Toxicology Letters 403 (2025) 132–143

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.journals.elsevier.com/toxicology-letters

Introducing the OECD guidance document on occupational biomonitoring: A harmonized methodology for deriving occupational biomonitoring levels (OBL)

Nancy B. Hopf[a,1], Jos Bessems[b], Tiina Santonen[c], Susana Viegas[d,2], Ludwine Casteleyn[e], Devika Poddalgoda[f,3], Farida Lamkarkach[g], Thomas Göen[h], Maryam Zare Jeddi[i,4], Michael Koller[j], Christophe Rousselle[g], Kate Jones[k], Kaspar Schmid[l], Rex FitzGerald[m,5], Michael Bader[n], Koki Takaki[o], Patience Browne[p], Virpi Väänänen[q], Radu Corneliu Duca[e,r,*], Robert Pasanen-Kase[l,**]

[a] Center for Primary Care and Public Health (Unisanté), University of Lausanne, Route de la Corniche 2, 1011 Epalinges, Lausanne Switzerland
[b] VITO Nv, Boeretang 200, Mol 2400, Belgium
[c] Finnish Institute of Occupational Health, Helsinki, Finland
[d] ENSP/UNL, NOVA National School of Public Health, Public Health Research Centre, Comprehensive Health Research Center, CHRC, NOVA University Lisbon, Portugal
[e] Katholieke Universiteit, Leuven, Belgium
[f] Health Canada, Existing Substances Risk Assessment Bureau, Healthy, Environment and Consumer Safety Branch, Health Canada, Government of Canada, Canada
[g] French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Maisons Alfort 94701, France
[h] University of Erlangen, Friedrich-Alexander University (FAU) Erlangen-Nuremberg, Schillerstrasse 25, Erlangen 91054, Germany
[i] Shell Global Solution international, BV., Netherlands
[j] SUVA, Fluhmattstrasse 1, Luzern 6002, Switzerland
[k] Health and Safety Executive, Harpur Hill, Buxton SK17 9JN, UK
[l] State Secretariat for Economic Affairs (SECO), Section Chemicals and Occupational Health, Holzikofenweg 36, Bern 3003, Switzerland
[m] Universities of Basel and Geneva, Switzerland
[n] BASF SE, ESG/CB - Medical Center Z130, Carl-Bosch-Str. 38, Ludwigshafen am Rhein 67056, Germany
[o] Ministry of the Environment, Japan
[p] OECD, rue André Pascal 2, Paris 75775, France
[q] ECHA, European Chemicals Agency, Telakkakatu 6, P.O. Box 400, Helsinki FI-00121, Finland
[r] Environmental Hygiene and Human Biological Monitoring, Department of Health Protection, Laboratoire National de Santé (LNS), 1, Rue Louis Rech, Dudelange L-3555, Luxembourg

ARTICLE INFO

Keywords:
Occuaptional exposure assessment
Occupational biomonitoring levels
Human
Biomonitoring

ABSTRACT

Derivation of occupational biomonitoring levels (OBLs) is needed to effectively utilize biomonitoring for assessing exposures to chemical substances, and consequently, implement risk reduction measures to reduce health risks among workers. OBLs are the appropriate option for chemical substances that can be absorbed through the skin. This methodology for derivation of OBLs has been developed in collaboration with scientific

* Corresponding author at: Katholieke Universiteit, Leuven, Belgium.
** Corresponding author.
E-mail addresses: Nancy.Hopf@unisante.ch (N.B. Hopf), jos.bessems@vito.be (J. Bessems), Tiina.Santonen@ttl.fi (T. Santonen), susana.viegas@ensp.unl.pt (S. Viegas), ludwine.casteleyn@icloud.com (L. Casteleyn), devika.poddalgoda@hc-sc.gc.ca (D. Poddalgoda), farida.lamkarkach@gmail.com (F. Lamkarkach), thomas.goeen@fau.de (T. Göen), Maryam.ZareJeddi@shell.com (M. Zare Jeddi), michael.koller@suva.ch (M. Koller), christophe.rousselle@anses.fr (C. Rousselle), Kate.Jones@hse.gov.uk (K. Jones), Kaspar.Schmid@seco.admin.ch (K. Schmid), rex.fitzgerald@unibas.ch (R. FitzGerald), michael.bader@basf.com (M. Bader), Koki_takaki@env.go.jp (K. Takaki), Patience.BROWNE@oecd.org (P. Browne), virpi.vaananen@echa.europa.eu (V. Väänänen), Radu.DUCA@lns.etat.lu (R.C. Duca), robert.pasanen-kase@seco.admin.ch (R. Pasanen-Kase).
[1] ORCID 0000–0002-4490–6109
[2] ORCID 0000–0003-1015–8760
[3] ORCID 0009–0007-1106–9168
[4] ORCID: 0000–0002-9505–812X
[5] ORCID 0000–0002-3028–2980

https://doi.org/10.1016/j.toxlet.2024.12.006
Received 4 August 2024; Received in revised form 6 December 2024; Accepted 10 December 2024
Available online 15 December 2024

Harmonized methodology
OECD

and regulatory experts from more than 40 institutes in 15 countries within the Organization for Economic Cooperation and Development (OECD) framework. This manuscript provides a summary of the guidance on derivation of OBLs destined for scientists, risk assessors, and regulators who are tasked with establishing OBLs for regulatory purposes and implementing occupational biomonitoring programs. The derivation methodology follows a tiered approach based on the strength of evidence and quality of the data that we have labeled level of confidence. The tiered approach serves as a practical framework in occupational health risk assessment and management. We distinguish between four OBL levels depending on the strength of scientific evidence and confidence level: health-based derivation of OBL based on robust epidemiological data showing causal exposure-health effect relationship and Provisional OBL (POBL) based on robust toxicological animal data showing dose-response relationship as well as two assessment values which are not health based: reference levels in the general population (Reference OBL or (ROBL)), and Technical achievable OBL or (TOBL). Four case studies illustrating the derivation methods for OBLs and POBLs are also provided. Using this state-of-the-art approach (OECD guidance document no. 370) will lead to a harmonized derivation of OBLs and subsequently to evidence-based risk management measures.

