. It should be noted that for methods 3 and 4, existing OELs* can be used as a starting point. The use of PBK* usually requires a validated substance or at least a substance group-specific model for all relevant exposure pathways. Such PBK* models were not or only partially available for the four selected case studies in this guide (e.g., for Aluminum there is a PBK* model only for oral exposure). Method 4 requires a minimum amount of toxicokinetic and health-related data, consequently, they may result more often in a Provisional OBL (POBL*) (see

chapter 3.3), hence the lower preference. Conversely, confidence assessment of data might alter the overall preference method for method 4. Data sets with high or at least medium to high confidence in the overall confidence assessment might give a more robust estimate compared to derivation methods 1-3, and thus, can be a preferred option for a refined OBL* derivation.

3.2. Derivation of OBL* for human toxicity data-rich substances

3.2.1. Application of OBL derivation methods for case studies*

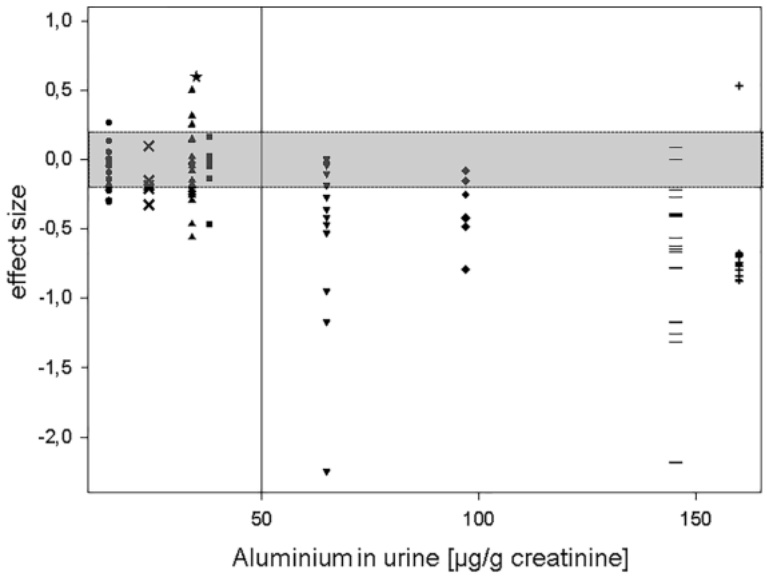
Two organic (DEHP* & HDI*) and two inorganic (chromium(VI) & aluminium) substances were chosen as case study substances because of their different toxicological profiles and wide use in several industry sectors. Since all of these substances have health- based limit values for biomarkers (set e.g., by German MAK Commission*, ANSES*, HBM4EU or ACGIH*), the descriptions given below are taken from these evaluations.

Aluminum data on direct correlations between biomarker and health effects are available. HDI* and Cr(VI) data on correlations between air and biomarker levels are available. Thus, approaches 1-2 can be considered for these substances. This kind of data is missing for DEHP*, nor does it have PBK* data specific for occupational exposure scenarios. Therefore, the German MAK Commission* and the HBM4EU* project used method 4, which is recommended for setting Provisional OBLs* (POBLs*). Setting refined OBLs* might be possible if the data set can be considered sufficiently robust according to the confidence assessment criteria (see chapter 3.2.3). In the following paragraphs these case studies are described.

Aluminium

Occupational exposure to aluminium occurs usually via inhalation of aluminium-containing fumes e.g., during welding processes. Inhaled aluminium may be retained in the lungs before a gradual release into the bloodstream, but this will depend on the exact form of aluminium. Aluminium can accumulate in the bones, which gives it a long half-life >20 years. A similar half-life is predicted for accumulation of aluminium in the brain. Lung and bone burdens explain the long serum and urinary half-lives (which may be more than one year e.g., in welders after the cessation of exposure). The main target organs for aluminium in humans are the central nervous system and lungs. Aluminium causes lung fibrosis (aluminosis) in occupationally exposed workers. Some epidemiological studies have suggested an association between urine or serum (U-/S) Al levels and effects on the central nervous system in workers. The data from this direct correlation between central nervous system effects and biomarker levels have been used as a basis for deriving the biological limit value for urinary aluminium (U-Al) concentration of 3 nmol/L (2.3 µmol/g creatinine or 62 µg aluminium/g creatinine) (Riihimäki and Aitio, 2012). The German MAK Commission has also derived a similar U-Al level earlier (in 2009) based on the correlation between air and urinary aluminum concentrations in aluminium welders. The German MAK* value for aluminium is 1.5 mg/m^3. The BAT value was based on the relationship between total dust concentration (mg/m^3) and the urinary excretion of aluminium (µg/g creatinine) in aluminium welders. This air concentration corresponds to approximately 60 µg aluminium/g creatinine. This U-Al value was an earlier BAT* value for aluminum, which was recently updated by the German BAT* value (Klotz et al., 2021). The updated BAT* value is based on the direct correlation between the occurrence of subclinical neurotoxic effects in aluminium-exposed workers and urinary aluminium levels, and was set at 50 µg/g creatinine. Sampling time for long-term exposures was set at the end of the shift after several shifts. Figure 1 (taken from the German BAT documentation for aluminium – (Klotz et al., 2021) combines the key information from nine epidemiological studies showing cognitive effect sizes identified in the studies related to the medians of urinary aluminium concentrations (effects sizes below zero mean an adverse motor or cognitive effect, see further details in Klotz et al., 2021).

Figure 1. Cognitive and motor effects identified in different studies; figure copied from (Klotz et al., 2021).



Generally, several epidemiological studies showing consistent effects are needed when using epidemiological data to derive a relationship between biomarker and health effects for the setting of OBLs. Also, the biological plausibility of the effect should be considered in addition to supportive animal data or other mechanistic data observing similar effects as in humans. When evaluating available data, the German BAT documentation on aluminium (Klotz et al., 2021) considered the following aspects when concluding on the relevance of the data for the dose-response setting:

- Magnitude/size of the exposure effect
- Number of exposure effects
- Type of effects
- Consistency of effects in various studies
- Lack of reversibility of exposure effects

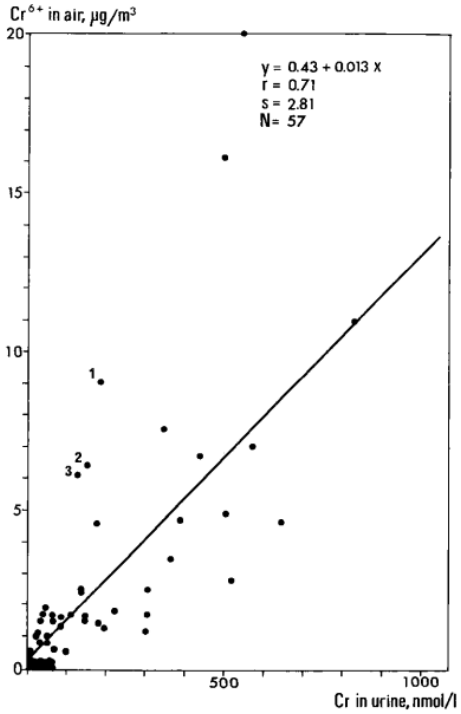
Chromium(VI)

Hexavalent chromium is a genotoxic carcinogen for which no safe level can be identified for its carcinogenic effects. A linear approach has been used to assess cancer risks associated with specific Cr(VI) air concentrations found in occupational settings. For example, (SCOEL, 2017) estimated that occupational exposures to hexavalent chromium at an air concentration of 1 µg/m^3 (8 h TWA*) over 40 years resulted in an excess cancer risk of 4/1000 exposed workers, while an air concentration of 5 µg/m^3 resulted in an excess cancer risk of 20/1000. SCOEL* did not propose an OEL* or BLV* because no threshold could be given for hexavalent chromium. In contrast, a binding occupational air limit value of 5 µg Cr(VI)/m^3 is found in the EU Directive 2004/37/EC on the protection of workers from risks related to exposure to carcinogens or mutagens at work (EU, 2004).

Urinary chromium (U-Cr) has been traditionally used for the biomonitoring of hexavalent chromium. This is an unspecific exposure biomarker that may be influenced by exposures to trivalent chromium. Although simultaneous exposure to hexavalent and trivalent chromium compounds may complicate the interpretation of U-Cr data e.g., in welding where exposure to both trivalent and hexavalent chromium species exists, a recent European study shows that it is still a valid biomarker for occupational Cr(VI) exposure with a strong correlation with air Cr(VI) levels (Santonen et al., 2021).

In France, ANSES recommends a pragmatic BLV* of 2.5 µg/l (1.8 µg/g creatinine) for U-Cr (sampling at the end of the shift and end of the week) for the plating sector. This is based on the air limit value of 1 µg/m^3 and established correlations between Cr(VI) air and U-Cr levels in workers exposed to soluble Cr(VI) compounds during chrome plating activities (ANSES, 2017). The value is restricted to chrome plating since the correlation data comes from that sector and established correlations might not sufficiently reflect the situation in other work tasks, e.g., welding. The correlation equations most frequently used for the setting of limit /guidance values for occupational exposure to Cr(VI) include those published by (Lindberg and Vesterberg, 1983) and (Chen et al., 2002), both considering the data from work tasks with plating baths. Figure 2 shows the correlation published by (Lindberg and Vesterberg, 1983) on-air and urine levels in chrome plating. Generally, when judging the reliability of established correlations, attention should be paid to the range of substance in air/urine concentrations covered by the measured data, the number of data points, and the strength of the correlation. If there are several studies on the same substance, then coherence between the studies should also be considered. In the case of Cr(VI), the air/urine correlations have been described from workplaces, taking into account possible Cr(VI) intake via the skin route or hands-to-mouth.

Figure 2. Air-urine correlation of Cr according to Lindberg and Vesterberg 1983



The ANSES air limit value of 1 µg/m^3 for Cr(VI) is not health-based but is set as a level that can be reliably measured in occupational settings. Using the same correlation equations as used by ANSES (based on studies by (Chen et al., 2002 and Lindberg and Vesterberg, 1983)) the currently applicable EU OEL* of 5 µg/m^3 was calculated to correspond to U-Cr-levels of ~10 µg/L. Since this is based on the regression data from chrome platers exposed to soluble Cr(VI) species the same correlation may not apply to workers exposed to other Cr(VI) species e.g., via the welding fumes. Recently, new worker exposure regression analyses became available (Viegas et al., 2022) which could be considered for following OBL* derivations. Additionally, in the EU project HBM4EU a derivation of a HBM guidance value for workers is close to finalization (HBM4EU, 2022 in prep.) which can be considered too as soon it becomes available. It should be noted that general population background levels (95th percentiles) for urinary chromium generally vary between 0.5-0.8 µg/L in different populations (Santonen et al. 2021).

HDI (1,6-hexamethylene diisocyanate)

Respiratory sensitization is the critical effect of HDI* exposures. The corresponding diamine, HDA*, in urine is typically used as a biomarker of exposure for HDI*. There are no data on the relationship between adverse effects and HDI* biomarker (HDA*) levels. However, there is some information on the relationships between concentrations of HDI* in air and HDA* in urine from occupationally exposed workers. These data have been used to set BAT* and BEI* values for U-HDA*. According to the correlation equations published by (Maitre et al., 1996), TLV* and MAK* values of 0.034 and 0.035 mg/m^3, respectively, correspond to U-HDA* concentrations of 15 µg/g creatinine in post-shift samples. Thus, for HDI*, the same approach (method 2) as in the case of Cr(VI), was used by MAK* commission to derive a BAT* value for HDI*. Although (Maitre et al., 1996) dataset is small with only 19 occupationally exposed individuals, it is supported by other data, including the data by (Gaines et al., 2010 and 2011) which would give U-HDA* concentrations of ~11 µg/g creatinine corresponding a TLV of 0.034 mg/m^3. However, it should be noted that both TLV* and MAK* values for air HDI levels are based on irritation effects and do not fully account for respiratory sensitization.

RAC* (ECHA, 2020) has recently published an opinion on diisocyanates, which establishes a dose-response between air levels of the "NCO (functional isocyanate group) group" and the occurrence of asthma. According to RAC*, no safe level, and therefore, no OEL* and BLV *can be proposed for diisocyanates. In addition, there may still be an excess risk of 1% for bronchial hypersensitivity at 0.11 µg/m^3 over a working lifetime and 5% at > 0.67 µg/m^3 expressed as NCO groups. These are clearly lower than the current TLV* and BAT* air concentrations, which are based on irritation. If 1% excess risk is considered an "acceptable" risk level, then it is not possible to use the correlation equation from (Maitre et al. 1996) (or other studies), to calculate urinary levels because this equation does not cover these low concentrations. In addition, a correlation has been established between air HDI monomer and urinary HAD* by (Maitre et al., 1996). In workplaces where prepolymers of HDI are used in coating applications, this may result in underestimation of exposure to reactive NCO groups coming from HDI* prepolymers, which are not reflected as elevated HDA* levels. These are the main limitations related to these correlations.

DEHP(di(2- ethylhexyl) phthalate)*

DEHP* is a plasticizer that has been shown to exert antiandrogenic effects resulting in adverse reproductive effects. There are no available data showing direct correlation between urinary DEHP metabolite concentrations with adverse health effects nor with DEHP air concentrations in exposed workers. Absent are also PBK* models concerning occupational exposure via inhalation and skin uptake. This means that it is not possible to use methods 1-3 above for setting biological limit values. The German MAK* Commission used a urinary mass balance approach to set a biological limit value for DEHP* corresponding to the MAK value of 2 mg/m^3. This has been set to a combined urinary concentration of the four metabolites (MEHP + 5-OH-MEHP + 5-oxo-MEHP + 5-cx-MEPP) and represents the steady- state level of these metabolites in urine. The sum of these four metabolites at steady state was set to 4 mg/g creatinine, which is considered a BLW*. Sampling time is for long-term exposure at the end of the shift after several shifts. A MAK* value of 2 mg/m^3 for the inhalable fraction has been calculated by toxicokinetic extrapolation from the lowest oral NOAEL* of 3.7 mg DEHP/kg body weight and day (90-day rat study). At the LOAEL* (38 mg/kg body weight and day) vacuolization of Sertoli cells was observed. Confidence for this BLW* was judged as "low" because a conversion factor was derived from oral DEHP* uptake studies and metabolite excretion data from a male volunteer study.

HBM4EU* set an HBM-GV* for DEHP* based on the urinary mass balance approach (method 4) to derive biomarker concentrations from air concentration values. The HBM-GV* for workers (HBM GV_{Worker}) was set for one metabolite; 5-cx-MEPP, as opposed to the sum of four metabolites, which make up the BLW* (4 mg/g creatinine). HBM GV_{Worker} for urinary 5-cx-MEPP was set to 0.62 mg/g creatinine and was based on fertility effects. The POD* for this fertility effect was 5.8 mg/kg bw/d (NOAEL*) and the onset of aspermatogenesis was seen in the study by (David et al., 2000). Confidence for this HBM GV *was judged as "low" because of the lack of validated PBK* models for occupational

DEHP exposure (Lange et al. 2021 and Deliverable D 5.2 in HBM4EU). There are also limited data for the development of a PBK* model for occupational exposure via inhalation and skin absorption.

3.2.2. Main uncertainties related to the derivation of an OBL for human toxicity data-rich substances*

The main uncertainties related to the derivation of OBLs* that are directly based on correlations between biomarker and health effects (method 1), are the strength of the evidence for the correlation, possible confounding factors, and biases. An experienced risk assessor needs to evaluate the consistencies of the epidemiological studies for the identified health effect as well as the biological plausibility of this effect and available animal or other mechanistic or kinetic data supporting these effects in humans.

OBLs*derived indirectly using established correlations between air and biomarker levels are associated with the existing OELs* uncertainties. These are related to: 1) the underlying toxicological and epidemiological data used to derive dose-response from external exposures, and 2) the correlations between external and internal exposures. The most significant uncertainties are often related to the human relevance of available animal data and extrapolations from animal to human. This is especially applicable to animal toxicity data used to derive NOAELs*, LOAELs*, and BMDs*. Although these uncertainties can be covered by assessment factors (which are often only “default” factors, not based on real data on the level of the uncertainty, see chapter 3.3.5, they do not remove the underlying uncertainty related to human relevance. If high assessment factors are needed to account for the uncertainties in toxicological (dose-response) data, small uncertainties, such as extrapolations of external exposure to internal biomarker level become less important. As discussed above in the case of Cr(VI), when evaluating the reliability of the established correlations, attention should be paid to: 1) the range of air and urine concentrations covered by the measured data, 2) the number of data points, 3) strength of the correlation, and if there are several studies for the same substance, 4) coherence between studies. Correlations obtained from controlled volunteer studies may be more reliable compared to the correlations obtained from the workplace with their inherent confounding factors.

Table 5. Summary of main uncertainties in OBL* derivations

Approach	Main uncertainties and reasons for variation
1. Derivation of health-based biomonitoring values directly based on the data on correlations between biomarker and health effects.	General uncertainties related to epidemiological data, i.e., confounding factors related to the data, biases. Consistency of the data Biological plausibility
2. Derivation of biomonitoring values indirectly using established correlations between air and biomarker levels and existing OELs* or OELV*.	1) the underlying toxicological and epidemiological data used to derive dose-responses from external exposures. High uncertainties related to the toxicological database, the greater the assessment factors. 2) the correlations between external and internal levels data. When evaluating the correlation data, attention should be paid to: the strength of the correlation, availability of multiple studies showing correlation, consistency of the correlations between the studies and possible reasons for the variation (e.g., the extent of skin exposure may explain variation in some cases), exposure ranges cover the interested concentration (necessary to extrapolate to much lower levels?) In case of metals and metalloids also the information on speciation of metal compound and health relevant fraction, e.g. percentage of the alveolar fraction with a specific diameter is needed for assessment of results

3. Use of PBK* modelling to estimate biomarker levels from external intake.	PBK* needs to cover all relevant exposure pathways (inhalation, skin uptake, and ingestion) and should predict the urinary biomarker excretion concentrations as well as central compartment (blood) concentrations. PBK* models should as far as possible incorporate human parameters and be adjusted or calibrated with human data.
4. Use of simple approaches, such as the urinary mass balance approach to calculate corresponding biomarker levels for PODs* (NOAELs* etc.), and applying assessment factors to account for uncertainties. (see chapter 3.3)	PODs* relevance and reliability Urinary fraction data Confidence assessment

*3.2.3. Confidence assessment of OBLs**

The confidence of the OBL* derivation needs to be assessed to allow appropriate risk-management. Confidence assessments have been applied in HBM4EU guidance value setting and in WHO/ICPS, ANSES, US-EPA, and Health Canada when setting limit values for the general population. Confidence assessment within HBM4EU has been described by (Apel et al., 2020). The level of confidence is considered in the following aspects for both occupationally exposed adults and the general population:

- nature and quality of the data
- choice of the critical effect and the mode of action
- key study
- critical dose & point of departure (POD*)
- extrapolations across and within species

In addition, HBM4EU (Apel et al., 2020) also highlights two main elements described earlier for assessing the confidence in the Biomonitoring Equivalent (BE*) values:

Understanding of the relationship between the measured biomarker and the critical or relevant target tissue dose metric; and robustness of the available toxicokinetic models and data.

The first five aspects are very much related to the general uncertainties related to the hazard and dose-response assessment and apply to any limit values (i.e., are not specific for OBLs*). Only the two latter aspects (1, 2) are specific for the OBL setting. The OECD working group considered that more emphasis could be put on aspects specific for the OBL* setting. One of the main issues highlighted by the OECD working group was whether deriving an OBL* (instead of an OEL*or OELV*) will or will not bring significant additional uncertainty to the overall uncertainties already caused by the uncertainties related to the hazard data. Thus, the OECD working group proposes to use three main aspects when assessing uncertainties:

Table 6. Confidence assessment categories for OBL*derivations

1st confidence category	Hazard and dose-response assessment, selection of POD*
2nd confidence category	Selection of biomarker (covering aspects related to the specificity and sensitivity of the biomarker, and e.g., analytical aspects including the likelihood of pre-analytical errors (like confounding exposure sources, contamination)
3rd confidence category	Toxicokinetic aspects, including excretion kinetics; quality & robustness of the toxicokinetic data, quality & robustness of the established correlations between external and internal levels or correlations between toxicological effects and biomarker levels, urinary fraction data

All these three aspects are scored as low, low-medium, medium, medium-high, and high, which feeds into an overall confidence score. Proposed numerical scoring 1=low, 1.5=low-medium, 2= medium, 2.5= medium-high, 3= high. If there are significant data gaps, meaning that two out of three scores are “low” (or there is one “low” and the other two scores are “low-medium”), the OBL* will be described as “provisional” (POBL*). Generally, an OBL* can be proposed, if the average confidence score is equal or better than medium. However, using expert judgement, when one score is low and others medium or high, a POBL* may be also justified instead of an OBL*, but the decision should be well justified and made only on case-by-case basis .

In chapter 9.1 Annex A in Table A1 we have presented confidence assessment examples for the (P)OBLs* derived for case study substances.