1. Introduction

Occupational exposure limits (OELs) are effective in controlling inhalation exposures to chemical substances, and consequently, implement Risk Reduction Measures (RRM). Quantifying measurements of chemical exposures that enter the human body via several exposure routes, e.g., inhalation and skin, using biomonitoring are often missing. A harmonized approach in deriving such biomonitoring values can lead to improved worker health. A collaboration among scientific and regulatory experts from more than 40 institutes in 15 countries within the Organization for Economic Cooperation and Development (OECD) framework set out to develop a harmonized method for deriving occupational biomonitoring levels (OBLs). "OBL" was introduced as a generic umbrella terminology to cope with the variety of terminologies and avoid confusion with national biomonitoring limit values that are associated with specific derivation methods. This collaboration resulted in an OECD Occupational biomonitoring guidance document that is open access and online (https://www.oecd.org/content/dam/oecd/en/publications/reports/2022/11/occupational-biomonitoring-guidance-document_53c29118/11bc2c7a-en.pdf). It is relevant for the occupational health field and was developed for Occupational Health and Hygiene Professionals (OHP), regulatory authorities, chemical industries, researchers as well as stakeholders interested in occupational and general population biomonitoring (Hopf et al., 2024). This manuscript summarizes the OBL derivation part of the guidance and provides an overview of the harmonized approach for risk assessors, scientists, and regulators tasked with establishing OBLs.

Commonly used OBL derivation methods are given in Table 1 and were the starting point for this guidance document, to achieve best possible harmonization of applied methods. The most relevant approach for worker in setting an OBL begins with exposure-response curves obtained from sound epidemiological data thus, establishing a causal relationship between an exposure biomarker and a specific health effect or disease. These kind of studies are only available for a limited number of chemical substances. Before such epidemiological studies are produced, exposure reduction strategies are needed to prevent occupational diseases from new chemicals that are introduced on the commercial market as well as well-known chemicals that are deemed hazardous to health based on newer studies. Forward dosimetry is one such method where the OBL is the concentration of an exposure biomarker in a biological media equivalent to the existing Occupational Exposure Limit (OEL) (e.g., TLV®, MAK,). Forward dosimetry is also used in deriving human biomonitoring guidance values for the general population (e.g., Total Daily Intake (TDI), Acceptable Daily Intake (ADI), and Reference Doses (RfD)). These forward dosimetry methods are calculated in many ways (Table 2) and used with a combination of approaches (Apel et al., 2020). Forward dosimetry of OELs cannot be used to derive OBLs for semi-volatile or non-volatile hazardous chemicals that cross the skin barrier leading to internal exposures because OELs are only derived for inhalation exposures. Derivation of OBLs for chemicals associated with systemic effects from skin exposure are often lacking because few derivation methods exist. OBLs can be derived using dosimetry principles and risk assessment methods similar to deriving OELs in the absence of epidemiological data. Accurate dose estimation is essential for dose-response assessments derived from animal toxicological data and several methods exist (point of departure, derived no effect levels, benchmark doses and interspecies extrapolation). These OBLs would still be health based but the strength of evidence comes from animal data. We have named these values Provisional Occupational Biomonitoring Levels (POBL), but they can become also refined OBL in case of a good quality and evidence in the derivation process. In cases where we know that the human populations are exposed (human biomonitoring data from large populations e.g., NHANES, (Terry et al., 2024)) but no epidemiological and animal studies exist, OBLs are needed because workers tend to encounter exposure to higher doses and over longer time periods compared to the general population increasing their risk of significant health effects. These known exposure levels can be used to set Reference Occupational Biomonitoring Levels (ROBL) and used to interpret occupational exposures in contrast to general population exposures. Workers at the production site might be exposed to novel chemicals and an OBL is useful to understand possible internal exposures, but these OBLs are not health-based, nor population based but rather what is technically feasible (e.g., known exposure biomarker, chemical analytical methods exist). We refer to these values as Technical Occupational Biomonitoring Levels (TOBL). Fig. 1 shows the increasing strength of evidence and quality of scientific data needed to develop OBLs, POBLs, ROBLs, and TOBLs.

The adoption of a harmonized approach for deriving OBLs can enhance the overall occupational risk management and well-being of workers. A harmonized methodology will likely increase the number of OBLs, which is needed as chemicals are continuously being authorized for commercial use. The harmonized OBL derivation approach also outlines procedures for handling chemicals with limited toxicological and exposure data is known (POBL, ROBL, and TOBL). Part of the harmonization process was to use terminologies that can straddle several scientific disciplines such as epidemiology e.g., health-based OBLs are established on exposure-disease relationships, toxicology e.g., health-based POBLs are based on dose-response curves derived in toxicological studies, exposure science e.g., ROBLs are human exposure studies, and engineering e.g., TOBLs are technical feasibility assessments. The differences between OBL, POBL, ROBL, and TOBL are presented in Table 4 and discussed in subsequent paragraphs.

2. Derivation of OBLs

The harmonized OBL derivation was based on four methods:

1. causal associations between biomarker and health effects.
2. established correlations between air (OELs) and biomarker levels.

3. physiologically based pharmacokinetic (PBK) modelling to obtain biomarker values from external exposure levels.
4. urinary mass balance approach to calculate corresponding biomarker levels for point of departures (PODs) (e.g., using the No Observed Adverse Effect Levels (NOAELs) and applying assessment factors to account for the uncertainties). A POD refers to the specific dose of a substance at which an initial measurable biological effect is observed in the toxicological dose-response curve established from experimental or observational data. The POD serves as the starting point for calculating exposure limits.

Irrespective of the method used, the first step in OBL derivation is the selection of an appropriate exposure biomarker. Fig. 2 gives an overview of the criteria for selecting the exposure biomarker as well as examples of these criteria. A recent publication is also available for this topic (Weistenhöfer et al., 2023). All OBL derivation methods inherently possess certain uncertainties and bias. It is imperative to acknowledge these and rate the confidence of the derived OBL. We used the vague terminology "level of confidence" to distance this process from different national processes that define their methods for weight of evidence and review processes. It should provide possible harmonization steps for the derivation. For instance, the most robust OBL derivation method; "Correlated exposure-effect biomonitoring" will yield health-based biomonitoring values based on sound scientific data that provide a causal relationship between the biomarker concentrations and measurable health effects. This approach may still have some uncertainties in the data (i.e., confounding factors related to the data, biases, consistency across studies, and biological plausibility), which need a confidence evaluation. Furthermore, this OBL derivation method requires a considerable amount of quality data to significantly associate the biomonitoring data (exposure) to the effect (Table 3).

The recommended health based OBL derivation methods were evaluated based on two criteria: the confidence assessments for both hazard and data requirements as well as the exposure-health effect response from epidemiological data and dose-response from the toxicological data. Confidence assessments considered pre-established criteria regarding hazard prioritization and dose-response relationship, biomarker selection, and toxicokinetics regarding the nature and quality of the data, the choice of the critical effect and the mode of action, key studies used, critical dose and POD, and the need for extrapolations across and within species. The quality of the scientific evidence should be systematically presented making their assessment transparent and defendable. Not only does the confidence assessment increase the transparency in the derivation of the harmonized OBL process but it also distinguishes the scientific evidence from the socioeconomical, and technical factors used in defining regulatory binding OBLs.

OBL derivation methods 1 and 2 described in Table 3 have traditionally been used in occupational health for setting OBLs for substances with a rich database on health effects and toxicokinetics. These are based on measured data with mostly human toxicological relevance. Sometimes only old scientific data exist, and these may not cover exposure ranges relevant of today. In such instances, the confidence assessment is reduced. Physiologically Based Kinetic (PBK) modeling can be used to support measured data for establishing correlations between air to urine biomarker concentrations in OBL derivation method 2. PBK models should include all relevant exposure pathways. One example is for 2-methoxy ethanol where the OBL was derived using a one compartment toxicokinetic model assuming not dependent linear kinetics to estimate urinary excretion after occupational exposure (SCOEL, 2006). For methods 2 and 3, existing OELs can be used as a starting point in deriving OBLs. The OBLs need to be revised in accordance with the OEL revisions as well as new toxicological knowledge. OBL derivation method 4 is used when only a minimum amount of toxicokinetic and health-related data are available. This derivation method often results in a POBL. Data sets with high or at least medium to high confidence in the overall confidence assessment might give a more robust estimate, and thus, is the preferred option for an OBL derivation.

Main uncertainties related to the derivation of OBLs with method 1 (Table 3) are the robustness of the scientific evidence for the epidemiological data and the three underlying categories: hazard prioritization and exposure-response assessment, appropriate biomarker selection, and toxicokinetic aspect considerations as well as the studies' potential sources of bias and confounding variables. Epidemiological studies need to show a causal inference for the chosen biomarker and the identified health effect. Furthermore, the application of the Bradford Hill criteria (Fedak et al., 2015) should incorporate data from molecular biology, toxicology including animal or other mechanistic studies, and other disciplines when assessing biological plausibility. Recent advancements in scientific tools and techniques that have been developed in recent decades across various scientific disciplines provide valuable support for the interpretation of epidemiologic studies and related data.

OBLs derived indirectly with method 2 (Table 3) have uncertainties

Table 1
Brief characterization for widely used derivation methods for Occupational Biomonitoring Level (OBL).

Derivation method	SCOEL / RAC (Europe)	MAK (Germany)	ACGIH (USA)	ANSES (France)	HBM4EU (Europe)
Values[a] substances with a threshold effect	BLV, BGV - Relationship between health effects and biomonitoring levels - Correlation between air values and biomonitoring levels	BAT, BLW, BAR, EKA 2 options - Relationship between health effects and biomonitoring levels – Correlation between air values and BME levels	BEI 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.	BLV, pragmatic BLV, BRV 2 options - Relationship between health effects and biomonitoring levels - Correlation between air value and biomonitoring[a] levels *Mass balance approach can be investigated* and PBK modelling used as support	HBM-GVworkers 3 options - Relationship between health effects and biomonitoring[a] levels - Correlation between air value and biomonitoring levels - based on a POD - experimental study on animals. *Tools used: Mass balance approach or PBK modelling widely used*
substances without a threshold effect	No BLV derived, only BGV.	Yes, BAR and EKA	Yes, if other health effects occur.	Excess risk and if not possible recommendation of a pragmatic value and/or BRV (2 options above)	No
substances with limited data	No BLV derived.	Yes, BLW	If negative feasibility assessment, then no BEI[a]	Recommendation of a BRV if no data? No value	Where lack of data? Low level of confidence attributed if no data? No value