3.3. Derivation of Provisional Occupational Biomonitoring Level (POBL) for substances with limited human toxicity datasets

3.3.1. Rationale

Provisional Occupational Biomonitoring Levels (POBLs*) can be derived for chemical substances with limited human toxicity data availability and used for identifying and managing possible occupational health risks. In addition, POBLs* may be used to select appropriate personal protective equipment and needed worker training. Many chemicals, including EU* REACH* regulation registered chemicals, have limited exposure-toxicological effects datasets as requirements for toxicity testing depend on their tonnage. For chemicals with limited datasets, PBK* models are often not available due to the lack of scientific data and time-consuming validation processes. Other approaches for deriving POBLs* are thus necessary to protect workers from possible health effects. For example, POBLs* can be derived with limited data with sufficient quality and a valid No Observed Adverse Effect Level (NOAEL*), a Lowest Observed Adverse Effect Levels (LOAEL*) or Benchmark Dose (BMD*). These approaches using NOAEL*, LOAEL* or BMD* are already described by the German Human Biomonitoring Commission (German HBM Commission, 2014), the Biomonitoring Equivalents approach (Hays and Aylward, 2009), and HBM4EU (Apel et al., 2020). All these incorporate urinary mass balances.

POBL* are the default outcome of refined OBLs* that fail to meet medium or high confidence assessments (see chapter 3.2.3).

3.3.2. Method description and guidance for urinary mass balance approach

A derivation of an HBM-I (German HBM Commission, 2014) value for the general population is intended for life-long exposures. It indicates a tolerable risk level in populations at which no adverse effects should occur based on current knowledge. To transfer this HBM-I approach to the occupational context and derive a provisional OBL, a few considerations need to be addressed: the exposure duration, the regulatory accepted Point of Departure (POD) and toxicokinetic aspects.

Exposure duration. Workers work 40 hours per week, five days per work-week over 40 years, as opposed to an estimate of life-long exposure for the general population.

POD. The preferred method uses a Derived No Effect Level (DNEL*) for oral intake instead of a Tolerable Daily Intake (TDI*) as the POD*. DNELs* are derived using assessment factors (AF), according to the REACH guidance. A DNEL tool has been developed by SECO to facilitate the calculation of DNELs* (https://www.seco.admin.ch/DNEL).

Toxicokinetic aspects. In the case of occupational exposures, the exposure pattern can be very different from the general population. For instance, more peak exposures (and less chronic exposure) related to specific tasks might occur in some cases. This can cause different toxicokinetic features due to more

frequent exceedances of metabolic pathways. This difference in exposure patterns cannot be generally taken into account in advance, but might justify case-specific additional assessment factors.

For the urinary mass balance approach, the preferred $DNEL_{oral}$ is multiplied by a urinary excretion factor F_{UE}, which is a steady-state concentration factor for urine measured after 24h or 48h exposure. When the $DNEL_{oral}$ is derived for metabolites, it is also multiplied by the ratio of the molecular weights (RM) to the parent substance. This product is then divided by the urine Volume (u) (0.02 L/kg bodyweight/24 h). (Aylward et al., 2015) observed that the urinary flow rates in adults were consistent across the range of ages from 15 to 80, averaging approximately 20 mL/kg bw/day with no consistent differences between men and women. Newer studies indicate (e.g., by Lermen et al., 2019 or Mengelers et al., 2019) 32-36% higher urinary flow rates (30 mL/kg bw/day) in men and women compared to historical values. As of yet, no harmonization has been reached for the urinary flow rate values (for details see Apel et al., 2020). We propose to use either of the two, and always indicate which 24-hour urinary flow rate (u) that was used in the derivation equation:

$$Provisional\ OBL\ (POBL) = \frac{DNEL_{oral}\ x\ F_{UE}\ x\ RM}{u}$$

This POBL* will then give an indication of acceptable or unacceptable risks for workers depending on the Risk Characterisation Ratio (RCR) given the current knowledge and data.

*Relevance assessment of POD**

The relevance of a POD needs to be evaluated before using a POD* for POBL* derivation. In contrast to the reliability, relevance does not concern the inherent quality of the study but mainly depends on the purpose of the assessment or regulatory framework for which it is evaluated. This assessment is always expert judgement driven, but includes questions such as:

- Are the reported endpoints relevant for humans and appropriate for the regulatory purpose (e.g., leading to adverse effects)?
- Are the reported endpoints appropriate for the investigated effects or the mode of action of the test substance and the target human population?
- Are the experimental conditions relevant for the tested species and the target human population?
- Is the exposure duration relevant and appropriate for the studied endpoints and species?
- Is the route of administration relevant for target human population exposure?

If the overall relevance of a POD* is rated relevant without restrictions or relevant with limited restrictions, then the POD* can be used for POBL* derivation. Please note: Exposure of pregnant and breast-feeding women at the workplace can have an effect on developing fetuses and infants, respectively, at lower concentrations.

3.3.3. Case study results for NOAEL urinary mass balance approach*

Two organic (DEHP* & HDI*) and two inorganic (Chromium & Aluminium) substances have been chosen as case study substances because of their different toxicological profiles and wide use in several industry sectors. To compare POBL* derivations with OBL* derivations most of the human toxicity data were excluded with a focus on animal toxicity data, trying to simulate a low human data availability. The primary source for these case studies was data compiled by biomonitoring experts. Dedicated experts added pertinent data at a later stage. Selected PODs* of these data were categorized into three categories of conservatism: “precautionary”, “balanced”, and “relaxed” data selections (with numerically low, medium and high NOAEL*/LOAELs*). The different data selections were used partially as case study scenarios to derive POBL* and to check the variability of method results, depending on the choice of toxicological PODs* (see Tables 8-11).

To compare the results in terms of toxicity reference values (TRV*), the urinary excretion factors (see Table 7) were kept constant and a urinary flow rate (u) was set equal to 20 ml/kg bw/d

Table 7. For case studies used urinary excretion factors

substance	F_{UE} (urinary excretion factor)
DEHP*	0.4
HDI*	0.21
Aluminium	0.00145 partially or less soluble Al substances 0.0074 for soluble Al substances
Chromium	0.8

Table 8. DEHP* case study scenarios for provisional OBL* derivation

DEHP* scenario	NOAEL* /LOAEL*, reference	Mode of action relevant endpoint	DNEL* oral	POBL*	Relevance of POD*
precautionary	LOAEL = 3 mg/kg bw/d, (Christiansen et al., 2010)	dysgenesis of genitalia in rat	0.01 mg/kg/d	**0.15 mg/L** **5-oxo and 5-OH-MEHP**	**Yes**
balanced	NOAEL= 4.8 mg/kg bw/d, (German HBM Commission, 2007)	reproduction toxicity in rats	0.096 mg/kg/d	**1.44 mg/L** **5-oxo and 5-OH-MEHP**	**Yes**
relaxed	NOAEL = 5.8 mg/kg/d, (David et al., 2010)	bilateral aspermatogenesis, reprotoxicity	0.116 mg/kg/d	**1.74 mg/L** **5-oxo and 5-OH-MEHP**	**Yes**

Table 9. HDI* case study scenarios for provisional OBL* derivation

HDI* scenario	NOAEL* /LOAEL*, reference	Mode of action relevant endpoint	DNEL* oral	POBL*	Relevance of POD*
precautionary	LOEC*= 0.035 mg/m3 (Mobay, 1989 in German MAK derivation, 1996)	hyaline degeneration of the respiratory epithelium in rats in study of	0.0886 µg/kg/d	**0.93 µg/L HDA***	**Yes, sensitisation**
balanced	NOAEL*= 0.005 ml/m3='ppm,' (German MAK derivation, 1996) for HDI	2 years chronic rat study was leading to adaptations in nasal epithelium, because of missing adversity of adaptations this LOAEL* was interpreted as NOAEL*	0.2656 µg/kg/d	**2.79 µg/L HDA***	**Yes, partially**
relaxed	LOEC*='3.5' mg/m3 (German MAK derivation, 1996) for HDI	maternal toxicity and fetotoxicity in rats	8.87 µg/kg/d	**93.14 µg/L HDA***	**No, not related to sensitisation**

Table 10. Aluminium case study scenarios for provisional OBL* derivation

Aluminium scenario	NOAEL* /LOAEL* reference	Mode of action relevant endpoint	DNEL* oral	POBL*	Relevance of POD*
precautionary	Chronic NOAEL* =2.5 mg Al/m3 (Piggot et al., 1981)	inhalation exposure to Al2O3 in a rat study was evaluated by ACGIH*.	0.019 mg/kg/d	**1.38 µg/L**	**Yes**
balanced	Sub-chronic LOAEC* for local effects= 50 mg/m3 , (Gross et al., 1973)	from ECHA* dossier: LOAEC* is based on local effects, such as lipid pneumonitis, granulomatous inflammation; collagenous scars but fibrosis was not evident. Measured in rats exposed to aluminium powders	0.127 mg/kg/d	**9.2 µg/L**	**Partially, due to local effects**
relaxed	Chronic NOAEL* for systemic effects = 158 mg Al/kg bw/day (Alberta Research Council Inc. 2010, as cited in REACH dossier, 2018).	used in ECHA* dossier:Chronic systemic effects. Developmental and One-Year Chronic Neurotoxicity Study of Aluminium Citrate in rats (NOAEL*corr = NOAEL * 5.27 = 30 * 5.27 = 158.0 mg Al/kg bw/day)	7.9 mg/kg bw/d	**2.92 mg/L**	**No, oral exposure**

Table 11. Chromium case study scenarios for provisional OBL* derivation

Chromium scenario	NOAEL* /LOAEL*. reference	Mode of action relevant endpoint	DNEL* oral	POBL*	Relevance of POD*
precautionary	LOAEL* inhalation 0.002 mg Cr/m^3 , (Lindberg and Hedenstierna, 1983)	inhalation exposure,for nasal irritation, mucosal atrophy, impaired lung function in 104 workers , median exposure 4.5 years	0.019 µg/kg/d	**0.76 µg/L**	**Partially yes for lung function, but carcinogenicity is missing**
balanced	NOAEL* inhalation 0.01 mg Cr/m^3, (Derelanko et al., 1999)	increased lung weight in rats after 13 weeks exposure	0.38 µg/kg/d	**15.2 µg/L**	**Partially yes for lung function, but carcinogenicity is missing**
relaxed	LOAEL* inhalation 4.3 mg Cr/m^3(Nettesheim and Szakal, 1972)	mice had epithelial necrosis after 18 months inhalation exposure study	10.975 µg/kg/d	**439 µg/L**	**No, too late effects with risk missing other adverse endpoints**

The relevance assessment of available data is of high importance in deriving POBL*, as it helps in prioritizing the identified occupational toxicological risks. The minimum relevance POBL* requirement is a link between the POD* and known toxicity endpoint, and was established for most case study substances (DEHP*, HDI*, and Aluminium). For Chromium, the lung cancer risk POD* was only indirectly linked with impaired lung function. We recommend using all potential reliable studies identified as relevant and leading to adverse effects. This can reduce expert judgement discussions, and the risk of missing available evidence in a crucial primary risk identification step.

3.3.4. Sensitivity comparison of POBL with refined OBL and other occupational Biomonitoring Limit Values (BLV)

Available BLVs* were compiled by several experts in the refined OBL* subtask. A systematic data collection approach was ensured by using templates and after discussion of these templates by all experts. The BLVs* were compared in a case study sensitivity comparison (see Table 11) with POBL* derivations from the urinary mass balance approach (derivations in Tables 8-11). A further normalization to creatinine levels is recommended before the application of POBLs, but this was not necessary for comparison purposes.

Table 11. Case study sensitivity comparison of Provisional Occupational Biomonitoring Levels (POBLs*) with refined Occupational Biomonitoring Levels (OBLs*) and available Biomonitoring Limit Values (BLVs)

Case study	POBL*	Refined OBL* or BLV*	Ratios between refined OBL* and POBL*
DEHP*	0.15 - 1.44 mg/L (S5-oxo and 5-OH MEHP)	4.52 mg/L # (SMEHP, 5-OH-MEHP, 5-oxo-MEHP and 5-cx-MEPP)	3-30

HDI*	0.93 - 2.79 µg/L	15 µg/L##	5-16
Aluminium	1.38 - 9.2 µg/L	57 µg/L	6-41
Chromium	0.76 µg/L	2.5 - 10 µg/L	3-13

Available in: DOI: 10.1002/3527600418.bb11781e2319
Available in (German BAT derivation for HDI, 2011)

Conclusion

The results show that the POBL* derivations were sufficiently sensitive (3 to 41 times more sensitive) in all four case studies to identify potential toxicological risks compared to the refined OBLs* and existing BLVs*. Using a POBL* can lead to risk identification, but we recommend always checking if a refined OBL* can be derived (see chapter 5.5). This will also need a final confidence and reliability assessment (see chapter 3.2.3). This can lead to refined OBL* derivations or improved risk. management options. We recommend deriving POBL* using the urinary mass balance approach as a screening method when relevant POD*s and urinary excretion factor data are available. This limits the use of additional safety factors. In cases where a POBL* is lower than a ROBL*, the POBL* should be set equal to ROBL* for this region to avoid an overestimation of risks.

*3.3.5. Limitations, uncertainties and confidence assessment of POBL**

The primary purpose of the POBL* is screening and health-risk identification. The POBL* can lead in some cases to an overestimation of toxicological risks compared to a refined OBL*, as shown by the sensitivity analysis results (Table 11). Therefore, after identifying risk, the potential for derivation of an OBL* should be checked (see chapter 5.5). Nevertheless, the urinary mass balance approach (adapted from Apel et al. (2020) can in principle be used for deriving refined OBLs*. In this case, a medium or high confidence level needs to be assessed for the related PODs* on toxicology and urinary fraction data. A confidence assessment scheme is generally suggested for the refined OBL* derivation (see chapter 3.2.3). The primary limitations and uncertainties in the urinary mass balance approach are related to the quality and confidence assessment of:

- Hazard and dose-response assessments, selection of POD* (see case study scenarios Tables 8-11)
- Urinary fraction data (should be based on a steady-state concentration)
- Toxicokinetic knowledge for investigated substances

An experienced toxicologist or risk-assessor needs to assess the validity and limitation of the relevant data.

If relevant experimental data are absent, modeling can be helpful. PBK *modeling can help identify target organ peak concentration as the metric for organ toxicity, which can be compared to NOAEL data from toxicity studies. PBK* modelling can simulate inhalation and skin exposures as well as oral intake separately, which will give an understanding of the major route of exposure. This can then be used in designing risk management strategies. PBK* modelling is useful in reaching scientifically sound regulatory decisions, but it still needs to reach regulatory acceptance in many fields. (more information on PBK* is available in chapter 6.5).

3.4. Derivation of Reference OBL* and Technically achievable OBL*

3.4.1. How to establish a Reference Occupational Biomonitoring Level– ROBL?*

*Introduction and use of ROBLs**

The ROBL* is a strictly statistically defined value and not linked to any threshold for or extent of any adverse health effect. The ROBL* relates to the internal exposure of a substance of interest, which is present in a reference population of working age who are not occupationally or otherwise specifically exposed to the substance. The purpose of comparing occupational biomonitoring data to a ROBL* is to understand the fraction of the internal exposure that most likely occurred at work. The occupational exposure fraction in the individual or a group of workers can be determined by comparing the biomonitoring results with this ROBL*.

Acquisition of data, use of data for statistical analysis to establish ROBL (P95 background)*

A ROBL* is established based on data from a large-scale general population biomonitoring study. Data from national surveys can be considered a suitable base due to their high participation rate. Individuals with a known non-occupational exposure, such as from leisure activities (e.g., lead exposure from hunting) or from point-sources (e.g., living near mining facility) should be excluded from the data set when establishing the ROBL*. This information should be collected with the survey. The assumption underlying the establishment of a ROBL* is that every individual is exposed to multiple chemical substances, often unknowingly, since many substances occur in environmental media (air, soil, etc), drinking water, food, and other consumer products. In the case where most of the values in the acceptable studies are below the LOQs*, the ROBL* could be set at the lowest LOQ* or half of the LOQ*. This means that any quantifiable BM* level in workers would indicate occupational exposure.

A quality control /quality assurance (QC/QA) is needed for the analytical chemical analysis and sample collection of the biomonitoring data (Göen et al., 2012b). Moreover, the reports of the population data shall provide sufficient evidence for analytical accuracy or comparability at least.

Evaluation procedure to establish a ROBL

The ROBL* for a chemical substance in human biological material is a value that is statistically derived from a series of human biomonitoring measurement. Generally, the levels of a human exposure biomarker in the general population do not show a normal distribution but a distinct right-skewed distribution, which requires a non-parametric evaluation of the reference value (Solberg, 1983). Accordingly, the ROBL* is usually derived from the 95th percentile of the distribution function (P95), as previously established for the reference value evaluation of HBM data (Angerer et al., 2011, German HBM Commission, 1996, Göen et al., 2012a, Holst and Molin Christensen, 1992, Vogel et al., 2019). In case most if not all measurement values are <LOQ*, the ROBL* could be set at the LOQ*. Statistical approaches and assumptions to be used if data seem to be lognormally distributed or if e.g., 50% of the values are below LOQ*, might be discussed further in the future.

Confounding factors, determinants and choice of reference population

Background exposure can be influenced by many factors, such as age, sex, social status, residential environment, nutrition, lifestyle, including leisure activities and geographical region (Schulz et al., 2011, Göen et al., 2012a). The extent and the priority of these influences are specific and different for the substance of interest as well as for the metabolites used as exposure biomarkers such as the following:

- Specific ROBLs* for different age groups might be necessary for exposure biomarkers that accumulate in the body.
- Specific ROBLs* for smoking status might be necessary for exposure biomarkers that are also generated from tobacco smoke exposures.
- Specific ROBLs* for different sexes might be necessary for very specific exposure biomarkers that are absorbed, distributed, metabolized and/or excreted differently by women and men.
- Specific urinary ROBLs* for the geographical region might be necessary for exposure biomarkers that are generated from exposure to regional environmental contamination or specific dietary consumption.

Altogether, the choice of the reference population is critical.

Period of validity

Reference values describe exposures at a distinct time in the general population. Re-evaluation is required due to the evolving general exposure situation, e.g., a decrease in environmental exposure (Göen et al., 2012). A suitable public health policy for tracking exposure changes in populations is to establish continuous biomonitoring programmes for defined groups of the general population, such as the German Environmental Survey (GerES), the National Health and Nutrition Examination Survey (NHANES) in the USA and Canadian Health Measure Survey (CHMS) (Kolossa et al., 2012, Göen et al., 2018, Calafat, 2012; Health Canada 2021).

3.4.2. How to establish a Technically achievable Occupational Biomonitoring Level – TOBL?*

Terminology and use of Technically achievable OBL (TOBL)*

The TOBL* is based on the ALARA principle ('As Low As Reasonably Achievable'). It is not based on exposure in a reference population nor health effects and thus, cannot be used for risk assessment purposes. A TOBL* is derived for hazardous substances for which there is insufficient scientific knowledge (epidemiology, toxicology) regarding health effects or for genotoxic substances. Instead, the TOBL* is the biomonitoring level found or anticipated in workers in a state-of-the-art occupational environment with potential exposures to known hazardous chemicals at levels that have been minimized to the largest extent. The actual level that is generally accepted to be achievable, may differ from one country to the other or even from one industrial sector to the other and may also depend on deliberations with e.g., trade unions. The TOBL* is set to mitigate exposures to hazardous chemicals as low as reasonably achievable.

Acquisition data

The TOBL* is derived using all available data on biomonitoring, personal and general air monitoring, exposure determinants (industrial processes, technical infrastructure, protection devices), exposure profiles (technical, organizational and individual measures, confounding factors), SEG* approaches collected from a representative sample of workers performing occupational tasks using the substance in question. Health questionnaires could help in associating exposures to potential health effects, but this requires legal and ethical approvals.

Derivation procedure

The derivation of a TOBL*relies on expert judgements on the state-of-the-art work conditions, followed by discussions with stakeholders and ultimately, an agreement between the parties concerned.

The state-of-the-art scenario shall consider the **STOP** principle (EU OSHA, 2018), which includes:

Substitution of the toxic agent by less harmful substitutes, to less exposure emitting production methods,

Technical infrastructure, which prevents or minimises the emission of chemical agents,

Organisational measures, which reduce the dwell time of the employees in exposed tasks and

Personal protection equipment, that is efficient and accepted by the workers.

The derived TOBL* should be evaluated by representatives from:

- specific trade associations, in particular health and safety officers
- workers concerned, e.g., labour unions
- health and safety authorities
- independent experts, e.g., engineers of production facilities and protection devices as well as occupational hygienists

The evaluation process should consider all workplaces which feature exposures to the substance in question. If reasonable, specific TOBL* can be elaborated for different industrial processes, workplaces and occupational tasks. To delineate a TOBL* from (personal) air monitoring data, a sound correlation between biomarker concentration and air concentration is needed which enables the science-based transformation from air monitoring levels to biomonitoring levels, e.g., exposure equivalents for carcinogenic substances (EKA).

Period of validity

A TOBL* value describes the technically achievable situation at the time of evaluation. A re-evaluation may be required after successful improvement of technically achievable reduction of airborne concentrations and/or improvements of personal protection equipment.

3.5. Effect-biomonitoring

3.5.1. Rationale

Despite the increasing awareness that both regulated and unregulated substances find their way into organisms as complex mixtures, the current legislation is still strongly single substance-oriented and is typically enforced based on limit values of a subset of substances. The regulatory progress on risk assessments of chemical mixtures is slow. Currently, predictive mixture assessment strategies only cover a very limited number of substances. This gap can be closed by using biomonitoring of effect biomarkers. This powerful tool can directly assess effects from exposures to complex chemical mixtures. An ideal effect biomarker* should be predictive, relevant, and allow for early detection of adverse outcomes, translatable, sensitive, specific, robust and non-invasive, applicable and preferably validated. Although, biomonitoring of effect biomarkers is the only tool for measuring effects from both known and unknown components of a chemical mixture in an integrative way, they are applied less often than exposure biomarkers. The reasons may be the lack of specificity with regard to chemical exposure and uncertainties in causal relationships to atypical endpoints and adverse effects. To identify specifc exposures the combination with other monitoring approaches, e.g. air, surface, dermal exposure monitoring is recommended. However, effect biomarkers have the unique ability to quantify effects from overall occupational exposures; and consequently, can refine the occupational safety and health risk management in prioritising tasks. Thus, integrating effect biomarkers into existing Human Biomonitoring (HBM) programs would improve occupational risk assessments. This is in line with the (European Union report, 2019) ‘Towards a Sustainable Chemicals Policy Strategy of the Union’, which aims to ensure that the combination effects of chemicals and the combined exposure of humans and the environment from all relevant sources are properly and consistently addressed in the risk assessment and risk management processes. HBM programs including effect-biomarkers can have an important role in occupational safety assessments since they identify group of workers with risks of health effects due to combined occupational exposures. Biological effect monitoring offers occupational health practitioners a tool in detecting early stages of effects in a population deemed at risk for chemical mixture exposures. Risk Management Measures (RMM) should then be elaborated for these workers (see chapter 5.6).

3.5.2. Modes of Actions (MoA)*

Mode of actions (MoAs) for toxicity are the description of key events and processes, starting with interaction of an agent with the cell through functional and anatomical changes, representing health related endpoints. Similar to chemical toxicity classification and labelling, there is a need to agree on priorities of effect biomarkers and propose priority MoAs* and endpoints to be addressed. The OECD occupational biomonitoring subtask on effect biomarkers has prioritized eight relevant MoAs*. We recommend these for assessing occupational health effects (consider Table 12).

Table 12. Proposed priority mode of actions /endpoints to be addressed by occupational biomonitoring and health effect assessments.

No	Mode of actions /endpoints	Abbreviation	Available methods as OECD guideline, DIN EN ISO standards or others
1	Carcinogenicity (including biomarkers for genotoxicity and oxidative stress)	C including genotoxicity, oxidative stress	yes
2	Mutagenicity	M	yes
3	Reproduction toxicity	R	yes
4	Endocrine disruption	ED	yes
5	Neurotoxicity (including acetylcholine esterase inhibition)	NT	yes
6	Developmental Neurotoxicity	DNT	yes
7	Developmental Toxicity	DT	yes
8	Respiratory toxicity (including methemoglobin binding)	ResT	yes

Some health effect endpoints already have associated MoAs (e.g., for CMR, ED), while others (e.g., for NT, DNT) are still missing in commonly used classification systems. Consequently, developing these could address important safety gaps for workers.

3.5.3. Recommendation and characterisation of effect-biomarkers

Recommended effect biomarkers:

The experts in the OECD occupational biomonitoring subtask on effect biomarkers were asked the following: Which effect biomarkers should be used? Which assays are promising for developing future effect biomarkers? Potential suitable effect biomarkers were compiled, and discussed. This was an iterative process including several meetings. The final list of discussed and recommended effect biomarkers is provided in chapter 9.2 Annex B: Effect-biomonitoring Table B1.

Characterisation of effect biomarkers:

Sixteen effect biomarkers were recommended from surveyed experts (see chapter 9.2 Annex B Effect-biomonitoring Table B1: for development of guidance) for further characterization. The experts were asked to characterize these in a separate follow-up online survey. These method for effect biomarkers are provided in Table 14 only with the names, more information can be found in (see chapter 9.2 Annex B Effect-biomonitoring Table B1.

Table 13. Coding and characterized methods for effect-biomarkers. The code number indicates the relevant mode of action and the code letter indicates the recommended effect biomarker.

No/coding	Characterized methods for effect-biomarkers
1a	DIN EN ISO 21427 is for the application of the *in-vitro* Micronuclei (MN) assay in water quality assessment. The in-vitro mammalian MN assay is better referred to OECD 487. Dividing cells are needed to apply this assay.
1b	buccal micronucleus approach
1c	cytokinesis-block micronucleus assay (CBMN-Assay) (similar to OECD 487)
1d	peripheral blood lymphocyte micronucleus test (similar to OECD 474) and buccal mucosa micronucleus test (see 1b)
1e	reduced/oxidized glutathione (GSH/GSSG) ratio
2a	Ames Test/Bacterial Reverse Mutation Test (OECD 471)
3a	reproductive Hormones - female hormones
3b	reproductive Hormones – male hormones
4a	ER CALUX
4b	AR CALUX
5a	acetylcholine-esterase-inhibition assay
5b and 6a	BDNF Assay
5c	neuroaxonal damage/ scaffolding proteins (small parameter selection)
5d	neuroaxonal damage/ scaffolding proteins (enlarged parameter selection)
6a	TSH assay
6b and 5b	BDNF Assay
8a	Methemoglobin binding assay

The following questions were asked in four different evaluation categories in the survey to characterize the effect biomarkers (the evaluation and scoring of questions are available in see chapter 9.2 Annex B: Effect-biomonitoring Table B2: These questions should also be used to rate a new effect biomarker or assay.

Questions for assessing relevance and invasiveness:

1) Has the biomarker been assessed in easily accessible human biological matrices?
2) Is there a plausible MoA*?
3) Is an Adverse Outcome Pathway (AOP*) reported for this effect-biomarker?
4) Is the biomarker able to detect relevant (adverse and severe) effects in workers during a long-term exposure?

Questions for assessing applicability:

5) Has the effect biomarker been applied in occupational or epidemiological studies and resulted in meaningful results for a workplace or chemical exposure?
6) Has the biomarker been applied in environmental risk assessment or other studies with regulatory relevance (e.g., drinking water, food regulation)?
7) How would you define workload and applicability for occupational settings?

Questions for assessing validation and cost:

8) Does the biomarker have a well-described standard operating procedure (SOP)?
9) Does an OECD guideline or a standardized DIN EN ISO exist for the effect-biomarker?
10) What is the cost per sample?

Questions for assessing sensitivity & specificity & robustness:

11) Is the Limit Of Quantification (LOQ) below an accepted occupational exposure limit for a relevant reference substance?
12) Is the specificity of the biomarker sufficient for the substances or effects of concern?

13+14) What are geometric mean concentrations and geometric standard deviations of the biomarker in the general population? Is the effect-biomarker sufficiently robust to compare different levels of exposure risks (e.g., does it have age dependent variations, body mass index or smoking dependency)?

Experts were asked to support their answers with relevant scientific references. These answers were then scored (see chapter 9.2 Annex B: Effect-biomonitoring Table B2), and the absolute score and relative score compared to the maximum possible score was evaluated for each assessment category for each effect-biomarker. Assessment results in category relevance and invasiveness: Most of the effect-biomarkers are scored highly relevant (mean 74 ± 15%, see Fig. 3a). Most of the effect biomarkers are strongly linked to an AOP* and have relevant MoA*s. Consequently, they can detect severe and adverse long-term effects in workers. The majority of these effect biomarkers can be assessed in blood samples, and five are also assessed in less invasive matrices (urine, saliva, etc.). Some effect biomarkers respond to acute and specific intoxications (example 5a, 8a), i.e., measuring the inhibition of the acetylcholine esterase or methemoglobin binding assay. The names of all effect biomarkers are provided in (see chapter 9.2 Annex B: Effect-biomonitoring Table B1)

Figure 3. Overall and specific relevance and invasiveness assessments of selected effect-biomarkers (effect biomarker codes given in Table 11)

Figure 3a. Overall relevance and invasiveness assessment of selected biomarkers

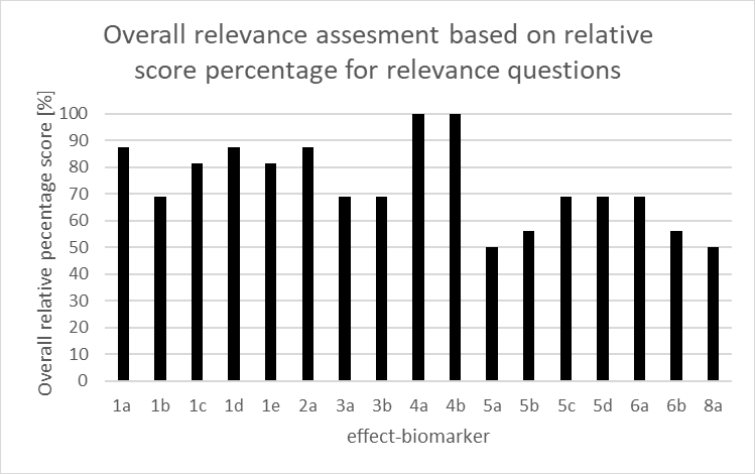
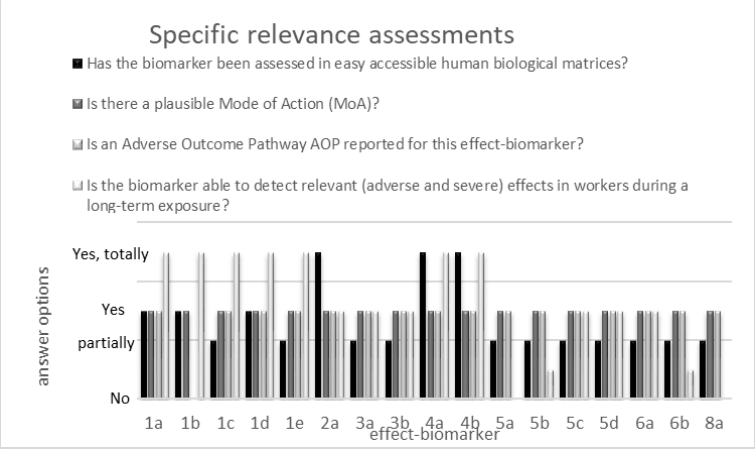


Figure 3b. Specific relevance and invasiveness assessment of selected biomarkers



Assessment results in category applicability (applicability questions are defined in appendix table 2):

Carcinogenicity (including genotoxicity and oxidative stress), mutagenicity, endocrine disruption and toxicity to the reproductive organs can be assessed with high applicability (mean score 76 ± 10%, see Fig 4a). Neurotoxicity (NT) and Developmental NT (DNT) effects (effect-biomarkers 5a-d) can be assessed to a lesser extent (mean score 36 ± 3%). Respiratory toxicity effect biomarker (8a) was assessed with very low applicability (see Figure 4).

Figure 4. Overall and specific applicability assessments of selected effect-biomarkers

Figure 4a. Overall applicability assessments of selected effect-biomarkers

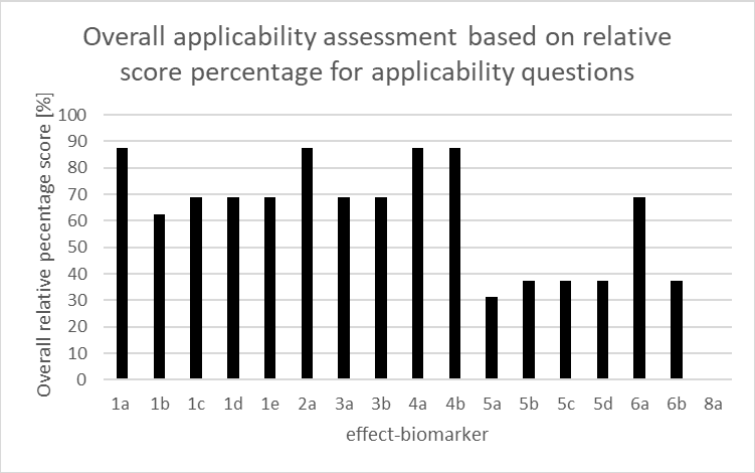
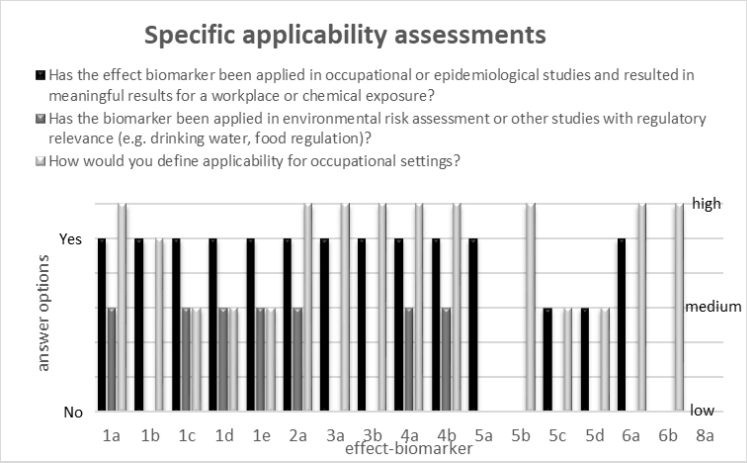


Figure 4b. Specific applicability assessments of selected effect-biomarkers



We concluded that for C, M, R and ED biomarkers, the clinical approaches are well established, and a transfer to occupational risk assessment is ongoing. This was not the case for NT and DNT biomarkers. Therefore, a potential for a knowledge transfer from clinical to occupational risk assessment was identified.

Assessment in category of validation and cost:

Quite variable validation scores were reported (mean score= 56 ± 20 %, see Figure 5a). Very good results (>80%) were obtained for effect biomarkers for mutagenicity (2a) and endocrine disruption (4a) as well as for classical effect biomarkers such as acetylcholine esterase inhibition and methemoglobin assay (5a and 8a).

Figure 5. Overall and specific validation & cost assessments of selected effect-biomarkers

Figure 5a. Overall validation & cost assessments of selected effect-biomarkers

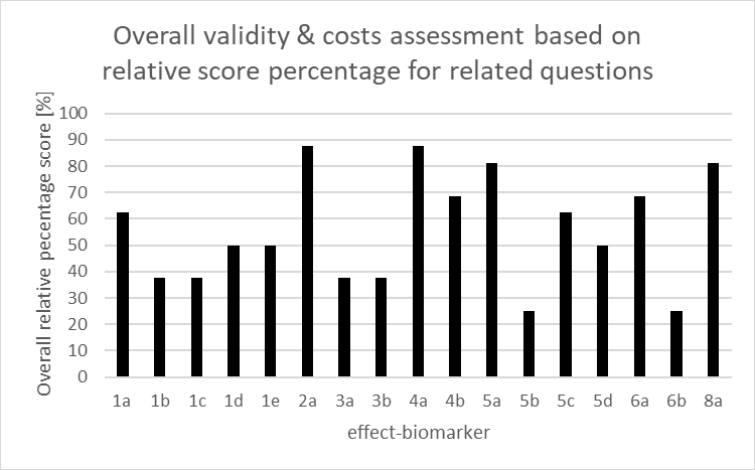
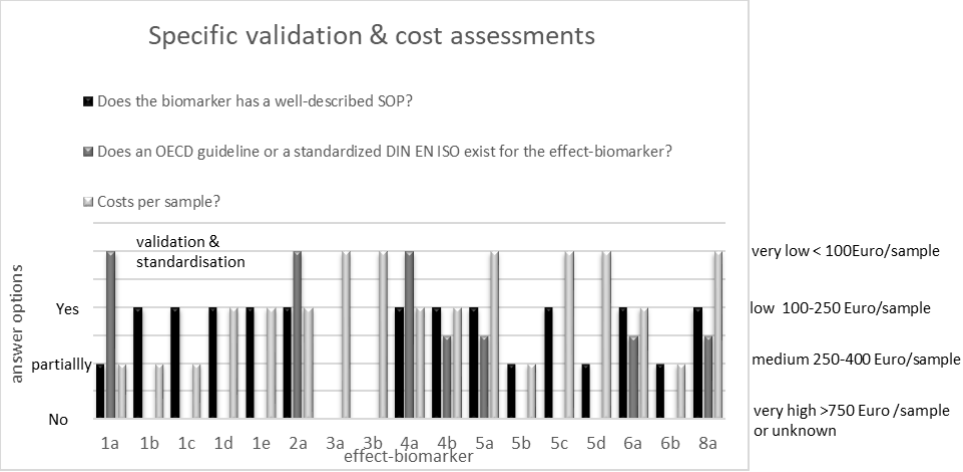


Figure 5b. Specific validation & cost assessments of selected effect-biomarkers



Eleven effect biomarkers have standardized operating protocols (SOPs). Seven effect biomarkers have OECD test guidelines including three with ISO standards (1a, 2a, 4a, see Figure 5b). The majority (twelve of sixteen) effect biomarkers have low costs with six <100 Euro /sample and six between 100 to 250 Euro/sample.

Assessment in category sensitivity, specificity, and robustness:

Quite variable (mean score= 58 ± 29 %) scores were obtained for all 16 effect biomarkers (see Figure 6a) regarding sensitivity, specificity, and robustness. Very good results (>80%) were achieved

for effect biomarkers related to oxidative stress, reproductive hormones, endocrine disruptive effects, and respiratory toxicity (1e, 3a, 3b, 4a, 4b and 8a).

Figure 6. Overall and specific sensitivity & specificity & robustness assessments of selected effect-biomarkers

Figure 6a. Overall sensitivity & specificity & robustness assessments of selected effect-biomarkers

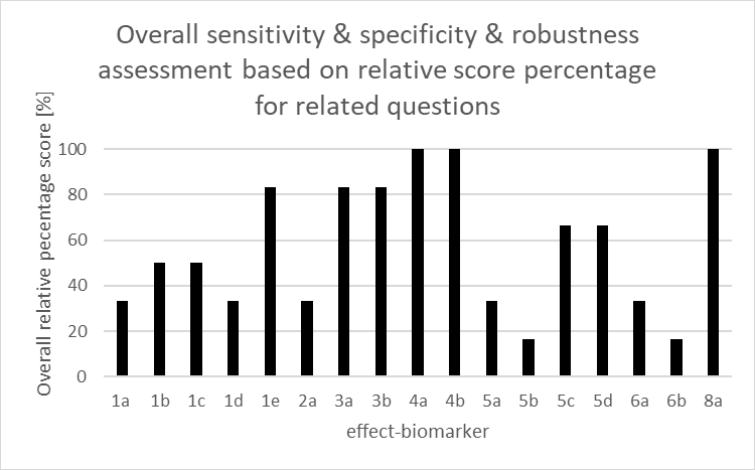
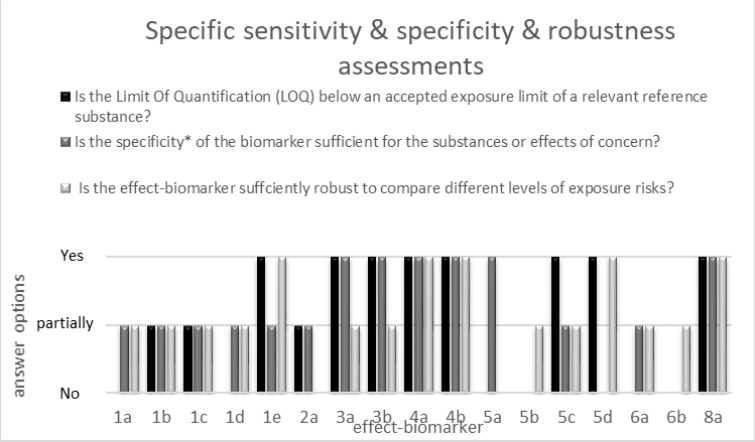


Figure 6b. Specific sensitivity & specificity & robustness assessments of selected effect-biomarkers



The surveyed experts concluded that specificity and robustness for MoA* specific reference substances were partially missing. There is therefore a need to have accepted exposure and effect levels for MoA* relevant substances to allow a sensitivity comparison. This means reference compounds able to initiate key events in an AOP* cascade need to be assessed according to their concentrations to initiate adverse effects, e.g., lead for some neurotoxicity biomarkers or estradiol for some estrogenicity biomarkers.

Overall assessment results:

Most of the recommended effect biomarkers can be used in occupational risk assessments and were scored highly regarding relevance and applicability. Many effect biomarkers have an associated OECD* test guideline and some also an ISO standard. The cost ranges were below 250 Euro/samples,

specifically 100 Euro/samples for the majority of the effect biomarkers (twelve of sixteen). Six of sixteen effect biomarkers were assessed with very good sensitivity, specificity, and robustness. Many effect biomarkers have not been assessed due to the absence of data and missing reference compounds for their evaluation in terms of sensitivity and specificity.