[a] Abbreviations: BAR Biological Reference values, Biologische Arbeitsstoff Referenzwerte), BAT (Biological tolerance values in blood and urine, Biologische Arbeitsstoff-Toleranzwerte), BGV (Biological Guidance Value), BLV (Biological limit value), BLW (Biological guidance value, Biologische Leitwerte), HBM-$GV_{workers}$ (Human Biomonitoring Guidance Values), EKA (Exposure equivalents for carcinogenic agents, Expositionsäquivalente für krebserzeugende Arbeitsstoffe)

associated with the existing OELs such as 1) the underlying toxicological and epidemiological data used to derive the dose-response curve from external exposures, and 2) the correlations between external and internal exposures. The most significant uncertainties are often related to assessing human relevance of available animal data and extrapolating from identified No Observed Adverse Effect Levels (NOAELs), Lowest Observed Adverse Effect Levels (LOAELs), and Benchmark doses (BMDs). Assessment factors (which are often only “default” factors, not based on real data for the level of the uncertainty) are used but they do not remove the underlying uncertainty related to human relevance. The reliability of the established correlations needs to be assessed for 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 4) coherence between studies when several studies for the same substance are available. Correlations obtained from controlled volunteer studies may be more reliable compared to the correlations obtained from the workplace with their inherent confounding factors, e.g., combined chemical exposures, multiple sources of chemical exposure (aggregate exposures), and multiple exposure routes (skin, inhalation, ingestion for different work rates).

OBLs derived using PBK models (method 3 Table 3) have uncertainties associated with the kinetic data used for the PBK model development. In general, the kinetic data obtained from controlled human studies have higher reliability than kinetic data obtained from animal studies.

The most significant uncertainty associated with the OBL derived using mass balance approach (method 4 Table 3) comes from the reliability of the urine excretion fraction and the assumption having a steady state balance reached after 24 or 48 h. In addition, both method 3 and 4 have underlying uncertainties associated with the OEL value or the POD selected for the OBL derivation.

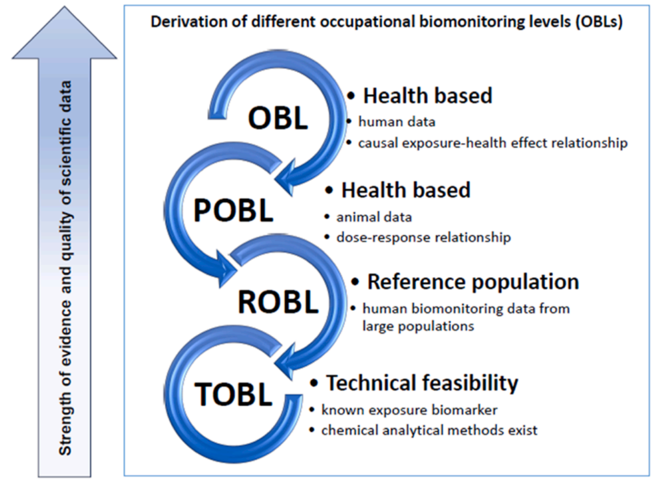

Fig. 1. The strength of evidence and the quality of the scientific data determines the feasibility of deriving: Occupational Biomonitoring Level (OBL), Provisional Occupational Biomonitoring Level (POBL), Reference Occupational Biomonitoring Level (ROBL), and Technical Occupational Biomonitoring Level (TOBL) depends on.

Data confidence need requirements were assessed using an ordinal scale consisting of three levels: high, medium, and low confidence. Generally, a refined OBL can be proposed when the average confidence

Table 2
General prioritization and review process for existing Occupational Biomonitoring Level (OBL) derivation schemes.

Steps	SCOEL / RAC (Europe)	MAK (Germany)	ACGIH (USA)	ANSES (France)	HBM4EU (Europe)
Working program	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 prepare 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 biomonitoring Expert Committee on Reference Values	Elaboration of a document by UBA/ ANSES *ANSES* : the working group on* biomonitoring *is contributing*
Validation process	SCOEL: (1) Document send to consultation to national experts ((2) Comments considered, and responses sent to commenting experts. RAC: (1) Public consultation of the ECHA scientific report. (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 considered in a final version) (3) Adoption of the conclusions	(1) Document send to consultation to national experts and experts from European agencies (2) Comments considered and responses sent to contributing experts
Diffusion and endorsement process	1. SCOEL recommendation published in EC website. RAC opinion/ECHA scientific report published in 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 socioeconomic and feasibility factors are considered. Note that although SCOEL/RAC has recommended > 20 BLVs, only blood lead has been included in legislation as a binding BLV.	Annual publication of the HBM assessment values in the “List of MAK and BAT values” (issue and delivery to the German Ministry 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	Annual publication of the TLV-BEI booklet by ACGIH.	1 – Publication of ANSES opinion 2- Social 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).	Sending to the EU Commission and Publication in peer reviewed journals and on the HBM4EU website