Effect biomarker applications:

To make effective use of effect biomarkers, they need to be sufficiently characterized with regard to relevance, predictability of adversity, sensitivity, specificity and robustness. The questions outlined above can be used for this purpose. Furthermore, they should lead to a causal relationship with the combined occupational exposures of chemicals. We suggest using biomonitoring of effect biomarkers in a tiered approach and with similar terminology (ROBEL*, POBEL*, OBEL*) as for biomonitoring of exposure biomarkers (ROBL*, POBL*, OBL*). The tiered approach and proposed terminologies are briefly described in chapter 5.6 and 1.3.1**.**

We suggest reporting biomonitoring of effect biomarkers for Similar Exposure Groups (SEG*) to ensure a consistent interpretation of occupational exposure data and to avoid over-interpretation of individual results. This approach is analogous to (Technical Committee CEN 137, 2020) for Occupational Exposure Limits (OEL* or OELV*) and the SEG* can be applied with some small effect biomarker modifications provided in see chapter 9.2 in Annex B in Table B3. This will allow to identify with the SEG* where intervention is needed first.

3.5.4. Outlook and AOP-validated effect biomarker follow up

Validated effect biomarkers can be used to address mixture effects and many relevant health effect endpoints and adverse MoAs* in humans. Some are not yet covered under current chemical labelling and classification systems. Biomonitoring of effect biomarkers can be used to assess exposures to chemical mixtures of known and unknown sources. For most of the recommended effect biomarkers, we found a strong link to the growing Adverse Outcome Pathway (AOP*) knowledge. AOPs* describe chains of key events from a Molecular Initiating Events (MIE*) to Adverse Outcomes (AO). This knowledge offers a systematic understanding of effects that can be translated into regulatory use by defining relevant biological effect thresholds for relevant MoAs*. These thresholds need to be related to concentrations/levels of well-understood, prototypical stressors (focusing primarily on chemicals), that produce the MoA* effect. A need to derive mixture threshold levels (OBEL*) for well-characterized effect biomarkers was identified and in the International Society of Exposure Sciences (ISES) Europe HBM group (Zare Jeddi et al., 2021a, HBM4EU, 2021). Moreover, we recommend developing guiding principles for their derivation within WPHA/WPEA and OECD* Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST) in an interdisciplinary follow-up activity called: Using Adverse Outcome Pathways (AOP*) to address combined exposures to chemicals with relevant effect biomarkers. The follow up activity was adopted in 2021 and is briefly described in (Zare Jeddi et al. 2021b). A systematic understanding of both the relevance and interpretation of effect biomarker data will lead to increased protection for workers.

4. Application of biomonitoring in practice

4.1. Basics and requirements

4.1.1. The relevance and optimal use of biomonitoring in practice

Biomonitoring (BM*) is an effective tool for assessing the individual exposure to and effects of hazardous substances. Its application in occupational settings may pursue the following objectives:

Assessment of individual's health risks associated with exposures to a chemical or a set of chemicals at the workplace (*Occupational Health Approach*)

Assessment of workers' exposures to chemicals at a specific workplace or during a specific working task (*Occupational Hygiene Approach*)

The Occupational Health Approach is, in general, part of *occupational health surveillance*. Occupational health surveillance aims to monitor the health status of workers exposed to specific agents by means of periodic medico-physiological examinations. Special consideration is given to:

- diseases or clinical symptoms that may be the result from exposures,
- signs of excessive absorption or diminished elimination of the respective chemical agent, and
- individual characteristics (e.g., pre-existing medical problems and specific health and life style characteristics) that might increase an individual's disposition for an exposure-related disease or health disorder.

These health examinations can also include BM*. In most countries, occupational health surveillances are performed by specialized occupational physicians. The individual biomonitoring results present medical findings and thus are liable to the obligation of medical activities and data protection regulations (see chapter 4.4).

In the Occupational Hygiene Approach, BM* can be used to complement other strategies and tools for exposure assessment, such as air monitoring (BOHS 2021, HSE 1997). Air monitoring alone does not fully assess workers' exposures to chemicals known to penetrate the skin and might therefore underestimate the total exposure. It is necessary to use BM* to capture and integrate all routes of exposures (skin uptake, inhalation, and hand-to-mouth contact). This gives justification, also from an ethical perspective, for a wider use of BM* in occupational settings as a means for better and more accurate exposure assessments (see also Boogaard et al., 2011).

In both approaches, the results obtained should provide the necessary information to evaluate the effectiveness of implemented preventive measures to reduce chemical exposures. BM results can be used to prioritise both collective and individual preventive and control measures. Implementing these measures require a collaborative effort from distinct groups of *occupational health and hygiene professionals* (OHP*, see chapter 9.3.1 Annex C). Exposure data can be obtained by ambient monitoring, e.g. personal air monitoring, dermal, or surface monitoring. BM* is particularly helpful when assessing the effectiveness of exposure controls, developing risk communications, and identifying failures of prevention and control already in place (Viegas et al., 2020). At an individual level, they can result in specific recommendations for a particular worker addressing individual control measures and working practices. On a worker population level, an appropriate approach is to divide the population into

Similar Exposure Groups (SEG*), and design biomonitoring programs that minimize both cost and effort. The SEG* (see chapter 4.3) approach is also used in testing compliance with occupational exposure limit values (Technical Committee CEN 137, 2020).

Sometimes the exposure biomarkers can in some individuals be unusually high even after preventive measures have been implemented. Human exposure biomarkers vary not only with exposure, but also according to characteristics of the individual worker such as lifestyle, diseases and variability in absorption, distribution, metabolism and excretion. Therefore, in cases of unexpected exposure findings, interpretation of the data and intervention at the individual level is advisable to improve or clarify the situation for the worker (see chapter 4.3).

Workflow of BM in practice*

When initiating a BM* programme, there are a number of items that need to be considered including defining the overall goal of the programme, designing the programme (sampling protocol), consulting the workers as well as work councils for ethical questions managing the results and deciding actions based on the results. BM* efforts generally require collaborative health professional teams (e.g., occupational physician, occupational hygienist). The first step is to get an overview of occupational exposures by:

- understanding possible exposure scenarios (workplaces conditions, including risk management measures in place and tasks to be performed, probability and magnitude of exposure, main exposure routes, exposure duration and frequency),
- measure of exposure prevention and occupational hygiene
- the compliance of workers with occupational hygiene measures during personal consultation and by workplace visits.

The occupational exposure investigation may result in the attribution of workers to special SEGs. After appraisal of the exposure characteristics of individual workers and/or SEGs, the requirements of the biomonitoring study shall be fixed including

- the selection of an appropriate BM* parameter, and actions to be taken when BM parameter exceeds specific fractions of the OBL*
- the selection of an adequate laboratory (see chapter 4.2) and,
- designing of a purposeful sampling strategy.

Workers need to be informed about the aim of the BM programme and their individual rights (see chapter 2.4.4). They may also be asked to sign a written informed consent (depending on the regional and specific legal obligations). The overall results from the BM* program shall be tested for compliance with an already established OBL*. Individual worker BM* results shall be incorporated in the counselling of the employee and for advising the employer with regard to preventive measures and possible additional prevention and protective measures at individual or group level (see chapter 4.3 and 4.4).

4.2. Preparation and conduction of a BM* study

4.2.1. Selection of an appropriate biomarker

A crucial task in the preparation of a BM* program is the selection of an appropriate biomarker, which clearly stipulates the sampling strategy and may also influence the selection of the laboratory. The main criteria for the selection of the biomarker are (besides others mentioned in chapter 3.1.1 in Table 3):

- the biomarker has an established OBL*, which can be used for the evaluation of the result.
- The biomarker is specific for the occupational chemical exposure in question.

- The biomarker elimination kinetics enables a convenient sampling method.
- The biomarker concentration reflects a defined exposure interval.
- The biological matrix is easily available and sampling is compliant with ethical standards.
- An analytical method with appropriate performance, which is offered by at least one laboratory.

Sampling strategy

The sampling strategy is part of the BM* programme and ensures that a sufficient number of samples are collected appropriately to have sufficient statistical power to decide if the BM value is compliant or exceed the established OBL*. The sampling strategy shall specify:

- the objective of the sampling
- the workers, who shall be included in the BM* programme
- the biomonitoring parameter (including biological matrix)
- the number of samples over a defined time period
- the sampling collection time points with respect to anticipated exposure time (e.g., spot urine samples collected post-shift or 24 h urine collection)
- the sampling collection interval (e. g. spot urine samples after every work shift over 3 weeks, aligned with elimination half-life time of the investigated analytes)
- storage and transport conditions
- the number of samples per worker
- the number of samples for group-based measurements (SEG approach: which and how many participants have to be included) (see also chapter 4.3)
- who to be included (when following SEG* approach),
- how to determine whether the biomonitoring measurement values generated during the campaign permits the assessment result ‘complied with the OBL*’ or ‘exceeding of the OBL*’ (including a-priori selection of appropriate statistical methods and models (see also chapter 4.3).
- whether the employee shall be assessed during a special working task associated with outstanding high exposure (worst-case scenario).

Some of these points are already addressed in the documentation of an OBL*.

Selection of an adequate laboratory

This section is intended to advise OHPs* in selecting appropriate laboratories for the BM programme.

Assessing the general suitability of a laboratory to perform chemical analysis

The selected laboratory should be able to demonstrate that they operate compliant with adequate laboratory quality standard (e. g. ISO 17025 and GLP).

Assessing the suitability of a laboratory to quantify the selected biomarker in the biological matrix, this might include:

- The selected laboratory should be able to demonstrate their ability to accurately analyze the intended biomarker, e. g. by accreditation of the method, by successful participation in external quality assessment schemes or by having high accuracy in analyzing certified reference materials.
- The selected laboratory should use a validated chemical analytical method for the intended biomarker (see also: (Bader et al., 2012)).
- The chemical analytical method for the intended biomarker and its validation parameters should be described in a standard operating procedure (SOP). The main features of the SOP such as the reliability of data and the limitations of the method should be specified to the OHP* upon request.

- The selected laboratory should inform the OHP* of chemical analytical requirements needed before sample collection such as specific sampling requirements, storage and shipment of samples, required materials, and additional data required by the laboratory in addition to sample identification data (e.g sampling date and time, storage conditions before shipment, personal identity code.

Conducting the BM programme*

All necessary measures to avoid contamination and prevent the loss of the samples' integrity while sampling and handling of the biological samples should be implemented in the BM* programme, and overseen by the OHP* in charge.

The participating worker shall be informed about the risk of contamination during urine sampling and shall be urged to act compliant to avoid contamination (e. g. wash their hands prior to urine collection, change working clothes).

Ethical requirements need to be detailed in the BM* programme as well as the dedicated OHP* conducting the communication with the workers such as:

- The workers have the right to be informed about the aim of the BM *programme prior to their participation. Other information requirements are stipulated in applicable laws and regulations (e.g., on who will have access to the data, etc.). Worker communication can also increase participation rate and participant compliance, if adapted to the audience.
- The workers might need to sign a written informed consent. In some countries such individual consent is not needed as the BM* programme is part of a legal obligation (see chapter 4.4).
- An occupational anamnesis might be included, which gives detailed descriptions on jobs, tasks, machines, emission rates, amounts of products used, production rates, use of personal protection equipment (PPE) etc..

4.3. Evaluation and communication

4.3.1. Laboratory report of BM results

The laboratory report with the biomarker concentrations in the biological samples should include:

- the sample identification with the associated BM concentration
- the name and address of the sender, the name and address of the laboratory
- the laboratory receipt date and the report date
- any anomalies of the sample

The biomonitoring results have the same measurement unit as the OBL* (e.g., mg/g creatinine). For each biomonitoring result and each integrity parameter result (e.g., creatinine), the following characteristics of the analytical procedure shall be reported at least on demand:

- the analytical method used
- the limit of quantification and the limit of detection
- the quality control and quality assessments used
- the uncertainty or analytical precision and

- notes on the interpretation of the results (if necessary)

All reporting needs to follow the data protection rules (see chapter 4.4) and should only be reported to OHPs* that sent the sample(s).

Criteria for compliance with the OBL

Compliance of an occupational exposure with the OBL* means that the risk management measures for workers working with the OBL* substance are effective.

Assessment of a worker's exposure

The OBL* can be used to monitor a worker's occupational exposures. The compliance with the OBL* can be checked with series of consecutive samplings from the individual. A sampling series consists of samples obtained at consecutive time points, for example, each day at the end of a shift over a work week or each week at the end of the work week over a work month.

For *routine working conditions* the most conservative option is to assess if all valid BM* measurements of a sampling series are below the OBL*. Another option is to calculate the arithmetic mean of the measurements of the sampling series. With this approach, it is sufficient if the mean value of several measurements in an individual worker is below the OBL* and the coefficient of variation (CV) is less than 30 % or the mean value is less than 0.5 x OBL* to be in compliance with the OBL*, but it is then necessary to specify a priori how far a single value is allowed to be above the OBL*. In any case, single values should not exceed a threshold for acute toxic effects. The sampling interval of consecutive samplings of a sampling series may be based on the apparent elimination half-life of the biomarker, which can be taken from the OBL* documentation. For the derivation of a sampling interval from the half-life of a biomarker, see, (e.g., Gagné et al., 2013) and Scheepers et al. 2014.

Assessment of a specific exposure profile

OBL* compliance for a specific exposure profile is achieved when all workers having the same exposure profile (similar exposure group – SEG*, according to Technical Committee CEN 137, 2020) comply with the OBL criteria (as outlined in previous subsection" Assessment of a worker's exposure").

OBL* compliance for an exposure profile can also be determined if only a subset of workers of the same SEG* participates. The minimum required participant proportion is given in the following Table 14.

Table 14. Minimum participant proportions

Number of employees in a SEG	Minimum participant proportion if all individual average values are below 0.2 × OBL	Minimum participant proportion if at least one individual average value is above 0.2 × OBL
1–3	100 %	100 %
4–6	75 %	100 %
7–9	60 %	100 %
10–13	50 %	85 %
14–16	40 %	85 %
17–19	35 %	85 %
20 or more	30 %	70 %

Assessment of exposure for a worker

A sampling series of at least two samples are required to demonstrate OBL* compliance *for routine conditions*. Whether more measurements are required depends on the average value and the coefficient of variation (CV). However, both are unknown until the measurement results are available. If the sampling results from previous sample collections are available (i.e., the sampling intervals are sufficiently long), these results can be considered and averages calculated to decide whether to continue the sampling series or not. The sampling series may provide enough valid data when:

- the average of two or more measurements values is above the OBL* (non-compliance scenario) or

- the average is less than 0.5 × OBL* and all single values are below the OBL* level (compliance scenario) or
- the coefficient of variation is less than 30 % and all single values are below the OBL* level (compliance scenario).

A compliance with the OBL* can also be declared, if the average of two or more measurements values is below the OBL*, also if single value(s) may exceed the OBL*. However, is this case a high awareness is requested whether the compliance scenario is sustainable and an early or more frequent reassessment should be considered.

If the results from the previous sampling is not yet available (i.e., in case of short sampling intervals), the number of samples required are estimated. If the sampling series were too small to demonstrate a compliance with the OBL*, it is necessary to repeat the series with a larger number of samples.

Assessment of a specific exposure profile

To demonstrate OBL compliance for a specific exposure profile, it is necessary that 30 to 100 % of the workers within a SEG participate. A stepwise approach is possible. A small group of workers participates in the first measurement round, and then additional workers are included until one participant does not comply with the OBL* (non-compliance). If the average of BM measurement values of a sampling series is below 0.2 × OBL* for all participants, it is initially sufficient to increase the participant rate to the value from column 2 of table 15 (30 to 100 %). Only if at least one participant has an average value above 0.2 × OBL* and all participants comply with the OBL, the participation rate must be increased to 70 % or more, as indicated in column 3 of Table 14.

Setting up a SEG* and validating a SEG* based on BM*

The SEG* shall be constituted using the information on the exposure profile and duration of the tasks performed in the working shifts throughout the year (Rappaport et al. 1995). This requires occupational hygiene expertise, and the information normally considered is:

- the job classification of the company
- the inventory of tasks within a job
- the task specific exposure profile
- the operational conditions and risk management measures in place
- the duration and location of the exposure within the shift and throughout time, determined by the frequency and period of the tasks
- experience of the workforce
- and other variables that can influence exposure.

If the BM measurement values of individual SEG* members deviate strongly from the rest of the results in the SEG, or if the BM results in the SEG* deviate strongly from a log normal distribution, it may be questioned whether the constitution of the respective SEG* was properly done and if the workers included in that SEG* were properly identified.

If the BM measurement values for an exposure profile do not achieve compliance with the OBL, additional risk management measures shall be taken. This can also imply the creation of a new exposure profile and consequently, new SEGs*

OBL compliance for an exposure profile and the validity of a SEG* should be at least reassessed annually. If the workplace or working tasks will change considerably, this may imply a revision of the

SEG and may indicate a BM* reassessment. The interval may be extended to every 2 years if the BM value average was less than 0.2 × OBL* for all participating members of the SEG*.

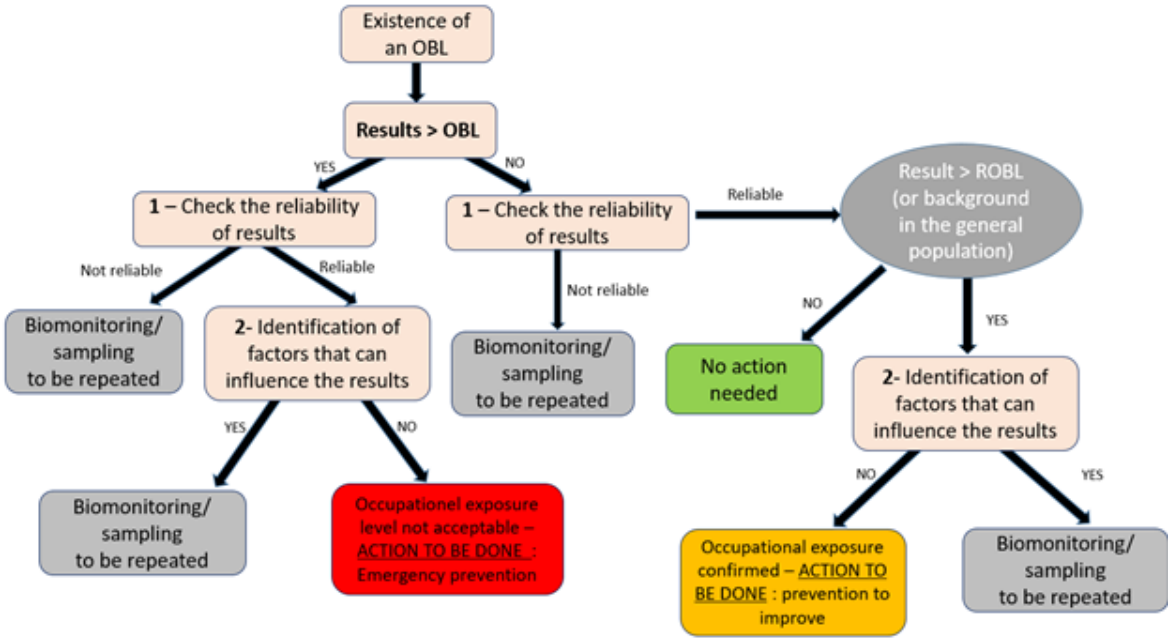
Interpretation of BM results

In all cases the reliability and validity of BM* results should be ensured in the design and evaluation of the sampling strategy.

Factors influencing the reliability are: Day of the sampling not representative of the usual occupational exposure, sampling time not appropriate according to exposure time, external contamination, storage and transport conditions inappropriate as well as urinary creatinine levels out of 0.3 - 3 g/L.

Additionally, an identification of possible confounding factors, e.g., exposure due to non-occupational sources (e.g., food, smoking, drugs), diseases promoting metabolic disorder or excretion disturbance may have to be considered. The comparison of BM* results can be done according to the following flow chart.

Figure 7. Interpretation of BM* results, adapted from (SFMT, 2016)



Non-compliance with OBL* is an indication of inadequate risk management measures. In addition to inadequate risk management measure, the following reasons for elevated BM values shall be considered:

- lack of compliance by individuals with personal hygiene requirements at work
- a specific co-exposure scenario which may affect the toxicokinetics of the biomonitoring parameter
- non-occupational exposures
- exposures that occurred a long time ago (for substances that accumulate in the body)

- individual health/medical conditions that influence substance uptake, excretion or metabolism.

Different roles of single BM* measurements

Although single measurements do not meet the requirements for the evaluation of OBL* compliance, they may serve valuable information for exposure and risk assessment. Single measurement values should mainly be used indicative, e.g. to identify worst-case exposure, and stimulate follow-up measurements (see Fig. 7), Additionally, single measurements of different workers can be used to indicate if an exposure at a workplace is measurable and assessable, for trend monitoring or to indicate if a non-compliant exposure is likely.

If BM* results are exceptionally high or low, the measurements must be repeated and the reason investigated. This investigation should include an assessment of sampling strategy, sampling method, storage, transportation and analytical errors.

In some cases, increased respiratory volume due to heavy physical load or unusual long shift length (e.g., 12-h shifts) can be the main reason for increased biomonitoring values for some substances. Exposure reduction strategies then need to be derived and implemented to minimize exposure.

Although the average value of several biomonitoring measurements for an individual may be below the OBL*, single measured values must always be considered regarding the risk of acute toxic effects. The margin between OBL* and acute toxicological levels can be extremely different for a single substance. Indication for the acute toxic effect level may be included in the evaluation report of the assessment value (OBL* and other).

Communication of BM* results and evaluation conclusions

In the Occupational Health Approach (see chapter 4.1), the BM* results shall be incorporated in the data set of the occupational health surveillance for the worker in question. The BM* results shall be communicated and explained to the worker by the OHP* according to national legislation. The worker shall be informed about compliance or non-compliance of her/his result with the OBL*. In the case of non-compliance with the OBL* or a result which may not guarantee the regular compliance with the OBL*, the counselling of the worker shall consider:

- indications for special conditions which may cause mainly the extraordinary exposure (increased respiratory volume due to heavy physical stress; special contribution of the dermal route to the exposure; high dwelling time in a high contaminated area)
- the possible impact of an insufficient compliance with occupational hygiene measures,
- indications for an individual predisposition to higher resorption rates or aberrant metabolism and toxicokinetics
- an assessment of the individual risk of adverse health effects and advices for improving the individual behavior
- Recommendations for individual protective measures addressed to the employer. The advice will only give information on the specific measures needed for this employee, without giving details on the BM* result or on the specific health/medical reasons.

Also reporting on a collective level might be needed. This may be realized by a statistical combination and evaluation of the results from several employees of a SEG*. In the Occupational Hygiene Approach BM* results shall be used in consulting the employer with regard to identified insufficient prevention measures and identifying possible beneficial interventions.

4.4. Ethical and Legal Aspects

4.4.1. Introduction

BM* is an effective tool for assessing exposure to and effect of hazardous substances in occupational health. It can be used to complement other strategies and tools for exposure or risk assessment. In contrast to other tools however, BM* requires the use of human samples and thus additional fundamental ethical principles and data protection legislation have to be respected. The application of these fundamental principles and regulations may be different according to the wider social, cultural and legal national context and according to the field in which they are applied. Therefore, practices in occupational health research respond to different conditions as compared with practices in routine surveillance programs, and also national laws and regulations differ whilst based on the same principles.

For instance, EU law requires that all EU workers should have access to 'workplace protective and preventive services', but gives EU Member States wide discretion in how they organize their occupational health system. In several (EU) countries BM* is performed within the obligatory periodic health examinations for employees exposed to hazardous substances. These can include BM*, either offered to the employee and requiring informed consent, or mandatory for the employee based on legal requirements. In other countries (especially non-EU) occupational physicians are not part of workplace protective and preventive services and BM* is performed by other OHPs*.

The text in chapter 4.4 considers ethical and legal aspects of routine BM* practices related to exposure assessment only. It does not cover the field of BM* research or effect monitoring. It addresses a limited number of questions that were raised during the preparation of this guidance.

4.4.2. Data protection

Regulations in data protection reflect the principal intention to protect fundamental rights and freedom of people. They specify the conditions under which personal data may be processed and include special requirements that apply to sensitive personal data related to health. Informed consent plays a major role here, but may be overruled for reasons of common public interest or because of specific legal obligations of the employer (see Q&A2 below). Data protection regulation does *not* apply to anonymous data (see also chapter 9.3.3 Annex C: Specific regulations on data protection).

International and national OSH regulations* give instruction on the practices of OSH* to protect the rights of employees with regard to the individual health and exposure data collected and stored (see also see also chapter 9.3.2 Annex C: Methods for de-identification of data).

4.4.3. Ethical guidelines

Specific to the field of occupational health, the International Commission on Occupational Health (ICOH) has developed an *International Code of Ethics for Occupational Health Professionals*. It covers chapters on basic principles, duties and obligations of OHPs, and conditions of executions of the functions of occupational health professionals. It offers a broad definition of OHP*s (ICOH, 2014) (see also chapter 9.3.1 Annex C: on Occupational Health Professionals (OHP*).

More general ethical guidelines exist as well. The Oviedo Convention for example, the Convention on Human Rights and Biomedicine, for example, covers medical and biological applications concerning human beings, including preventive, diagnostic, therapeutic and research applications and addresses issues such as informed consent, right to be informed about your health, the right not to known (Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: convention on Human Rights and Biomedicine, 1999, Dumez et al., 2011, Casteleyn et al., 2015)

4.4.4. Questions and Answers

Q&A 1: Who can implement a BM programme in an OSH context?*

The employer has a duty to ensure the protection of health and safety for all employees at the workplace and finances the related costs (ILO, 1981). The employer has to hire relevant experts (OHPs*) to implement the BM* programme. OHPs* can only be considered experts in their field if they acquire and maintain the competences necessary for their duties as well as adhering to good practice and professional ethics. The OHPs* have an advisory role, as the decisions and the ultimate responsibility lie with the employer. Basic requirements for acceptable OHP* functioning, often specified by national law or set down in written agreements – at least for occupational physicians - include the protection of the professional independency of the OHP*, free access to the workplace, the possibility of taking samples and assessing the working environment, evaluating tasks and workplaces and participating in enquiries and consulting the competent authority on the implementation of occupational safety and health standards. Special attention should be given to ethical issues which may arise from pursuing simultaneously objectives that may be competing. Examples are the protection of employment and the protection of health, the right to information and confidentiality, and the conflicts between individual and collective interests of the workers within the company (ICOH, 2014). In many EU countries a physician trained in the field of occupational health and informed on the entire situation (workplace exposures and worker's health) is in charge of the BM programme the interpretation of the results. In other countries interpretation of biomarkers of exposure is done by other OHPs*.

Q&A 2: What are the preconditions?

Informed consent

In most cases, informed consent is a central precondition of BM*. However, the basis for a lawful processing might also be the specific legal obligations of the employer towards the worker, instead of worker's informed consent (see EU GDPR, art. 9 mentioned in chapter 9.3.3 Annex C: Specific regulations on data protection). The EU GDPR takes into consideration that, in occupational settings, it might be doubtful that a consent would be really free and authentic, given the power inequality between employer and worker (EU, 2018, Article 29 Data Protection Working Party).

When BM* is voluntary, it should be implemented in a manner that the worker can decline BM* without disadvantages in terms of employment law. Where BM* is mandatory for all workers, declining may imply that the worker cannot continue working in the function where he would be exposed to the risk. If no alternative function is available, further employment can be ended. Financial consequences will differ according to national laws (social security, recognition of occupational diseases, etc.).

Information

According to most guidelines, rules, and conventions, workers have the right to be informed about the collection and use of their personal data, which leads to a variety of information obligations on the OHP* and the employer.

Prior information, given in a language and terminology workers understand sufficiently, may include the purpose of the BM* programme, what is going to be measured, how by whom and why, the eventual recipients when transmitting such personal data, how the results and the meaning of the results are going to be communicated to the worker, how the confidentiality of individual results will be assured, the duration of storage, the rights of the workers and what actions might be taken depending on the results. It is to be noted that the EU GDPR conveys the rights of rectification of incorrect data on a data subject. However, this right might be limited based on the justification that a medical record must remain a complete record on all events. Whilst in some countries 'material' information (names, addresses, etc.) can be changed, 'medical' information cannot. In other countries even a 'material' information is recorded as a new entry rather than a correction (EU Commission, 2021)

Q&A 3: What are the requirements regarding collection, storage and access to the data?

Major elements

The OHP* has to keep the data under methods that secure strict confidentiality. They shall be kept in a suitable form to permit consultation at a later date, taking into account any confidentiality. The individual BM results and the additional individual data required for interpretation must be securely stored for an appropriate time specified by the regulation. National laws may require that individual data should be available even if the worker no longer works in that company. According to some national laws individual data can be asked by authorities under specified conditions. Where an undertaking ceases to trade, the health and exposure records shall be made available to the competent authority, the OSH service of the next employer of the worker or to other instances according to national regulations.

The individual worker has a right for information on the health and exposure records relating to him personally.

The employer has no access to the individual data. The employer can only have access to the aggregated or anonymized data provided by the OHP* (see also chapter 9.3.1 Annex C).

Q&A 4: Who should receive the BM results, and in which form?*

At the individual level

The OHP* has to inform the workers of their individual biomonitoring results. If the BM* results indicate the need for further preventive actions (e.g., adapting the working conditions or temporal or definitive ending exposure), the OHP* discusses these with the worker. According to national regulation, possible consequences for his employment should be explained. Clarifying results, possible causes of abnormal results, and remediations is considered a way to improve compliance. The OHP* also recommends exposure reduction strategies to the worker and the employer. This is often done via a certificate defined by law. Information to the employer can never contain any information on results of examinations, including individual BM* results.

These recommendations can lead to job loss or financial loss for the worker if no effective adaptations of his working conditions are possible. If BM* is not mandatory, communication to the employer for action at individual level might need consent of the worker.

At the collective level within the company

BM* measurement results need to be communicated by the OHP* in a form that does not violate the confidentiality of personal data. In practice, the OHP* shall report exposure data and recommendations for risk management measures without containing any specific information on the status of any workers. These recommendations should not allow any conclusions to be drawn about identifiable workers (see also chapter 9.3.2 Annex C: Methods for de-identification of data). Obviously, this might pose particular problems in very small companies. In addition, small companies might not always have appropriate structures, such as health and safety committees, which generally exist for collective debate and negotiation between employers, OHP and workers' representatives. OHPs* often have a legal duty to report on a regular basis at these committees, where they can for instance present and discuss the duly aggregated data of the BM results for clarifying the need for risk assessment/management or for evaluation of the strategies in place.

BM* individual results may only be transmitted between OHPs* under specific conditions of confidentiality. Alternatively, if the OHP* receiving the data works under the responsibility of the OHP* who was charged with the collection of the data, then exchange is easier, again on the condition that

the confidentiality agreement is shared. As mentioned earlier, the worker has the right to be informed in advance on who will have access to the data, within the company and outside the company.

Q&A 5: Do workers have an individual right to BM* for themselves within a programme?

All workers have in principle equal rights for the protection of their health When a BM* programme is relevant for the health protection of a group of workers with possible hazardous exposures all workers in this group should be *offered* BM (in countries where BM is not mandatory), or should be *obliged* to participate in the programme (in countries where BM is a mandatory part of the surveillance). An individual worker cannot demand his inclusion when he does not belong to the exposed group.

In the SEG* approach, as applied in BM, only a selection of a representative subgroup of similarly exposed workers is tested. Identification of those workers of the group who are to be included in a BM* programme should primarily follow a scientific rationale. The individual worker cannot change the design of the BM* campaign by demanding his inclusion.

However, following the above-mentioned principle of equal rights, all workers should have the same opportunity to fully benefit from the BM* programme and have their data assessed at individual and at collective level so to provide the most adequate information for further actions. If such actions are not possible due to the sampling approaches or to anonymization of the results, the ethical justification of BM* campaigns might be critically diminished.

5. Tiered approaches and decision trees for derivation and application of OBLs*

5.1. General description for exposure BM* with a tiered approach and decision tree

5.1.1. Summary

This chapter focuses on the practical use of OBLs* and POBLs* by occupational hygienists and occupational physicians as well on what can be done when an OBL* or a POBL* cannot be established. The options and choices are described in the context of data availability to establish the health-based (OBLs* and POBLs*) and levels which are not health-based (ROBL* and TOBL*) but based on measured biomonitoring levels in the general population (non-occupationally exposed) or on technically achievable internal levels, respectively. All these options are compiled into a decision tree that incorporates the current situation in various countries as much as possible and generalizes where needed. In addition, it includes conclusions and consequences of compliance with or exceedance (non-compliance) of the various levels.

If a health-based OBL* cannot be derived, a “Reference OBL" (ROBL*) could be established when relevant biomonitoring levels in the general population (not occupationally-exposed) are available. If suitable and high-quality data to derive ROBL* are lacking, a “Technical OBL” (TOBL*) could be established based on what is techno-economically achievable at the workplace using the best available techniques to lower the exposure (see chapter 3.4.2).

Non-compliance with health-based OBL* or POBL* means that occupational health risks cannot be excluded. Whereas exceedance of a ROBL* only means that occupational exposure probably exceeds the non-occupational exposure. Exceedance of a TOBL* only means that exposure probably has occurred above the lowest external exposure level that is technically achievable, potentially including the use of personal protective equipment (PPE*).

5.1.2. Objective

The objective of this chapter is to provide guidance on how tiered approaches can be used in interpreting occupational biomonitoring data to protect workers from adverse health effects due to chemical exposure at work. To achieve this objective, two types of guidance values, namely health-based (OBL* and POBL*) and non-health-based (ROBL* and the TOBL*) are considered. The overall tiered approach includes a decision tree aimed to help risk assessors in this process. Moreover, the tiered approach intends to help occupational physicians and occupational hygienists to control and manage workplace exposures using occupational biomonitoring and to provide a framework to use and interpret occupational biomonitoring measurement data.

5.1.3. Introduction

A tiered set of four occupational exposure levels is presented, two of them being lower tiers, not health-based, but more practical OBLs* and two higher tiers of health-based OBLs*. The aim should always be to establish and use the highest tier OBL*. The lowest exposure levels group encompasses the pure technically-achievable Tier 1 TECHNICAL OCCUPATIONAL BIOMONITORING LEVEL – TOBL* and the Tier 2 REFERENCE OCCUPATIONAL BIOMONITORING LEVEL

– ROBL*. The highest group are health-based levels: a more screening health-risk Tier 3 PROVISIONAL OCCUPATIONAL BIOMONITORING LEVEL – POBL* with some lower tier precautionary assumptions underlying, and a Tier 4 OCCUPATIONAL BIOMONITORING LEVEL – OBL*. The derivation of OBLs* and POBLs* is described in chapters 3.2 and 3.3

5.1.4. Tiered approach OBLs explained*

The tiers are such that they run from relatively simple assessment, interpretation and preliminary decision making to more complex assessment with more conclusive options in a health context. Exceedance of the Tier 1 TOBL* only means that exposure is indicated. It is not clear whether that exposure is work-related or not. Exceedance of the Tier 2 ROBL implies that there is exposure in workers in addition to general population exposure. Exceedance of the Tier 3 POBL* means a warning that health-risk maybe indicated. Non-exceedance means that health risks are unlikely according to the state of current knowledge. Exceedance of the Tier 4 OBL* means a stronger warning that health risk maybe indicated. Non-exceedance means that health risks are unlikely according to the state of current knowledge but with more confidence than non-exceedance of Tier 3 POBL*.

Non-health-based

TOBL*: The "Technical Occupational Biomonitoring Level" is not derived from a threshold or extent of health effects or linked to any risk level but is based on the ALARA principle ('As Low As Reasonably Achievable') and tries to follow the best available technique (BAT) approach. The TOBL describes the biomonitoring level in employees working in a state-of-the-art occupational environment, for which chemical exposure is limited as low as reasonably achievable. TOBLs are mainly derived for substances for which it is not possible to derive OBL*, POBL*, or ROBL*. Any exposure may imply an actual but non-quantifiable but still existing health risk, e.g., for genotoxic carcinogens for which insufficient data are available to set risk numbers. See lowest tier in Table 16. The suggested evaluation of a TOBL* is described in chapter 5.3.

ROBL*: The "Reference Occupational Biomonitoring Level" is a strictly statistically defined value, which is not linked to any health-related threshold or extent of health effects. The ROBL* describes the background level of a substance that is present concurrently at a particular time in a reference population of individuals of working age who are not occupationally exposed to the substance. The 95th percentile biomarker concentration from a general population biomonitoring survey is often used as a ROBL*. The ROBL* takes into account that every person is in somehow, usually to a limited extent, exposed to almost any substance even without a specific exposure situation. Supplemental occupational exposure in the individual or a group of workers can be identified by comparing the biomonitoring results with the ROBL*. A Standard Operating Procedure (SOP) for ROBL* is described in chapter 3.4.1.

Health-based

POBL*: The POBL* is the health-based "Provisional Occupational Biomonitoring Level". The main purpose of POBL is risk screening. POBLs* are intended to identify and manage possible occupational health risks (see chapter 3.3.1 on POBL*). A POBL* can be derived for data-poor chemical substances and can be derived similarly to the derivation of the OBL* but with a lower quantity of data and less confidence than the OBL derivation. In principle, all methods used for refined OBL* derivation, but having a low overall confidence assessment might be used as POBL* for indicative risk assessment purposes.

OBL*: The "Occupational Biomonitoring Level" is the level for which there is high confidence. An OBL can be used for occupational risk assessment. The derivation is always health-based and can be derived with/via different main methods (see chapter 2.3):

- Establishment of OBL* using toxicity data (BMDL* or NOAEL*) or human epidemiology data and if needed appropriate assessment factors e.g., for interspecies

extrapolation and either available and corresponding biomarker levels or calculation of OBL* using toxicokinetic information.
- Starting from an existing OEL* or OELV* (external). Use measured external exposure and internal (biomarker concentrations) data (either from workplaces or experimental exposure settings) to derive an empirical correlation between biomarker concentration and external exposure to extrapolate an Occupational Exposure Level (OEL*or OELV*) to an OBL*.
- Use of available toxicokinetic measurements or PBK* modelling or a simple kinetic relationship to estimate an acceptable biomarker level from an external OEL*or OELV*.
- Use of simple approaches, like the urinary mass balance approach and the urinary excretion fraction to calculate corresponding biomarker levels to external limit values (ADI*, RfD*, HGBV*, DNEL*$_{oral}$ etc).

It should be noted that based on a current confidence assessment of data used in the derivation (e.g., POD*, selection of biomarker and toxicokinetic aspects), when an OBL* has low confidence, then it should be considered as a POBL*. However, with increasing confidence over time, POBL* can become an OBL* ('refined' OBL*). See chapter 3.2.3 confidence assessment of OBL*.

5.2. Practical use of tiered approach using the decision tree in interpreting exposure BM*

The health relevance of conclusions of biomonitoring-based assessment increases from Tier 1 to Tier 3. The confidence increases from Tier 3 to Tier 4. At Tier 1 level (TOBL*) no health context related assessment is possible. AtTier 2 level (ROBL*) one can only say that health risks are not higher than in the general population. For worker exposure that exceeds the Tier 3 level (POBL*), a health risk cannot be excluded. And if the Tier 4 level ('refined' OBL*) is exceeded, the direct conclusion is the same (health risks not excluded) but there is more certainty and more reason for follow-up actions. The confidence level in any conclusion increases with increasing underlying confidence in the OBL* (refined) derivations (see chapter 3.2.3 confidence assessment of OBL*). The statistical requirements to assess an exposure or a health risk are discussed in chapter 4.3 Evaluation and communication). Starting "at the top of the stairs" and aiming to use the highest tier, the following tiered approach is proposed:

- Are there high-quality health data available to establish an OBL* and is a threshold mode of action (MoA*) relevant?
    - Yes, yes: go immediately to Tier 4 to establish an OBL* (Category 1A OBL*).
    - Yes, no: are there high-quality health data available and is non-threshold mode of action (MoA*) relevant so a risk-based OBL can be derived?
    - Yes, yes: go to Tier 4 to establish an OBL* (Category 1C).
    - No, no: go to the next question
- Is there an external OEL* or OELV* available as well as toxicokinetic information of sufficient quality?
    - Yes, go to Tier 4 to establish an OBL (Category 1B OBL*).
    - No, go to the next question.
    - For non-threshold MoA* risk based OBL*values (1C,+1D) analogue to 1A or +1B can be derived (see Fig.8).
- Are there data available to establish a POBL*?
    - Yes, go to Tier 3 to establish a POBL*.
    - No, go to the next question.
- Are there data available to establish a ROBL* for the general population?

- Yes, go to Tier 2 to establish a ROBL*.
- No, go to the next question.

- Are there technical and occupational biomonitoring data available to establish a TOBL*?