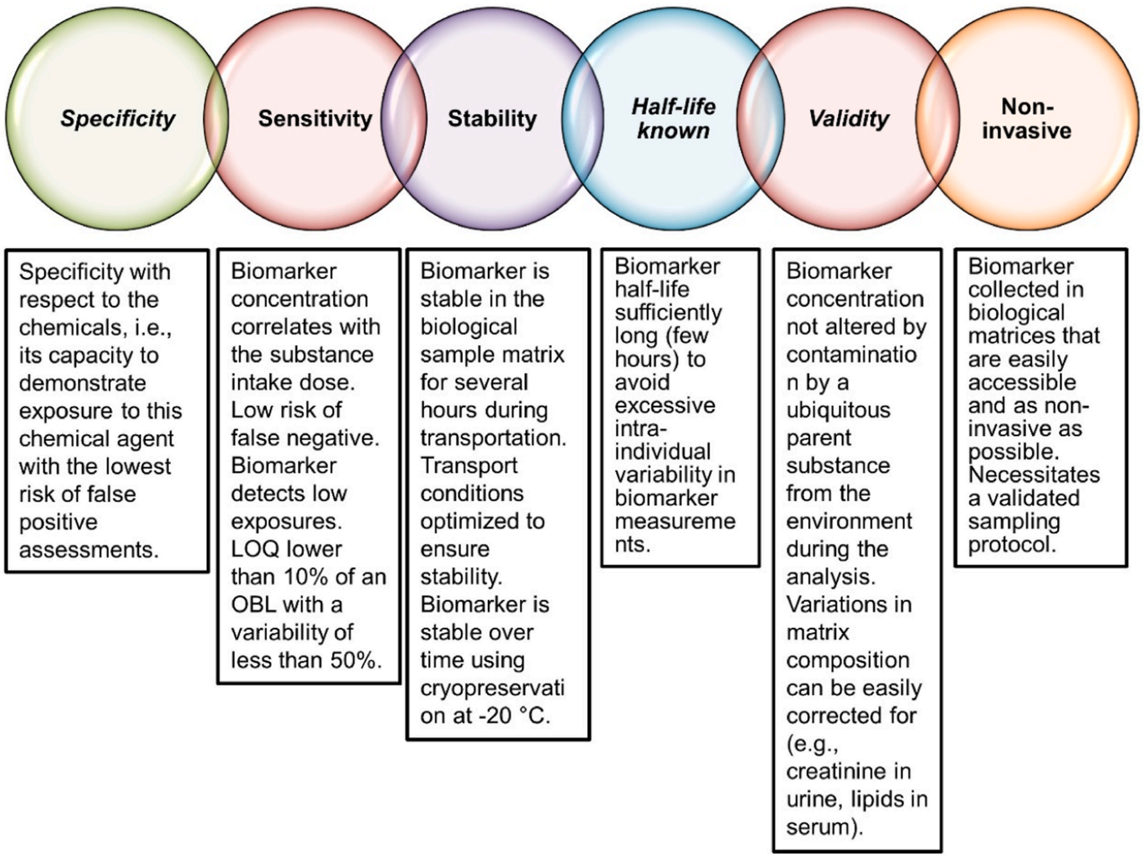

Fig. 2. Criteria for selection of biomarkers.

score is equal or better than medium. In the cases with less confidence or without confidence assessments, POBLs should be derived. Three main confidence assessments should be scored during the OBL derivations for appropriate risk management. The first confidence assessment is the **hazard prioritization and exposure-response assessment** and the selection of the POD. The second is the **selection of the biomarker** including specificity and sensitivity of the biomarker as well as analytical aspects (e.g., confounding exposure sources, contamination). The third confidence assessment is the **toxicokinetic aspects** including quality and robustness of the toxicokinetic data, established correlations between external and internal concentrations and between toxicological effects and biomarker levels, and urinary fraction data.

For practical purposes, the three confidence assessments are qualitatively scored and then an arbitrary numerical value assigned to each score: 1 =low, 1.5 =low-medium, 2 = medium, 2.5 =medium-high, 3 = high. These ordinal values for the qualitative confidence scoring were assigned to establish a numerical value, a cut-point for which the scientific evidence supported the derivation of a health-based OBL, or the lack of evidence pushing it down to the derivation of a POBL. Generally, an OBL can be proposed if the average confidence score is equal or better than 2. If there are significant data or quality gaps meaning that two out of three scores are “low”, the OBL will be described as a POBL. However, when one score is low and others medium or high, the value can be justified and declared as an OBL instead of a POBL.

3. Derivation of POBL

Generally, POBLs are the default outcome of a refined OBL derivation that failed to meet medium or high confidence assessments. POBLs can be derived based on data with a valid NOAEL, LOAEL, or BMD by incorporating urinary mass balances. The urinary mass balance approach can be used for deriving a POBL with limited human toxicological datasets. For example, in Europe, the Regulation (EC 1907/2006) concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) requires manufacturers or importers of chemicals of quantities exceeding ten tons per year to establish a Derived No Effect Level (DNEL) for oral intake (DNELoral). DNELs are the concentration for a substance that does not adversely affect human health and is derived according to criteria set out in the regulations (see: (ECHA Guidance, 2012; Boogaard et al., 2011)). The established DNEL is multiplied by the urinary steady-state concentration factor for the biomarker measured after 24 h or 48 h exposure, the so-called urinary excretion factor (FUE) (Eq. 1). If the biomarker is a metabolite, then the F_{UE} needs to be multiplied with the ratio of the molecular weights (MW) to the parent compound. This product is then divided by the urine volume (u) (0.02 L/kg bodyweight/24 h) (Aylward et al., 2015). Note that the F_{UE} has not been harmonized and several values appear in the literature. For a given chemical, several F_{UE} values can be found in the literature. Expert judgement should be used when selecting the most appropriate value based on study quality or an average value based on several high-quality studies (e.g., human controlled dosing studies). If several F_{UE} studies with similar qualities appear also the lowest F_{UE} can be also taken to derive the most conservative POBL.

$$POBL = \frac{DNEL_{oral} x F_{UE} x \mathrm{MW}}{\mu} \quad (1)$$

The relevance of a POD needs to be evaluated before using it in the derivation of a POBL because they are usually based on a POD derived from animal data and extrapolated to workers. Relevance depends on the purpose of the assessment or regulatory framework for which it is evaluated. This assessment is always expert judgement driven and includes five typical questions (Fig. 3).

PODs rated relevant without restrictions or relevant with limited

Table 3
Recommended methods for refined Occupational Biomonitoring Level (OBL) derivation with associated rankings of uncertainties, data needs, and preference.