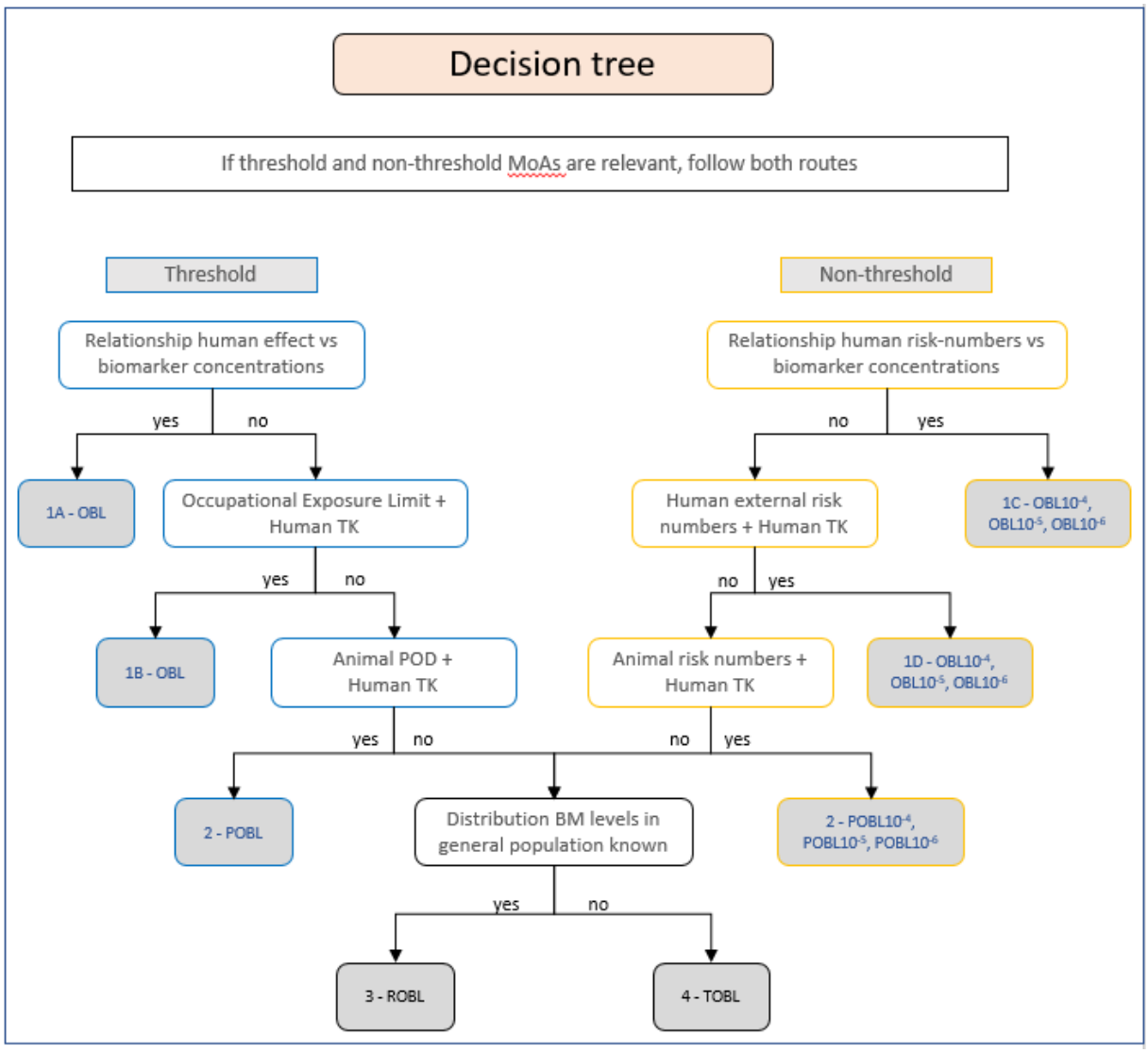
  - Yes, go to Tier 1 to establish a TOBL*.
  - No, are we talking about a non-threshold chemical substance?
  - Yes, is there an OBL* or POBL* available for a threshold mechanism?
  - Yes, use that OBL* as a pragmatic value for the time being.
  - No, new data need to be generated to either establish a TOBL*, a ROBL*, or, preferable of course a POBL* or an OBL*. Depending on the situation and available provisional data, these can be exposure data, occupational biomonitoring data, technical data regarding external exposure or animal toxicity/epidemiological data dose-response data.

In Table 1 an overview is presented on the subcategories of the health-based OBL* categories (OBL* and POBL*). Finally, the decision trees are presented for practical applications in threshold effects and non-threshold effects scenarios (Figure 8). It should be noted that the decision tree was designed with the intention of capturing potential scenarios as much as possible; however, in practice, those scenarios may not exactly fit the steps described in one of these decision trees. In those cases, the decision trees should be used based on expert knowledge with transparent reasoning to achieve best possible results. In addition, in case threshold and non-threshold effects apply, both arms of the decision tree need to be followed. General practice in risk management is to take the lowest value forward (most critical). However, final conclusions on which value to use in practice depend on uncertainty and confidence assessment around each OBL*.

Table 1. Main- and subcategories of different OBLs* and their derivation types

Category	Type	Tier	Sub-category	Basis
OBL*	Health or health risk	IV	1A	Direct relation between biomarker concentration and health effect
			1B	Available OEL*or OELV* (DNEL, TLV, …) and a (TK-based) relation between external and biomarker concentration
			1C	Non-threshold effect data (e.g., genotoxic carcinogenicity) and risk numbers. E.g., biomarker level corresponding to 10-6, 10-5, 10-4 cancer risk
			1D	Option if OBL Cat 1C based on internal concentrations cannot be derived e.g., due to lack of sufficient (reliable) dose-response data. Then external risk levels corresponding to 10-6, 10-5, 10-4 cancer risk can be used instead.
POBL*	Health or health risk	III	2	Provisional OBL; if no Cat 1 OBL available; often based on animal NOAEL a POBL can be derived (chapter 3.3). POBL can also result from OBL with low confidence assessments (chapter 3.2.3). They follow then the same A-D subcategories as for OBL (2A, 2B, 2C, 2D).
ROBL*	Reference population	II	3	Sstatistically based reference Level (e.g., P95) in general population
TOBL*	Technical feasibility	I	4	Technically set, chemical exposure is limited as low as reasonably achievable

Figure 8. Decision tree for practical derivation of OBLs* (threshold and non-threshold, health-based and non-health based)



5.3. Interpretation and practical use of different OBLs* in risk management using exposure BM* data

In Table 2, an overview is presented on the interpretation of compliance or exceedance of the various OBL* categories in a risk assessment and risk management context.

Table 2. Compliance with OBLs* or exceedance of OBLs* – What does it mean?

TERM	BASIS	BM* LEVELS AT OR BELOW	BM* LEVELS ABOVE
OBL*	Health or risk-based Sufficient confidence	Risk for health risks or effects is not indicated and not likely	Health risks or effects cannot be excluded with reasonable certainty
POBL*	Health or risk based - based Less confidence	Health risks or effects not indicated	Health risks or effects not excluded Try to refine to an OBL*
ROBL*	BM* levels in a Reference population	Occupational exposure is not likely	Occupational exposure likely Health effects unclear
TOBL*	Technical achievability	Exposure at or below the lowest or technically achievable exposure	Exposure above the lowest technically achievable exposure Health effects unclear

*5.3.1. Practical use of OBL*s in risk management*

In Table 3, further guidance is provided as to how industrial hygienists and occupational physicians can interpret exceedance and compliance with various levels.

Table 3. More extensive interpretation and perspective for action following compliance vs exceedance of OBL*

		Group exposure (aggregated data)	Individual worker exposure
OBL*	Exceeded (non-compliant)	Risk cannot be excluded with reasonable certainty Exposure mitigation is strongly indicated.	Unacceptable exposure cannot be excluded. Mitigation of personal exposure necessary, e.g.: Ensure adequate handling or proper use of PPE and other RMM*. Consider refined exposure assessment, also other workers might be exposed. Or even advise change of job tasks to protect the individual from becoming ill. Propose health surveillance (if not already in place)
	Compliant	No current concern	
POBL*	Exceeded (non-compliant)	Indication that exposure too high. Consider exposure	Mitigation of personal exposure indicated. E.g., proper handling or proper use of PPE* and other RMM*. Consider additional biomonitoring, also other

		mitigation. Consider OBL* derivation.	workers might be exposed. Suggest discussing the situation with OHP* and check e.g., use of PPE* and other RMM*.
	Compliant	No current concern indicated	
ROBL*	Exceeded (non-compliant)	Occupational exposure indicated. Check potential other sources. Can it be mitigated? Follow-up dependent on the seriousness of potential health effect.	
	Compliant	No occupational exposure is likely	
TOBL*	Exceeded (non-compliant)	Improve technical options to reduce exposure	
	Compliant	No exposure above the lowest technically achievable exposure	

5.4. Limitations of tiered approaches in interpreting exposure BM*

As with any approach, there will always be limitations to the tiered approaches described in this chapter. The way the tiered approach works out depends on the quality rating given by experts to various sorts of information used for the OBL* derivation. The type of adverse effects (e.g., body weight gain versus cancer), the confidence in the effect, and the relevance of the effect (sex-dependent, age-dependent etc.), are prone to expert judgement biases (see chapter 3.2 on OBL*). This guidance tries to help and guide in typical cases and streamline the process. The practical use of the tiered approach in occupational risk assessments will be influenced by several factors, including the quality of the data, the frequency of exceedances, the number of workers with exceedance, the access to individual worker data (often only the occupational physician) or not (often the occupational hygienist).

New developments, new (inter)national consensus, e.g., on threshold versus non-threshold effects or the relevance of sex-specific adverse effects and improvement of chemical analysis or the generation of new data could have direct consequences on how the tiered approach is used in occupational risk assessments. The current tiered approach for the biomonitoring-based occupational assessments that use exposure biomarkers is based on many discussions at the international level and it follows the OECD consensus approach.

5.5. Tiered approach conclusions for exposure BM*

This guidance started with advice on how to elaborate an OBL*. Establishing an OBL* (also called 'refined' OBL) provides the best scientific basis for assessing internal exposure (highest tier possible; Tier 4). An OBL* is associated with minor uncertainties and a high level of confidence. In the case where a good knowledge base is present but due to practical constraints (time, budget, expertise) the scientific information (epidemiology and toxicology) cannot be scrutinized sufficiently, an already established health-based guidance value for airborne exposures (HBGV*, OEL*,OELV*, MAK*, VLEP[1] etc.[2]) can be used as a basis for the derivation of an OBL*. It should be noted that relevant toxicokinetic data of sufficient quality is required for deriving an OBL (see chapter 3.2 on OBL*). In some cases, however, establishing an OBL* is not possible because of insufficient scientific knowledge (epidemiological, toxicological, toxicokinetic data). Consequently, a provisional OBL at a lower tier, i.e., the POBL* should be derived (see chapter 3.3 on POBL*). The second highest tier is the POBL* (Tier 2), which is still a health-based OBL. Guidance for that is provided in chapter (see chapter 3.3 on POBL*).). Health-based OBLs cannot be established if epidemiological or toxicological data are completely lacking. In that case, the option in a lower tier (Tier 3) is to consider internal exposure levels in the general population of about the same age and establish a statistically-derived OBL, termed a ROBL* (mostly P95 of the distribution of exposure levels). With a ROBL* one can establish whether there is any significant occupational exposure, i.e., in case it is clearly above the ROBL* that has been set. If even

this cannot be achieved because of a lack of non-occupational (reference population) internal exposure data, the lowest tier (Tier 1) is left, which means the establishment of a TOBL*.

5.6. Preliminary tiered approach for effect BM*

Similar to exposure biomonitoring, a tiered approach and terminology is proposed for using effect biomarkers to indicate exposure and health risks (adapted from Zare Jeddi et al., 2021a). Terminologies can be found in chapter 1.3.1.

5.6.1. Specific requirements for data interpretation

Effect biomarkers need to be sufficiently characterised with regard to relevance, sensitivity, specificity and robustness (Zare Jeddi et al., 2021a). In addition, at least exposure-response information should be available for one key chemical substance known to be able to affect the specific effect-biomarker. In the absence of an OBEL*, group-based assessments of workers are generally recommended, due to the inter-individual variabilities of some effect-biomarker responses. Collective assessments can be performed with the SEG* approach (see chapter 1.1.7 and 4.3 and 2.3.3 and chapter 9.2 Annex B Table B3) in comparison with a control group or adequate population group. Effect biomarker responses should always be interpreted with caution and in the context of all available information to avoid confounding factors. A direct comparison of an individual effect biomarker response is only possible once the effect biomarker is well characterised and a clear dose response relating the OBEL* to an Adverse Outcome level has been established. A follow up activity at the OECD level is foreseen in 2022 to establish OBEL* and POBEL* for relevant effect-biomarkers (Zare Jeddi et al., 2021b). The use of effect biomarkers in occupational settings have yet to be an established tool in practical situations. At present, establishing guidance based on the same level of knowledge and expertise as for exposure biomarkers is simply not possible for effects biomarkers. The feasibility of using effect biomarkers as a tool in risk assessments and the potential of Adverse Outcome Pathways (AOP's) to establish mixture thresholds (OBEL*) was discussed and adopted in an effect-biomarker activity at the OECD WPHA/WPEA (at the time of writing of this guidance planned to start in 2022).

*5.6.2. Proposed tiers and actions for effect BM**

Table 4. Practical use of a tiered approach for for effect BM* and what exceedance of the tiered levels indicates

Effect-BM*		Level	If exceeded
Term	Tier		
OBEL*	3	Refined	Health-risk indicated
POBEL*	2	Provisional	Health-risk maybe indicated
ROBEL*	1	Reference	Occupational exposure indicated
Not yet defined		Technical	Exposure indicated

Relevant MoAs/endpoints are or could be observed as being activated based on measurement of significantly elevated MoA/endpoint-specific effect biomarker levels in the exposed workers.

5.6.3. Tiered approach assessment for effect-biomonitoring:

Tier 1: Exceedance of the Reference Occupational Effect-Level (ROBEL*). If no ROBEL* is available, please check Tier 2.

Proposed action:

→ Try to determine a provisional Occupational Biomonitoring Effect level (POBEL), see chapter on effect-biomarker

Tier 2: Exceedance of the POBEL*

Proposed action:

→ Improve exposure assessment and/or hazard assessment (to set OBEL*) and if possible, improvement of Risk Management Measures (RMMs*)

→ Try to determine a refined Occupational Biomonitoring Effect level (OBEL*) in order to decrease uncertainty

Tier 3: Exceedance of the OBEL*

Proposed action:

→ Prioritization and further exposure assessment investigations to exclude chemical exposure risks.
→ Improvement of Risk Management Measures (RMMs*)

-> Recommend health surveillance of workers, because the worker is already exposed to concentrations of chemicals which can initiate adverse effects.

6. Main findings & international context

6.1. Key findings from subtasks

6.1.1. Key messages derivation of OBL for human toxicity data rich substances (chapter 3.2):*

- An OBL* derivation is needed for many substances posing significant risk via dermal or oral exposure or where air measurements are inappropriate.
- An overview, description and ranking of commonly applied OBL* derivation methods is provided.
- A guidance on confidence assessment used in the OBL* derivation is provided.
- OBL*derivations without confidence assessment can only lead to Provisional OBL (POBL*) derivations.
- With our harmonized approach for OBL* derivation, we intend to stimulate a harmonized worker protection and increase of available OBL*.

6.1.2. Key messages derivation of POBL for substances with limited human toxicological datasets (chapter 3.3):*

- POBLs* can be derived for human toxicity data-poor chemical substances.
- POBLs* can be used for identifying and managing possible occupational health risks for a large number of chemicals in a time and cost-effective manner.
- A guidance for using a urinary mass balance approach for POBL or OBL derivation is provided.
- POBLs* derivations were sufficiently sensitive to identify potential toxicological risks compared to refined OBLs* and existing BLVs*.
- POBLs* derivation should be implemented in a tiered approach and can stimulate a refined OBL* derivation and availability.

6.1.3. Key messages from effect-biomonitoring (chapter 3.4):

- Effect biomarkers are the only option available for addressing unknown mixture effects from chemical exposures, but are rarely applied.
- Several relevant effect biomarkers are validated and offer a direct assessment of the overall risks of health effects.
- A guidance for the identification of relevant effect biomarkers and their mechanistic pathways following the Adverse Outcome Pathway (AOP*) framework is provided.
- Effect biomarkers can serve as early warning systems in risk assessment and to define intervention priorities when planning risk management.
- Availability of high-quality, validated, high-throughput analytical methods is crucial to ensure that the biomarker data obtained from studies are accurate and precise.
- Biological effect threshold levels can and need to be derived based on mechanistic knowledge coming from the AOP* framework to implement the use effect biomarkers in risk assessment of chemical mixtures.

6.1.4. Key messages from application of biomonitoring in practice (chapter 4):

- We indicate the selection of appropriate BM* parameters and the design of a purposeful sampling strategy as basic prerequisites of an efficient biomonitoring program.
- BM* values can be affected by both the individual exposure and the individual disposition factors; contaminations need to be avoided.
- An OBL* compliance check needs BM* measurements during representative or worst-case exposure scenarios, averaging of repetitive BM* measurements for balancing of inter-day variability and an adequate participation rate in the case of the SEG* assessment.
- We recommend that the priority of OBL* grades shall be considered for the interpretation of BM* results, e.g., well-verified health based OBL* favored over reference or technical-based OBLs*.
- Assure by regulation that BM* and its related communication at individual and collective level is based on sound scientific and ethical guidelines and solely aimed at a better protection of workers health.

6.1.5. Key messages from the tiered approach (chapter 5):

- The “Tiered approach – Decision tree” explores the idea of a hierarchical approach in deriving hierarchical OBL’s* based on (health) data availability, and their practical application in occupational health risk assessment and management.
- Exceedance (non-compliance) of OBL* or POBL* means risk management measures are indicated (exposure mitigation), preferably by reducing ambient exposure and as a last resort, by personal protective equipment (PPE).
- Exceedance (non-compliance) of ROBL* or TOBL* is an indication that occupational exposure may occur but might need more investigation (ask workers about their extra-professional activities/habits to exclude unexpectedly high non-occupational exposure) before exposure mitigation is being implemented.
- In order to guide the user, a decision tree for the derivation of different kinds of OBLs* is provided.
- In order to guide the risk manager, a tiered approach for an interpretation of BM data and stimulation of Risk Management Measures (RMM*) is proposed.
- In addition, a very first proposal is included for a similar tiered approach concept for occupational effect biomonitoring with the establishment of occupational biomonitoring effect level (OBEL*), provisional occupational biomonitoring effect level (POBEL*) and a Reference OBEL* (ROBEL*).

6.2. How to unlock the potential of Occupational Biomonitoring

Until now, the most common reference to BM* in regulatory text and technical guidance is made in the scope of health surveillance and, consequently, this limits its use in exposure and risk assessment. This also explains the differences between countries concerning how BM* data is stored and communicated but, ideally, the individual data should be added in the worker’s clinical file, with the results being communicated individually to each worker and, also, to the employer, in an aggregated manner, guaranteeing data anonymization.

Therefore, better clarification and guidance of all the possible BM* applications in the context of OSH* should be developed for who works in the field but also for the Regulatory Agencies that can promote the use of BM* data during the assessments needed to be developed. Those applications should be supported by dedicated guidance, where in a simple and comprehensive manner information on how the sampling should be performed and on how the results can be interpreted and communicated should be provided. Additionally, the information should be adapted to the different applications/aims of the BM* campaigns (e.g., exposure and risk assessment, to provide information to define the RMMs* to be implemented or even to improve the ones already in place).

6.3. Related ongoing research projects

Workers are usually exposed to higher levels of specific substances than general population, and represent often a high-risk population. This is due to the fact that work and workplaces are constantly changing with the introduction of new technologies, substances and work processes. This may give rise to new risks and challenges that must be anticipated and addressed. Moreover, the most common exposure scenario in workplaces is exposure to mixtures known to some extent, therefore being useful for creating and validating new approaches for risk assessment. A typical challenge in undertaking occupational biomonitoring studies is the low number of workers that can be recruited in national studies. In addition, the studies are usually performed by different research groups in individual countries and consequently these are usually not aligned with respect to sampling, data collection or analytical methodologies. This hampers the comparison of the findings and the use of the data in regulatory risk assessment throughout Europe. HBM4EU Project (HBM4EU website, 2021) demonstrated how to overcome this challenge, conducting three targeted occupational studies, focusing on priority substances identified within the project. The first one was targeted at hexavalent chromium [Cr(VI)] exposure, which began in 2018. Sample and data collection have been completed across eight countries, with data analysis and reporting of the results currently ongoing with several papers already published and others being prepared (Karen et al., 2021; Santonen et al., 2022). The two further occupational studies, focused on exposure to diisocyanates and chemical exposure in E-waste handling, have been planned, with sample and data collection already started and following also harmonized procedures allowing comparison the use of the data to support regulatory risk assessment through Europe. Within the HBM4EU project several procedures and guidelines were developed which may support the application of BM in practice. Access to this information enables the HBM4EU platform (HBM4EU website 2021).

PARC intends to continue to address the challenges that occupational health faces, such as from the new (e.g., low carbon) technologies and circular economy that may bring new risks to workers. Taking into account EU goals on green energy, circular economy, zero pollution and non-toxic environment, ensuring the high-level risk management in these activities should be a high priority (EU-OSHA, 2022). Therefore, these new risks need to be identified, specific approaches for assessment and control need to be developed, and their effectiveness needs to be followed. Moreover, targeted occupational studies focusing on new technologies, processes and raw materials related to circular economy or in settings where climate change can modify the exposure trend will provide useful information for risk assessment and to define priorities concerning risk assessment, policy action or even regulatory and/or enforcement purposes.

6.4. Building of analytical capacity

The capacity of laboratories with experience in BM* analysis differs between regions and countries. Thus, it might be necessary to build up or increase the number of laboratories, which can offer a reliable analysis of BM* parameters. Issues, which may support the establishment of robust analytical capacity for BM*, are:

- the accessibility of standard operating procedures for the determination of BM* parameters
- the supply of products or procedures for testing the analytical accuracy or comparability for BM* parameters.

Descriptions of analytical procedures for BM* parameters are available by peer-reviewed publication and unaudited reports in large quantity. However, implementation of these methods can sometimes pose a severe challenge for unexperienced laboratories. Those problems can be overcome by accessing analytical procedures, whose reproducibility has been proven and confirmed by independent laboratories. Documentation of BM* procedures, which passed such examination process successfully, have been published by the DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area for more than four decades. The methods are available in open-

access in the MAK-Collection for Occupational Health and Safety (MAK Commission, 2021). The testing of analytical accuracy and comparability, respectively, can be performed by:

- the analysis of certified reference materials (CRM) for BM* parameters and/or
- the participation in an external quality assurance scheme (EQUAS) for BM* parameters.