	Derivation method	Uncertainties	Data need
1	*Correlated exposure-effect biomonitoring*		
	• health-based biomonitoring values directly based on the relationship between biomarker and health effects.	In epidemiological data, i.e., confounding factors related to the data, biases, consistency across studies, and biological plausibility	high
2	*Correlated OEL and biomarker level*		
	• biomonitoring values using measured data and correlations between external exposure levels and biomarker levels. The OBL is usually set to correspond to health based OELs.	• underlying data used to derive dose-responses from external exposures. High uncertainties related to the toxicological database, the greater the assessment factors. • correlation data between external and internal concentration.	medium-high
3	*Simulated PBK levels*		
	• the PBK needs to cover all relevant exposure pathways (inhalation, skin uptake, and ingestion) and should predict urinary biomarker excretion concentrations as well as central compartment (blood) concentrations. • The PBK models should as far as possible incorporate human parameters and be adjusted or calibrated with human data.	In PBK models incorporate parameters from animal and/or human studies, adjustments, and calibration with human data.	medium-high
4	Health based mass balance approach		
	• urinary mass balance approach to calculate biomarker levels corresponding to existing OELs or to health PODs. • application of AFs to account for the uncertainties.	PODs relevance and reliability. Urinary fraction data. Confidence assessment	low-medium

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

restrictions can be used for POBL derivation. Furthermore, the identified studies, selected for the POD, are then categorized according to their corresponding NOAELs or LOAELs with the lowest value labeled as "precautionary", the next highest "balanced", and the highest "relaxed". We recommend incorporating all potentially reliable studies leading to adverse effects. This approach can minimize expert judgement discussions, and the risk of missing available evidence in a crucial primary risk identification step. The primary purpose of the POBL is the identification of possible toxicological risks. In some instances, however, the POBL can lead to an overestimation compared to a refined OBL. Therefore, after identifying the toxicological risks, the potential for derivation of an OBL should be considered.

4. Derivation of ROBL

The ROBL is a strictly statistically defined value and not linked to any adverse health effect. It relates to the internal exposure of a substance of interest present in a reference population of working age who are not occupationally or otherwise specifically exposed to the substance. A ROBL is established on background levels quantified in large-scale general populations in biomonitoring studies. Data from national surveys can be considered appropriate because of their high participation rate. The purpose of comparing collected occupational biomonitoring data to a ROBL is to understand the fraction of the internal exposure that most likely occurred at work. For example, some substances are not detected in the general population and consequently, the exposure observed in the workers are attributed to occupational exposures.

Biomarker concentrations measured in the general population do not show a normal but a distinct left-skewed distribution (Solberg, 1983). The ROBL is usually set at the 95th percentile of the distribution function (P95) of a larger population to accommodate possible background levels (Angerer et al., 2011; Commission., 1996; Göen et al., 2012; Holst & Christensen, 1992; Vogel et al., 2019). General population exposures can be influenced by many factors, such as age, sex, social status, residential environment, nutrition, lifestyle, including leisure activities and geographical region (Göen et al., 2012; Schulz et al., 2011). These factors may influence an individual at different time-points in life. ROBL might therefore need to be developed for specific populations (e.g., age groups for accumulating biomarkers, smoking status, and others) reflecting different Absorption, Distribution, Metabolism, and Excretion (ADME) and geographical region due to environmental contamination. Reference values describe exposures at a distinct time in the general population, consequently, reevaluations are required because exposures are dynamic.

5. Derivation of TOBL

The TOBL is based on the ALARA principle ('As Low As Reasonably Achievable') and can thus not be used for health risk assessment purposes. A TOBL should be derived for hazardous substances for which there is insufficient scientific knowledge regarding health effects. The TOBL should be viewed as a biomonitoring level in workers where state-of-the-art exposure controls have been implemented to limit any associated exposures to known hazardous chemicals. A generally accepted TOBL may vary between countries and even industrial sectors.

The TOBL is derived using all available data and relies on expert judgements followed by discussions with stakeholders and ultimately, an agreement between the parties concerned. The last step in a TOBL derivations is the evaluation from trade associations and in particular, health and safety officers, concerned workers and authorities, and independent experts, e.g., engineers of production facilities and protection devices as well as occupational hygienists. Evaluations of the TOBL should as for the other OBLs be continuously assessed on new scientific evidence, but in addition for TOBLs, technical advances need to be evaluated.

6. Tiered approach in derivation of OBLs

The main type of OBL derivation as well as POBL, ROBL, and TOBL are given in Table 4 and Fig. 1. The tiered approaches consider both types of OBLs; health based (OBL and POBL) and non-health-based (ROBL and TOBL). The aim should always be to establish and use the highest tier: OBL > POBL > ROBL > TOBL. The overall tiered approach includes a decision tree aimed to help Occupational Health and Hygiene Professionals (OHPs) to control and manage workplace exposures using occupational biomonitoring and provide a framework for using and interpreting occupational biomonitoring data. Fig. 4 is a flow chart describing the steps for developing either of the four OBLs and starts with dividing the data into threshold and non-threshold substances.

Depending on the situation and available data, these can be exposure data, occupational biomonitoring data, technical data regarding external exposure or animal toxicity/epidemiological data dose-response data. The decision tree is a series of questions and yes/no answers (Fig. 4):

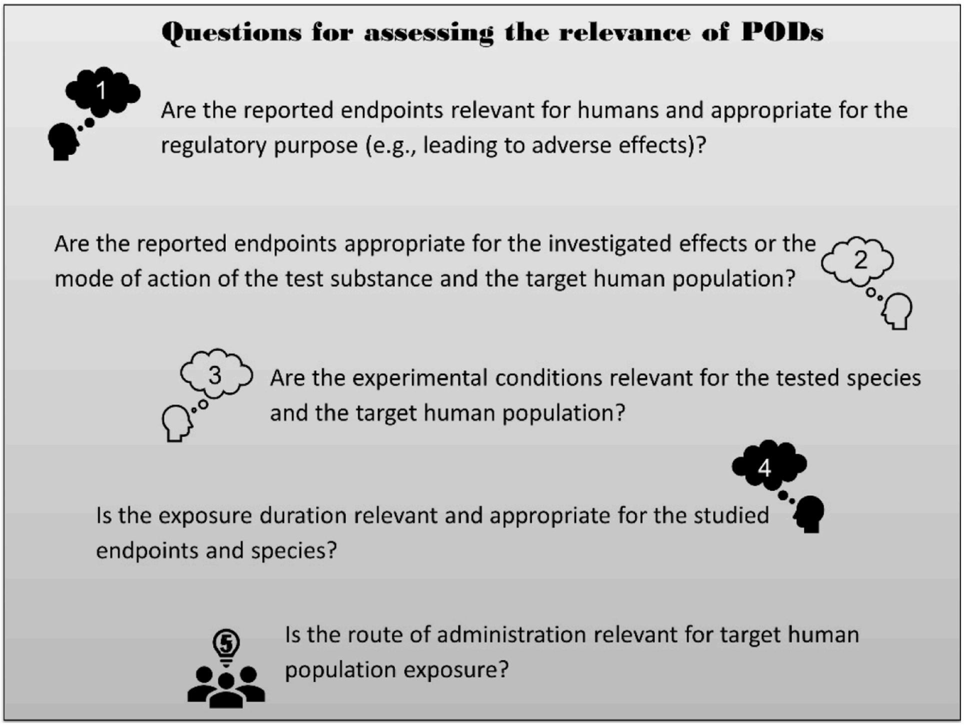

Fig. 3. Typical questions to answer when assessing the Point of Departures (PODs) for deriving Provisional Occupational Biomonitoring Level (OBL) ((P)OBLs).

- Question 1: Are there strength of scientific evidence from high quality data available to establish a causal relationship between a specific exposure biomarker and health effect and a relevant threshold mode of action (MoA)? If the answer is **yes** and **yes,** then the decision is to go immediately to Tier 4 to establish an OBL (Category 1 A OBL). If the answer is **yes** and **no**, then the following question is: Are there high-quality health data available and is non-threshold mode of action (MoA) relevant so a risk based OBL can be derived? If the answer to this is **yes** and **yes**, then the decision is to go to Tier 4 to establish a 1 C OBL. If the answer is **no** and **no**, then answer the next question.
- Question 2: Is there an external OEL available as well as toxicokinetic information of high quality? If the answer is **yes**, then go to Tier 4 to establish a 1B OBL. If the answer is **no**, then answer the next question. For non-threshold MoA risk based OBLs analogue to OBL without threshold can be derived (see 1D OBL).
- Question 3: Are there high quality and relevant data available to establish a POBL? If the answer is **yes**, then go to Tier 3 to establish a POBL. If the answer is **no**, then answer the next question.
- Question 4: Are there high quality and relevant large population biomonitoring data available to establish a ROBL for the general population? If the answer is **yes**, then go to Tier 2 to establish a ROBL. If the answer is **no**, then answer the next question.
- Question 5: Are there technical and occupational biomonitoring data available to establish a TOBL? If the answer is **yes**, then go to Tier 1 to establish a TOBL. If the answer is **no**, then assess if this is a non-threshold chemical substance. If **yes**, then find out if there is an OBL or POBL available for a threshold mechanism. If **yes**, then use that OBL as a pragmatic value for the time being. If **no**, then new data need to be generated to establish a TOBL, a ROBL, or, a POBL or an OBL.

7. OBLs in risk management

The tiered approach depends on the strength of scientific evidence and the confidence rating given by experts used for the OBL derivation. The type of adverse effects, the confidence in the effect, and the relevance of the effects are prone to expert judgement biases. This OECD occupational biomonitoring guidance tries to harmonize the OBL derivation process and with a tiered approach help guide the OHPs in interpreting biomonitoring results. The practical use of the tiered approach in occupational risk assessments will be influenced by several factors other than the strength of evidence and quality of the data, such as the frequency of exceedances, the number of workers with exceedance, and the access to individual worker data. Also, national, or international political and regulatory windows of opportunity might lead to derivations or revisions of OBLs. New developments, new (inter)national consensus, e.g., on threshold versus non-threshold effects or the relevance of gender-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. These risk management approaches based on the exceedances of various levels of OBLs are interpreted in Table 5.

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. We recommend making use of this harmonization progress to improve and give comparable protection levels to workers across countries and companies.

8. An illustration using case studies for OBL derivation and for POBL derivation

The OECD occupational biomonitoring guidance includes four case studies: di-2-ethyl hexyl phthalate (DEHP), hexamethylene diisocyanato (HDI), aluminum, and chromium, elaborated for OBL derivation and for POBL derivation on the human. Furthermore, information using effect biomarkers for monitoring exposures to complex chemical mixtures are presented in supplementary material.

Four case studies were selected to illustrate the process in deriving OBLs: (1) aluminum, (2) chromium (VI), (3) 1,6-hexamethylene diisocyanate (HDI), and (4) di(2-ethylhexyl) phthalate (DEHP). The derivation process is dynamic and will change depending on available scientific data. Therefore, we have completed the case study exercise by

Table 4
Main- and subcategories of different Occupational Biomonitoring Level (OBL) and their derivation types.