Certified reference materials are characterized by a metrologically valid procedure for one or more analytical parameters engaging several well-experienced laboratories, accompanied by a certificate that provides the parameter's level, its associated uncertainty, and a statement of metrological traceability. The most important bodies, which offer such CRMs, are National Institute of Standards and Technology in the US (NIST) (NIST, 2021) and Joint Research Center of the European Union (JRC) (JRC, 2021). However, the number of BM* parameters, which are covered by CRMs, is low.

External quality assessment schemes for the determination of chemical elements (mainly metals) in human biological material are available in several countries. However, the supply of EQUAS for BM* parameters of organic hazardous compounds is marginal. EQUAS, which offer the proficiency testing of organic BM* parameters internationally, are provided by the Centre de toxicology du Québec (CTQ, 2021), hosted by the Institut National de Santé Publique du Québec (INSPQ), Canada) and the German External Quality Assessment Scheme (G-EQUAS, 2021, provided by the Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg, Germany).

6.5. Current gaps on physiologically-based kinetic (PBK*) modeling

PBK* modeling simulates the concentration development over time of parent compounds and its metabolites in one or several body compartments, which depends on the routes and rates of absorption, protein binding, distribution within the body, metabolism, and excretion (ADME*) (OECD, 2021). In occupational risk assessments, a PBK* model can also be used to:

- Understand the importance of the various routes of absorption e.g., inhalation, skin uptake, or ingestion, which will help in developing exposure reduction strategies (e.g., ventilation for inhalation).
- Assess systemic exposure after peak exposures (Cmax) as well as after chronic exposures (AUC), and thus, help in describing the relationship between external and internal exposure e.g., linear or non-linear relationship and possible accumulation.
- Estimate target organ doses from exposures that can be compared to mechanistic in vitro concentration-response relations.
- Extrapolate tissue dosimetry: from high dose to low dose, route-to-route, inter- and intra-species.
- Calculate the excretion rate and fractions, such as urinary fraction excreted (F_{UE}) that can be directly used to develop human biomonitoring guidance values, such as OBLs*.
- Estimate external exposure associated with human biomonitoring data (i.e., exposure biomarker concentrations) (reverse dosimetry)

Basic toxicokinetic parameters are needed to create PBK* models. These are obtained from *in vivo*, *in vitro* and *in silico* studies, which add uncertainties but provide valuable a priori information on individual ADME processes that altogether over time determine the toxicokinetics (e.g., absorption rate constants, protein binding, tissue-blood partitioning, metabolic breakdown described e.g., with Km and Vmax) ((Bessems et al., 2014); (Paini et al., 2021); (OECD, 2021)).

Currently, there are few PBK models publicly available, but the database is expanding rapidly. In vivo human toxicokinetic data are based on highly regulated controlled human volunteer exposure experiments (e.g., in exposure chambers) or on detailed air and dermal exposure monitoring in the workplace with aligned sampling of blood or urine. Both approaches are rather costly and need thorough medical-ethical evaluation compared to in vitro testing or testing in vivo with animals. Currently, some

databases containing ADME* (e.g., ICRP 2002) parameters exist, but data quality and collection process are often unknown. For example, aluminum kinetic data prior to the 1990s were considered less reliable than the current databases due to the lack of ability to differentiate between administered doses and endogenous doses and lack of knowledge of potential contaminations. Some of the existing PBK* models are complicated and may be difficult to communicate when used in health risk assessments. In addition, PBK* models for vulnerable populations, such as pregnant individuals or infants, are scarce. Software used to code toxicokinetic models is diverse, thus operating a given existing model might require specific software. The first step in promoting the development of toxicokinetic modeling is to harmonize toxicokinetic data and store the systematically collected data in a global registry. The second step is to make toxicokinetic models accessible for users to develop human biomonitoring methods and OBL*s. An outline of how this can be achieved has recently been described in (Zare Jeddi et al., 2021c).

6.6. Vulnerable populations at the workplace

Vulnerable populations at the workplace include some individuals within the workforce that could have (a) an increased risk of experiencing adverse health effects due to a special disposition and greater sensitivity or (b) a greater potential for elevated exposure to industrial chemicals (NEJAC, 2004, deFur et al., 2007).

- Susceptibility is a component of vulnerability and can be defined as the increased likelihood of an individual worker or workers to be more affected by a chemical as compared to the rest of the workers because of intrinsic biological factors such as life stage, pregnancy, genetic polymorphisms, prior immune reactions, disease state or prior damage to cells or systems (US-EPA, 2003).
- The probability of exposure in a specific work situation can be elevated, for example, due to the poor ability of an individual worker to follow occupational health and safety rules ((ATSDR, 1997); (NEJAC, 2004); (deFur et al., 2007); (US EPA, 2003)).

Traditional workplace risk assessment and management approaches may include vulnerable populations; however, there is no globally accepted approach for HBM-based risk assessments of these sub-populations. HBM data of vulnerable populations can be used as a tool to identify systemic exposure in individuals, who are exceeding biomonitoring guidance values, such as BEI® (USA ACGIH* committee), BLV (ANSES 2021). If exceedances are identified, additional risk management options should be targeted to specific vulnerable groups, such as maternity protection for pregnant or breastfeeding women at the workplace (EEC, 1992). Generic approaches in defining guidance values for exposures at work are usually made for 'healthy workers'. In some specific cases, additional risk management options are targeted to specific vulnerable groups, see for example maternity protection laws (EEC, 1992). There is no globally accepted approach for HBM-based risk assessments for vulnerable populations. One of the advantages of applying individual biomonitoring for exposure and health assessment estimates is that it facilitates the identification of both factors of vulnerability: an eventual higher probability of exposure as well as the higher susceptibility (toxicological vulnerability) influenced by individual kinetic characteristics of substance (uptake, distribution, metabolism, excretion). HBM results can therefore be helpful in identifying vulnerable individuals when exceeding biomonitoring guidance values, such as BEI® (USA ACGIH* committee), BLV (ANSES 2021) and allow taking appropriate measures. Establishing effective communication between key parties (i.e., employers, workers, industrial hygienists, risk assessors and managers, etc.) is crucial in protecting vulnerable workers from health risk from industrial chemicals (Viegas et al., 2020). Finally, it is important to note that labelling individuals into a specific group as vulnerable or marginalized may negatively impact the mental health of affected workers and their career possibilities. Therefore it is important that occupational biomonitoring is based on sound scientific and ethical guidelines, allowing better protection for every worker.

7. Occupational biomonitoring conclusions & recommendations

7.1. Main conclusions

BM* is an important tool for protecting workers' health and for controlling exposures to hazardous chemicals. BM* can have a high relevance and broad application field for chemicals and related occupational exposure scenarios (see chapter 1.2). It needs to be applied in accordance with current ethical standards, respecting the individual rights and freedoms of workers. Despite this, BM* was recently identified as a largely underused exposure assessment tool in occupational safety and health context (Viegas et al., (2020). This becomes more obvious looking at the large number of chemicals having a skin notation and likely a dermal uptake, but having "only" an OEL* or OELV* available, so the health-risk assessment is limited to inhalation risks and is mostly ignoring dermal and oral exposure pathways.

For example, in Germany 34% of 1060 chemicals or groups record in the MAK list have a skin notation, but only for 12% different kinds of Biomonitoring values (BAT*, BAR*, BLW*) are available. In Switzerland this situation looks similar 38% of 795 substances having an OEL* or OELV* (MAK*) have a skin notation, but only 12% of them have an OBL*(BAT*). Looking at the international developments at WHO* and EU* the processes are too slow to generate a sufficient number of harmonised OELs* and corresponding OBLs* to generate a broad workplace safety. Currently, for by far less than 1% of work place relevant substances internationally harmonised OEL*, OELV* or OBL* are available. No international mid-term solution to cope with this challenge is in sight.

To close this international safety gap of lacking OELs* and OBLs*, national BM* and specifically OBL* derivation and implementation is needed to increase workplace safety at the national levels (by regulators, risk assessors and OHP*), followed by a transfer to international level and use. With this guidance we aimed at reflecting the current state of knowledge in occupational biomonitoring, with a focus on exposure biomonitoring, in order to support a harmonised approach for:

- Deriving health based human biomarker guidance or limit values, called Occupational Biomonitoring Level (OBL*)
- Using biomonitoring in exposure assessment and risk management.

Following the main aims this guidance tries to combine international knowledge and offers a harmonised approach for four generally accepted methods in OBL* derivation and their confidence assessments (see chapter 3.1.2 and 3.2.3). A confidence assessment will overcome quality discussions for implementing OBL on all levels, making their assessment transparent and defendable. This will facilitate the availability of refined or revised OBL* which can be used in risk assessments. Moreover, this transparency is also needed to allow distinguishing between the impact of health aspects and socio-economical and technical factors in defining the final regulatory binding OBL*. As part of the work offering a harmonised approach we provide a review of widely applied methodologies in OBL* derivation (see chapter 2) and information on general or occupational biomonitoring databases (see chapter 9.4 Annex D).

Moreover, we strengthen the option of deriving Provisional Occupational Biomonitoring Levels (POBLs*) for chemical substances with limited human toxicity data availability, which can be used for identifying

and managing possible occupational health risks (see chapter 3.3). An early risk identification via POBL* will also stimulate a refined OBL* derivation in parallel.

We offer ways to integrate and use effect biomarkers in parallel to exposure biomarkers, which are the only options available for addressing unknown mixture effects from chemical exposures (see chapter 3.5). This approach can even speed up risk identification for eight relevant MoAs* covering several thousands of chemicals workers may be exposed.

Furthermore, we provide practical guidance on using, evaluating and communicating BM* results in an ethical and regulatory context (see chapter 4). Using harmonised approaches in conducting and evaluating BM* campaigns will also facilitate the usability and interpretation of BM* data in an international context. This is an important step to bring BM* in future into a global registry framework (Zare Jeddi et al., 2021c), at least from an occupational perspective. HBM samples and results are precious both in surveillance practices as in research. Their use should be optimised in both fields. Data from routine collections in the frame of surveillance should be shared and re-used as much as possible in research, to facilitate further developments in the field. This requires a close collaboration between all parties involved, including regulators, representatives of workers and employers, and academia. Data protection and confidentiality of health related data is a major concern.

As BM* is at an interface between technology and health, involving technical, medical, and socio-legal aspects, BM* would benefit from a better outlined and stronger collaboration between occupational physicians, occupational hygienists and other OHP*s. Such collaboration should be rooted in defined frameworks that guarantee practices according to sound scientific, ethical and privacy rules and a good protection of the professional independency of each expert. As practices differ amongst regions and countries, such framework might be defined at international national and/or regional level.

Finally, within this guidance we provide a tiered approach and decision tree, which is based on data availability for the development of occupational biomonitoring levels and on their practical application in occupational health risk assessment and management (see chapter 5). This approach aims to facilitate an efficient derivation and use of different kinds of OBL* and leading to advice on how to improve work-place safety by reducing workers' exposures and ultimately, occupational diseases.

7.2. Main recommendations for national & international authorities

As mentioned previously BM* is important for protecting workers' health and for controlling exposures to hazardous chemicals, but is largely underused in the national and international context. Therefore, we recommend the more systematic use of BM* for hazardous substances which have significant dermal or oral uptake. This is especially important for all chemicals which have or should have a skin notation. For a skin notation the dermal absorption potency and the toxicity due to dermal absorption have to be taken into account individually in the assignment of a skin notation to a chemical substance (Drexler H, 1998).

Furthermore, we recommend to coordinate population biomonitoring studies with occupational biomonitoring studies by regulatory authorities in order to allow better comparison of occupational data with general population data, which will enable to assess different sources of chemical contaminations (e.g., exposures via food, etc. vs. occupational exposures). Despite the important differences between population BM* programmes and BM* programmes in occupational health (in terms of for instance aims, organisation, funding, possible consequences of the results) we recommend a closer collaboration between these two fields with respect to comparability of BM* data. This would contribute to better assessments of sources of chemical contamination (via food or via occupational exposure). This is also advisable to identify occupational exposures compared to general population exposures (e.g., for ROBL* derivation). This approach requires consistency between the data generated in these different contexts and stresses the need for further harmonisation efforts. Such harmonisation will also facilitate sharing of data and results within the research field and between the research field and surveillance practices. It also serves increased international knowledge transfer and sharing of work and will facilitate

the development of OBLs* for a large set of chemicals. Ultimately the aim is to decrease the gap between the huge number of chemicals having a skin notation and likely a dermal uptake, and the relatively small number of OBLs* available.

Therefore, we recommend to include and make practical use of the proposed methods of OBL* and POBL* derivations, to stimulate the availability of risk assessment options for BM*for a large set of hazardous and relevant chemicals on national and international levels and make them transparently available. The included confidence assessment (see chapter 3.2.3) of OBL* derivations will also allow to avoid redundant risk assessment work and to transfer work.

To be able to make use of this work, we recommend to bring the OBL* derivations, which can have different national abbreviations, in national or international databases (see chapter 9.4 Annex D), with refence to the date of derivation, the included key studies and their confidence assessments. This will allow to interpret BM* findings and to update them easily based on recent toxicological developments.

In order to address exposures of mixtures we also recommend to work on mixture thresholds (OBEL*) for relevant MoAs* and validated effect-biomarkers. This work is foreseen to be continued in OECD* WPHA*/WPEA* context (Zare Jeddi et al., 2021 ab) with a knowledge transfer to upcoming PARC* activity. Generally, we recommend a consideration of complementary use of exposure and effect biomonitoring to identify exposures leading to adverse effects.

With the provided tiered approach and decision tree we support (see chapter 5) a harmonised derivation & interpretation of different BM* assessment options, allowing evidence based RMM* options to increase workplace safety. Any improvement with BM* will be related to its practical and ethical use (see chapter 4.4), therefore we recommend to make use of this guidance. Finally, we recommend to revise and update national and international regulations to enable a better worker protection via BM*. Our recommendations with respect to wider use of BM* in occupational settings and its benefits are:

- Facilitate the further implementation of BM* in national OSH* regulations.
- Develop methods for increasing the cost-effectiveness of BM*, without compromising the health protection of workers.
- Consider data-sharing and re-use of BM* data (see Zare Jeddi et al., 2021c).
- Facilitate the interdisciplinary collaboration between OHPs* (more expertise will improve the efficiency and relevance of BM* campaigns).
- Give more attention to the communication of HBM results to the companies (employer & workers), national authorities, scientific communities and public.
- Assure by regulation that BM* is based on sound scientific and ethical guidelines and solely aimed at a better protection of workers health. This implies risk assessment and management approaches leading to improving the workplaces rather than excluding the more vulnerable workers. Give additional attention to protect vulnerable populations at work (see chapter 6.6) with adequate health and BM* assessments.
- Create a regulatory usable infrastructure allowing a better BM* data exchange between national and international authorities.

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9. Annexes

9.1. Annex A. Confidence assessment examples for refined OBL* and POBL* derivations based on selected case studies and datasets

Annex Table A.1. Examples for confidence assessments of case studies

CASE STUDY:	1st confidence category	2nd confidence category	3rd confidence category	Overall score
DEHP	*medium-high*	*medium-high*	*low-medium*	**Medium**
Most relevant references	Low-dose perinatal exposure to DEHP induces anti-androgenic effects in male rats. (Christiansen et al., 2010)	Several studies, reviews, show usability of biomarkers (BAT Value Documentation, 2018)	(Anderson et al., 2011)	
Comments	High: LoC for critical effect and MoA LoC for key study Critical effect (testicular developmental impairment) and MoA Evidence for anti-androgenic effects in humans Medium-High Animal toxicity study conducted according to OECD guideline 416 (Two-Generation Reproduction Toxicity Study) with small deviations	High: metabolites are known and the best biomarkers of DEHP. Specificity and sensitivity good. Daily variation due to short half-life; sampling time critical.	High: urinary excretion (F_{ue}) of MEHP at 24 and 48 h from data on n='10' men and 10 women. Based on steady state levels Medium-High only one single oral dose. No data on the kinetics after occupational exposure) F_{ue} from one volunteer (Koch et al. 2005)	

CASE STUDY:	1st confidence category	2nd confidence category	3rd confidence category	Overall score
HDI:	**15 µg/g crea in post-shift samples corresponding OEL of 0.035 mg/m³**			
confidence score	low (for sensitization no threshold can be given, current OELs* do not protect from sensitization)	medium	low-medium	**Low**
Most relevant references	(ACGIH, 2015) (MAK Commission (DFG, 2012) (ECHA, 2020)	(Maitre et al., 1996) Urinary hexane diamine as an indicator of occupational exposure to hexamethylenediisocyanate. Also other studies suggesting a similar correlation.	(Maitre et al., 1996). Urinary hexane diamine as an indicator of occupational exposure to hexamethylenediisocyanate.	
Comments	OELs* are based on irritation, however, no threshold for sensitization identified.	-background levels of HDA low in general population - HDA not specific marker for HDI	Good statistical basis and good correlation but only from one study and a limited number of subjects: (Maitre et al., 1996) investigated in 19 men from HDI* monomer production. HDI* in the air during the 8-hour shift and HDA* in the urine after the shift. The HDI air levels ranged from 0.30 to 97.7 g/m3 (median: 4.4 g/m3; mean: 14.3 ± 26 g/m3). HDA in urine was found between 1.36 and 27.7 g/g creatinine (median: 6.6 g/m³; mean: 8.52 ± 7.46 g/g creatinine). There was a linear correlation between HDI in air and HDA in urine (r = 0.6981, p = 0.001).	
ALUMINIUM (Al, Al oxide and hydroxide)	**OBL* of 50 ug/g creatinine based on human data**			
confidence score	High	High	Medium-High	**High**
Most relevant references	pool of occupational studies (exposed vs non exposed), see e.g. German BAT documentation on aluminium (Klotz et	see e.g. (Klotz et al., 2021 or Aitio and Riihimäki, 2011)	see e.g. (Klotz et al., 2021 or Aitio and Riihimäki, 2011)	

CASE STUDY:	1st confidence category	2nd confidence category	3rd confidence category	Overall score
	al., 2021),			
Comments	- Based on a direct relationship between effect (on human/workers) and biomarker level - criteria for selection of relevant study defined and detailed (size, effect, consistency)	- biomonitoring of U-Al well established - more sensitive than Al in blood - Due to long half-life in long term exposure, U-Al is not so sensitive to daily variation	Human data on the toxicokinetics after occupational exposure available. In long term repeated exposure results in accumulation and long half-life. However, absorption depends on several factors (e.g.solubility, particule size, nature…).	
CHROMIUM VI:	**OBL of 2.5 ug/L corresponding a cancer risk of 4:1000**			
confidence score	Low-Medium	Medium	Low-Medium	**Medium**
Most relevant references	(ANSES, 2017) (SCOEL, 2017)	e.g. (SCOEL, 2017)	(Lindberg and Vesterberg 1983) (Chen et al., 2002)	
Comments	Dose-response for the lung carcinogenicity have been derived based on human epidemiological data -According to current knowledge there is no threshold for the carcinogenicity, thus, the value is not fully protective ad can be calculated to correspond a cancer risk of 4:1000	-U-Cr well established biomarker for Cr(VI) -However, U-Cr not specific for Cr(VI) -long term Cr lung burden may contribute to the U-Cr levels together with the recent exposure -sensitivity at low exposure levels poor, better at higher levels	-gives correlation between air Cr(VI) levels and U-Cr levels -there are however variations between different studies in air-urine correlations -correlations at the current, rather low exposure levels uncertain since the data is derived from higher exposure levels	
CHROMIUM VI:	**POBL of 0.76 ug/L based on animal data**			
confidence score	Low	Medium	Low	**Low**
Most relevant references	(Derelanko et al., 1999)	e.g. (SCOEL, 2017)	French Biotox database	
Comments	Gives NOAEC of 0.01 mg Cr/m^3 for non-cancer lung effects in 13 week animal study.	-U-Cr well established biomarker for Cr(VI) -However, U-Cr not specific for Cr(VI) -long term Cr lung burden may contribute to	F_{UE} of 0.8 given for Cr. This is based on steady state level and does not take into account specific toxicokinetics after occupational exposure:	

CASE STUDY:	1st confidence category	2nd confidence category	3rd confidence category	Overall score
	Carcinogenicity not taken into account.	the U-Cr levels together with the recent exposure -sensitivity at low exposure levels poor, better at higher levels	https://www.inrs.fr/publications/bdd/biotox/dosage.html?refINRS=Dosage_23Chrome et chromates (7440-47-3) / Chrome urinaire - Biotox - INRS	

9.2. Annex B. Effect-biomonitoring

Annex Table B.1. Potential suitable effect biomarkers characterized for occupational use or already applied in other contexts. Grey marked effect-biomarkers were not characterized

No	Covered MoA or endpoint	Name of the assay or effect biomarker	Biomarker categorization	Measured endpoint
1a	C including genotox	DIN EN ISO 21427 is for the application of the Micronuclei (MN) assay in water quality assessment. The MN assay is better referred to OECD 487. Dividing cells are needed to apply the MN assay	*in vitro*	induction rate of micronuclei
1b	C including genotox	buccal micronucleus approach	*ex vivo*	induction rate of micronuclei in buccal cells micronuclei frequencies epithelial buccal cells
1c	C including genotox	cytokinesis-block micronucleus assay (CBMN-Assay) (similar to OECD 487)	*in vitro or ex vivo*	induction rate of micronuclei in mammalian cells
1d	C including genotox	peripheral blood lymphocyte micronucleus test (OECD 474) and buccal mucosa micronucleus test	*ex vivo*	micronuclei frequencies in lymphocytes and epithelial buccal cells
1e	Oxidative stress level indicative for C and genotox	reduced/oxidized glutathione (GSH/GSSG) ratio	*in vitro or ex vivo*	increase or decrease of the GSH/GSSG ratio
2a	M	Ames Test/Bacterial Reverse Mutation Test	*in vitro*	measuring reverse mutation in bacterial cells
3a	R	reproductive Hormones - female hormones	*ex vivo*	measuring estradiol levels in serum
3b	R	reproductive Hormones – male hormones	*ex vivo*	measuring testosterone or 2-DHT levels in serum
4a	ED- ER receptor activation	ER CALUX	*in vitro*	measuring the receptor activation of the human estrogen receptor

No	Covered MoA or endpoint	Name of the assay or effect biomarker	Biomarker categorization	Measured endpoint
4b 4c	ED- AR receptor activation ED- TR receptor activation	AR CALUX TR CALUX, anti-TR CALUX, TTR-TR CALUX, TTR-FITC assay, TPO assay	*in vitro* *in vitro*	measuring the receptor activation of the human androgen receptor measuring the receptor activation of the human thyroid receptor
4d	ED-steroidogenesis modulation	H295-R-steroidogenesis modulation assay	*in vitro*	measuring steroidgenesis modulation
5a	inhibition of acetyl-choline-esterase	acetylcholine-esterase-inhibition assay	biochemical/biological	measuring inhibition of acetyl-choline- esterase
5b and 6b	Brain Derived Neurotrophic Factor (BDNF) (indicative of neuronal survival, development and synaptic plasticity)	BDNF Assay	biochemical/biological	peripheral BDNF levels in blood cells (gene expression and protein) are used as potential biomarker for psychiatric disorders, Parkinson (PD) and Alzheimer's disease (AD).
5c	neuroaxonal damage/ scaffolding proteins, neurofilament light-chain (NF-L) in serum	neuroaxonal damage/ scaffolding proteins (small parameter selection)	biochemical/biological	Neurofilament-light chain (NF-L) in serum
5d	neuroaxonal damage/ scaffolding proteins (Glial fibrillary acidic protein (GFAP), neurofilament light (NFL), medium and heavy chains (NFH), S 100 beta (a Ca2+-binding protein and is expressed primarily by astrocytes)	neuroaxonal damage/ scaffolding proteins (enlarged parmeter selection)	biochemical/biological	neurofilament light chain (NfL), neurofilament medium chain (NfM), neurofilament heavy chain (NfH), a-internexin and peripherin in serum/ blood
6a	Thyroid stimulating hormone (TSH), free triiodothyronine (T3) and thyroxine (T4) and anti-thyroperoxidase (TPO) antibodies in serum for addressing developmental neurotoxicity	TSH assay	biochemical/biological	levels in serum during pregnancy
6b and 5b	Brain Derived Neurotrophic Factor (BDNF) (indicative of neuronal survival, development and synaptic plasticity)	BDNF Assay	biochemical/biological	peripheral BDNF levels in blood cells (gene expression and protein) are used as potential biomarker for psychiatric disorders, Parkinson (PD) and Alzheimer's disease (AD).
7a	The murine embryonic stem cell test	Sarcomeric myosin heavy chain and	*in vitro*	Quantitative expression of sarcomeric myosin heavy

No	Covered MoA or endpoint	Name of the assay or effect biomarker	Biomarker categorization	Measured endpoint
	(EST) – to assessembryo-toxicity (teratogenicity) potential of chemicals*	alpha-actinin proteins		chain and alpha-actinin proteins in beating cardiomyocyte's as well as counting of contracting cardiomyocyte agglomerates. The morphological analysis of beating cardiomyocytes in embryoid body outgrowths compared to cytotoxic effects on murine ES cells and differentiated 3T3 fibroblasts.
7b	Male-mediated developmental toxicity and mutagenicity*	dominant lethal and specific locus mutation tests: *in vivo*; DNA methylation: *in vitro*	Different biomarkers in battery	Battery of tests to identify germ cell mutations, such as dominant lethal and specific locus mutation tests, epigenetics (DNA methylation e.g. acrylamide, lead)
8a	Methemoglobin respiratory toxicity	Methemoglobin binding assay	*ex vivo* / biochemical	measurement of building of methemoglobin which is functional inactive

*Were not characterized further due to expected sensitivity coverage under DNT.

Annex Table B.2. Scoring method for effect-biomarker characterisation questions & answers.

Question No	Answer Options	Score
Questions for assessing relevance and invasiveness (score 0-16)		
1) Has the biomarker been assessed in easy accessible human biological matrices?	Non-invasive: urine (5 points) saliva (4 points) buccal or nasal cells (3 points) Invasive: blood (2 points) other (1 point) None (0 points)	0-5
2) Is there a plausible MoA?	Yes - please report your MoA in the comment field (3 points) No (0 points)	0-3
3) Is an Adverse Outcome Pathway AOP reported for this effect-biomarker?	Yes - please report it in the comment field, add the link (3 points) No (0 points)	0-3
4) Is the biomarker able to detect relevant (adverse and severe) effects in workers during a long-term exposure?	High - please provide proof of evidence via DOI or ref. in the comment field (5 points) Medium (3 points) Low (1 point) No adversity expected (0 points)	0-5
Questions for assessing applicability (score 0-16)		
5) Has the effect biomarker been applied in occupational or epidemiological studies and resulted in meaningful results for a workplace or chemical exposure?	Yes - please report it, provide the DOI in the comment field (5 points) Can be applied in a modified form (3 points) No (0 points)	0-5
6) Has the biomarker been applied in environmental risk assessment or other studies with regulatory relevance (e.g. drinking water, food regulation)?	Yes - please report it, provide the DOI (3 points) No (0 points)	0-3
7) How would you define workload and applicability for occupational settings?	High - minimal work load and training necessary (5 points) Medium - moderate work load and training necessary (3 points) Low - high work load and expert judgement necessary (0 points) Certified commercial labs offer this bioanalysis (3 points)	0-8
Questions for assessing validation and cost (score 0-16)		

Question No	Answer Options	Score
8) Does the biomarker have a well-described standard operating procedure (SOP)?	Yes - publically available in a peer reviewed journal. Please provide DOI in the comment field (4 points) Partially - as internal or non peer reviewed SOP (2 points) No (0 points)	0-4
9) Does an OECD guideline or a standardized DIN EN ISO exist for the effect-biomarker?	Yes - OECD guideline. Please provide links in the comment field (3 points) Yes - standardized DIN EN ISO. Please provide links in the comment field (3 points) No (0 points)	0-6
10) What is the cost per sample?	Very low - <100 EURO/sample (6 points) Low - 100-250 EURO/sample (4 points) Medium - 250-400 EURO/sample (2 points) High - 400-750 EURO/sample (1 points) Very high - >750 EURO/sample (0 points)	0-6
Questions for assessing sensitivity & specificity & robustness (score 0-12)		
11) Is the Limit Of Quantification (LOQ) below an accepted occupational exposure limit for a relevant reference substance?	Yes - please provide reference or DOI and LOQ in the comment field (4 points) Partially (2 points) No or unknown (0 points)	0-4
13) **Is the specificity* of the biomarker sufficient for the substances or effects of concern?**	Yes - please provide reference or DOI and LOQ in the comment field (4 points) Partially (2 points) No or unknown (0 points)	0-4
13+14) What are geometric mean concentrations and geometric standard deviations of the biomarker in the general population? Is the effect-biomarker sufficiently robust to compare different levels of exposure risks (e.g. does it have age dependent variations, body mass index or smoking dependency)?	Yes - please provide reference or DOI and LOQ in the comment field (4 points) Partially (2 points) No or unknown (0 points)	0-4

* specificity means the method is less prone to detect false positive results , e.g. specificty of 95% means only in 5 % of cases the biomarker detects false positive results. Weak point: We have currently no agreement which level of specificity is sufficient. It can be 90% or lower or higher. Preliminary we can work with 80% specificity as preliminary treshold.

Annex Table B.3. Similar Exposure Groups (SEG) or as Working Contributing Scenario (WCS) approach template adapted to effect-biomarker reporting

RAC Template adapted V1.1_SV.xls

9.3. Annex C. Biomonitoring in practice

9.3.1. Occupational Health Professionals (OHP)*

The International Commission on Occupational Health (ICOH) has developed an International Code of Ethics for Occupational Health Professionals (OHP):
For the purpose of this Code, «occupational health professionals» includes all those who, in a professional capacity, carry out occupational safety and health tasks, provide occupational health services or are involved in an occupational health practice. A wide range of disciplines are concerned with occupational health since it is at an interface between technology and health involving technical, medical, social and legal aspects. Occupational health professionals include occupational health physicians and nurses, factory inspectors, occupational hygienists and occupational psychologists, specialists involved in ergonomics, in rehabilitation therapy, in accident prevention and in the improvement of the working environment as well as in occupational health and safety research. The trend is to mobilise the competence of these occupational health professionals within the framework of a multidisciplinary team approach. More info at:
http://www.icohweb.org/site/multimedia/code_of_ethics/code-of-ethics-en.pdf

9.3.2. Pseudonymization and Anonymization

Results as such or in conjunction with other data can reveal information on specific (health) characteristics of an individual worker. This aspect should be carefully addressed when BM results are shared within and outside the OSH system.
To protect such sensitive data, the records could be modified in a way that the BM results can no longer be assigned to identifiable individuals. Whilst common data protection rules promote processing data in anonymized form (all personal identifiers, direct[1] and indirect[2], are removed), this technique may devalue the data, so that it is no longer useful for some purposes. Therefore, pseudonymization is often preferred above anonymization.

Pseudonymization

One way to prevent the assignment of BM results to specific persons is replace or remove information in the data set that identifies an individual. Such pseudonymization may involve replacing names or other identifiers which are easily attributed to individuals with, for example, a reference number. Whilst this number can be tied back to the individual, technical and organizational measures are in place to ensure that this additional information is held separately. Keeping the possibility for re-identification (under strict rules) might be relevant for exposure control, intervention and back reporting.
However, third parties who receive pseudonymized data can - in particular cases - assign the data records to individual persons even without access to the link between the identifiers (the key). For example, carrying out BM* on only a few persons facilitates assigning results to one person, especially if additional information is available.

Anonymization

The term anonymization is used when personal data are rendered anonymous in such a manner that the data subject is no longer identifiable. The link with the identifiers is deleted. Also anonymized data may present the above-mentioned risk for re-identification.

[1] An individual may be *directly identified* from their name, address, postcode, telephone number, photograph or image, or some other unique personal characteristic.

[2] An individual may be *indirectly identifiable* when certain information is linked together with other sources of information, including, their place of work, job title, salary, their postcode or even the fact that they have a particular diagnosis or condition

Anonymization by aggregation of results

For evaluation of and communication on the exposure assessment and for the decision on RMMs, it is useful to statistically aggregate BM results of several participants. This is done by estimating parameters of the statistical distribution of the measured values, e.g. a mean value or the 90th percentile. The aggregation also makes the data anonymous as a side effect. The disadvantage of this approach is that information is lost with every data aggregation. If the distribution is described in much detail, e.g. with confidence intervals or ranges, and if the third party has further information, this procedure does not completely exclude the possibility that the third party can assign approximate BM results to individual persons.

9.3.3. Specific regulations on data protection

EU GDPR

The General Data Protection Regulation 2016/679 (EU GDPR) for example, implemented in 2018, is a regulation in EU law on data protection and privacy in the European Union and the European Economic Areas. It extensively describes rights and duties of all parties concerned when processing personal data. Important principles are lawfulness, fairness and transparency, purpose limitation, data minimization, accuracy, storage limitation, and integrity and confidentiality. Though it was drafted and passed by the European Union (EU), it imposes obligations onto organizations anywhere, so long as they target or collect data related to people in the EU.
http://data.europa.eu/eli/reg/2016/679/2016-05-04 http://data.europa.eu/eli/reg/2016/679/2016-05-04

9.4. Annex D. Information on existing biomonitoring databases

9.4.1. Biomonitoring guidance databases

- Biomonitoring Guidance Value Database and Comparison Tool (predominantly HBM guidance values for general population): https://intlexposurescience.org/i-hbm/
- Further developments to this database are expected under IHBM guidance value initiative: https://intlexposurescience.org/i-hbm-working-group

9.4.2. Access to derived occupational biomonitoring guidance/assessment values

More biomonitoring guidance/assessment values can be found at deriving organisations/activities:

- SCOEL/RAC: https://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684 / and on https://echa.europa.eu/fi/oels-activity-list
- MAK-Commission: https://series.publisso.de/pgseries/overview/mak
- ACGIH: https://www.acgih.org/protecting-workers/
- ANSES: https://www.anses.fr/en/content/biological-limit-values-chemicals-used-workplace
- HBM4EU: https://www.hbm4eu.euhttps://www.hbm4eu.eu and https://www.hbm4eu.eu/deliverables/
- Finnish list of concentrations of impurities in workplace air known to be harmful (HTP values) and a list of corresponding indicative limit values for biological exposure indicators: http://urn.fi/URN:ISBN:978-952-00-5658-2

An overview about assessment schemes is provided in chapter 2.

9.4.3. HBM databases/publications for occupational exposure

- Biotox database: https://www.inrs.fr/publications/bdd/biotox.html
- BAuA-Biomonitoring information system: https://www.baua.de/DE/Themen/Arbeitsgestaltung-im-Betrieb/Gefahrstoffe/Biomonitoring/Biomonitoring-Auskunftssystem/Biomonitoring-Auskunftssystem_node.html
- HBM4EU: Occupational exposure: https://www.hbm4eu.eu/occupational-exposure/
  -chromium (VI): https://www.hbm4eu.eu/wp-content/uploads/2018/12/Brief_Exposure_CRVI_EN.pdf
- UK: Biological monitoring in the workplace: https://www.hse.gov.uk/pubns/books/hsg167.htm
- National Institute for Occupational Safety and Health (NIOSH) - https://www.cdc.gov/niosh/programs.html
  -an industrywide biomonitoring evaluation of Bisphenol A (BPA) among manufacturing workers: https://doi.org/10.1093/annweh/wxw021

Finland occupational biomonitoring: https://www.ttl.fi/en/service/biomonitoring/

- Work-life knowledge service: https://www.tyoelamatieto.fi/en/themes/occupational_safety
- Background documentation of the FIOH action limit values for biomarkers (in Finnish): https://www.ttl.fi/teemat/tyoturvallisuus/altistuminen-tyoympariston-haittatekijoille/kemiallisten-tekijoiden-hallinta-tyopaikalla/kemiallisten-altisteiden-raja-arvot
- Finnish industrial hygiene and biomonitoring measurements, statistics from years 2009-2019 and 2012-2019, respectively: https://www.julkari.fi/handle/10024/143799

HBM databases/publications for the general population

Arctic:

- Arctic monitoring and assessment programme (AMAP): https://www.amap.no/about/the-amap-programme
    - Technical reports (including mercury, POPs reports): https://www.amap.no/publications?keywords=&type=10&page=2
- International Polar Year Inuit Health Survey (IPY-IHS) (2007–2008): https://www.tunngavik.com/files/2012/06/IHS_Report_Nunavut-English-Final.pdf

Australia:

- The Australian Environmental Specimen Bank: https://qaehs.centre.uq.edu.au/australian-environmental-specimen-bank

Belgium:

- Belgium (Flanders): The Flemish Environment and Health Study (FLEHS): https://www.milieu-en-gezondheid.be/en/research-program/flehs-iv-2016-2020

Brazil:

- Human Biomonitoring of Chemical Substances in Brazil (a national program under development)

Canada:

- The Canadian Health Measures Survey (CHMS) (representative samples from Canadian general population): https://www.canada.ca/en/health-canada/services/environmental-workplace-health/environmental-contaminants/human-biomonitoring-environmental-chemicals/canadian-health-measures-survey
    - CHMS biobank analysis of certain metals, metalloids and rare earth elements: https://doi.org/10.1016/j.jtemb.2021.126830
- Maternal-Infant Research on Environmental Chemicals (MIREC) Study: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/environmental-contaminants/human-biomonitoring-environmental-chemicals/maternal-infant-research-environmental-chemicals-mirec-study.html
- Northern Contaminants Program: https://science.gc.ca/eic/site/063.nsf/eng/h_7A463DBA.html
- Alberta Provincial Government biomonitoring data (pregnant women and children): https://open.alberta.ca/opendata/alberta

Czech Republic:

- Human Biomonitoring Project (CZ-HBM): DOI: 10.1016/j.ijheh.2011.09.007

EU:

- HBM4EU: HBM4EU is a joint effort of 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. The initiative is coordinating and advancing human biomonitoring in Europe: https://www.hbm4eu.eu/about-hbm4eu/

- HBM4EU Project: PARC Project: The role of human biomonitoring in assessing and managing chemical risk in the Nordic countries.: https://pub.norden.org/temanord2021-528/
- IPCHEM: the Information Platform for Chemical Monitoring: https://ipchem.jrc.ec.europa.eu/

France:

- The French National Survey on Nutrition and Health (ENNS): This survey describe the patterns of food consumption, not an HBM survey.: http://ghdx.healthdata.org/record/france-national-nutrition-and-health-survey-2006-2007
- The study of the French Public Health Agency (Santé Publique France) (ESTEBAN) : Health Study on Environment, Biomonitoring, Physical Activity and Nutrition : https://www.santepubliquefrance.fr/etudes-et-enquetes/esteban

Germany:

- German Environmental Survey (GerES): https://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/german-environmental-survey-geres

Israel:

- Israeli National Biomonitoring Program: https://www.ehf.org.il/en/national_biomonitoring_program

Italy:

- Program for Biomonitoring the Italian Population Exposure (PROBE): A journal publication in 2017: https://www.sciencedirect.com/science/article/pii/S0013935117315736?via%3Dihub

Japan:

- National Institute of Environmental Studies, Japan: https://www.nies.go.jp/kanko/kenkyu/index-e.html
- Biomonitoring of mercury, cadmium, and lead exposure in Japanese children: https://doi.org/10.1007/s12199-014-0416-4

New Zealand:

- Biological Monitoring Study of Selected Chemicals of Concern: http://publichealth.massey.ac.nz/home/research/research-projects/biological-monitoring-study-of-selected-chemicals-of-concern/

Norway:

- Norwegian mother, father and child cohort Study (MoBa): https://www.fhi.no/en/studies/moba/

Russian Federation:

- Arctic biological monitoring laboratory: https://narfu.ru/biomonitoring/en/
- North-West public research center: https://s-znc.ru/en/

South Korea:

- Korea National Survey for Environmental Health Survey (KoNEHS) Cycle 3: https://doi.org/10.3390/ijerph19020626

Spain:

- BIOAMBIENT.ES. The study protocol published in 2013 is available online: https://pubmed.ncbi.nlm.nih.gov/23184128/
- Also, journal articles on blood/serum levels of lead, cadmium, PCB, organochlorinated pesticides and urinary levels of PAH metabolites are available online from the Bioambient.es project.

Switzerland:

- Human biomonitoring projects in Switzerland: https://www.bag.admin.ch/bag/en/home/gesund-leben/umwelt-und-gesundheit/chemikalien/chemikalien-im-alltag/human-biomonitoring/human-biomonitoring-projekte-in-der-schweiz.html

Taiwan:

- Taiwan environment survey for toxicant (Phthalate publication): https://doi.org/10.1016/j.ijheh.2021.113769

UK:

- UK biomonitoring network: https://www.hsl.gov.uk/online-ordering/analytical-services-and-assays/biological-monitoring/uk-biomonitoring-network

UN:

- Global mercury monitoring: https://www.unep.org/explore-topics/chemicals-waste/what-we-do/mercury/global-mercury-monitoring
- Global persistent organic pollutants (POPs): https://www.unep.org/explore-topics/chemicals-waste/what-we-do/persistent-organic-pollutants-pops

USA:

- National Health and Nutrition Examination Survey (NHANES): https://www.cdc.gov/nchs/nhanes/index.htmhttps://www.cdc.gov/nchs/nhanes/index.htm

This occupational biomonitoring guidance document was elaborated in a joint activity including more than 40 institutes/ organisations in collaboration with the OECD Working Party on Exposure Assessment and the OECD*Working Party on Hazard Assessment. The goal was dual. First, the guidance document presents current approaches used to derive biomonitoring values; and second, it provides globally harmonized recommendations on how-to derive and apply occupational biomonitoring assessment values. The derived health-based human biomarker assessment values are referred to as Occupational Biomonitoring Levels (OBL*s). OBLs* are suitable for the use in exposure assessment and screening a level of health-risk and finally, workplace risk management. Moreover, we strengthen the option of deriving Provisional Occupational Biomonitoring Levels (POBLs*) for chemical substances with limited human toxicity data availability, which can be used for identifying and managing possible occupational health-risks.

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