Category	Type	Tier	Sub-category	Scientific basis
OBL	Health based on epidemiological evidence	IV	1 A	Causal relationships between biomarker concentration and health effect.
			1B	Available OEL or OELV (e.g., DNEL, TLV) and a (TK-based) relationship between air and biomarker concentration
			1 C	Non-threshold effect data (e.g., genotoxic carcinogenicity) and risk numbers (e.g., biomarker level corresponding to 10^{-6}, 10^{-5}, 10^{-4} risk of cancer)
			1D	Option if OBL Cat 1 C 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} risk of cancer can be used instead.
POBL	Health based on toxicological evidence	III	2	POBL; if no Cat 1 OBL available; often based on animal NOAEL. POBL can also result from OBL with low confidence assessments and follow the same A-D subcategories as for OBL (2 A, 2B, 2 C, 2D).
ROBL	Reference population	II	3	Statistically based reference Level (e.g., P95) in the general population.
TOBL	Technical feasibility	I	4	Technically derived where chemical exposure is limited as low as reasonably achievable.

presenting the same four case studies but this time omitting the human toxicity data to derive POBLs (Table 3). The urinary excretion factors were kept constant (FU_E for DEHP 0.4, HDI 0.21, Aluminum: 0.00145 for partially or less soluble Al substances and 0.0074 for soluble Al substances, and Chromium 0.8) as well as the volume (u set equal to 20 mL/kg bw/d) to be able to compare the results in terms of toxicity reference values (TRV).

8.1. Case study 1 – Aluminum

Inhaled aluminum e.g., welding fume during welding processes, may be retained in the lungs before gradually being released into the bloodstream and accumulate in the bones (Hadrup et al., 2024). Consequently, aluminum has a long half-life (>20 years), which has also been predicted for aluminum accumulated in the brain. The main target organs for aluminum in humans are the central nervous system and lungs (e.g., lung fibrosis (aluminosis) in occupationally exposed workers).

Occupational epidemiological evidence suggested an association between urine or serum (U/S) aluminum concentrations and effects on the central nervous system. This correlated exposure-effect (method 1 in Table 2) was used in deriving an OBL for urinary aluminum (U-Al) (3 nmol/L or 2.3 μmol/g creatinine or 62 μg/g creatinine) (Riihimäki & Aitio, 2012). An OBL for U-Al was also derived using correlated OEL (total dust concentration 1.5 mg/m^3) and biomarker levels (method 2 in Table 2). This corresponded to 60 μg/g creatinine (Klotz et al., 2021) and later revised to 50 μg/g creatinine based on new evidence showing a direct correlation between the occurrence of subclinical neurotoxic effects in aluminum exposed workers and their U-Al concentrations (method 1 in Table 2). Here, cognitive effect sizes of subclinical neurotoxic effects from nine epidemiological studies were combined and associated with the medians of U-Al concentrations (Klotz and Weistenhöfer, 2019). The urine collection for long-term exposures was set at the end of the shift after several shifts. The derived OBL gave U-Al concentrations of 50–62 μg/g creatinine.

Assuming we do not have scientific evidence for workers, then we would derive a POBL based on relevant animal studies (see Fig. 3). A precautionary POBL derivation using a chronic NOAEL for inhalation exposure to Al_2O_3 in rats of 2.5 mg/m^3 gave a $DNEL_{oral}$ of 0.19 mg/kg/d resulting in a POBL of 1.38 μg/L. The POD was relevant. A balanced POBL derivation with a sub-chronic LOAEC for local effects such as lipid pneumonitis, granulomatous inflammation, and collagenous scars in rats of 50 mg/m^3 gave a $DNEL_{oral}$ of 0.127 mg/kg/d resulting in a POBL of 9.2 μg/L. The POD was partially relevant because it included local effects. Sensitivity was assessed as the ratio between the POBL (1.38–9.2 μg/L) and OBL (57 μg/L) and was for aluminum between 6 and 41. Please note: Al HBM-GV for worker is also in the workplan of PARC.

8.2. Case study 2 – Chromium (VI)

Hexavalent chromium is a genotoxic carcinogen, consequently, no concentration limits can be set to protect against carcinogenic effects. However, a linear approach has been used to assess cancer risks associated with specific Cr(VI) air concentrations found in occupational settings. For example, occupational exposures to Cr(VI) air concentrations of 1 μg/m^3 (8-hour time weighted average (TWA) over 40 years resulted in an excess cancer risk of 4/1000 exposed workers and increasing the air concentration to 5 μg/m^3 gave an excess cancer risk estimate of 20/1000 (SCOEL, 2017). Generally, the range of substance in air and urine concentrations covered by the measured data, the number of data points, and the strength of the correlation should all be considered when assessing the reliability of established correlations. When several studies for the same substance exist, then coherence across studies should also be considered. It should be noted that general population background levels (95th percentiles) for urinary chromium (U-Cr) generally vary between 0.5 and 0.8 μg/L in different populations. Note that OBLs are continuously revised with the accrued scientific knowledge and available research. For example, a revision of the biomonitoring assessment value for Cr VI (OBL) is foreseen in the Partnership for the Assessment of Risks from Chemicals (PARC) in Europe and ongoing.

Biomonitoring of Cr(VI) has traditionally used urinary chromium (U-Cr). Although, this is an unspecific exposure biomarker influenced by exposures to trivalent chromium, it is still a valid biomarker for occupational Cr(VI) because its strong correlation with air Cr(VI) levels (Santonen et al., 2022). An OBL of 2.5 μg/L (1.8 μg/g creatinine) for U-Cr has been proposed and was based on the OEL of 1 μg/m^3 and established correlations between Cr(VI) air and U-Cr levels in workers exposed to soluble Cr(VI) compounds (method 2 in Table 2) (ANSES, 2017). This OBL is restricted to chrome plating activities because the correlation data comes from that sector and established correlations might not sufficiently reflect the situation in other industries. The urine collection time was set to end of the shift and end of the week. Cr(VI) correlations equations (method 2 in Table 2) considering data from work tasks with plating baths were used (Chen et al., 2002; Lindberg & Vesterberg, 1983). In the case of Cr(VI), air and urine correlations were described from several workplaces and took into account possible Cr(VI) intake via the skin route or hands-to-mouth. The OBL for U-Cr will need to be revised as new exposure regression analyses are available (Viegas et al., 2022). Currently in PARC there is also an activity updating the

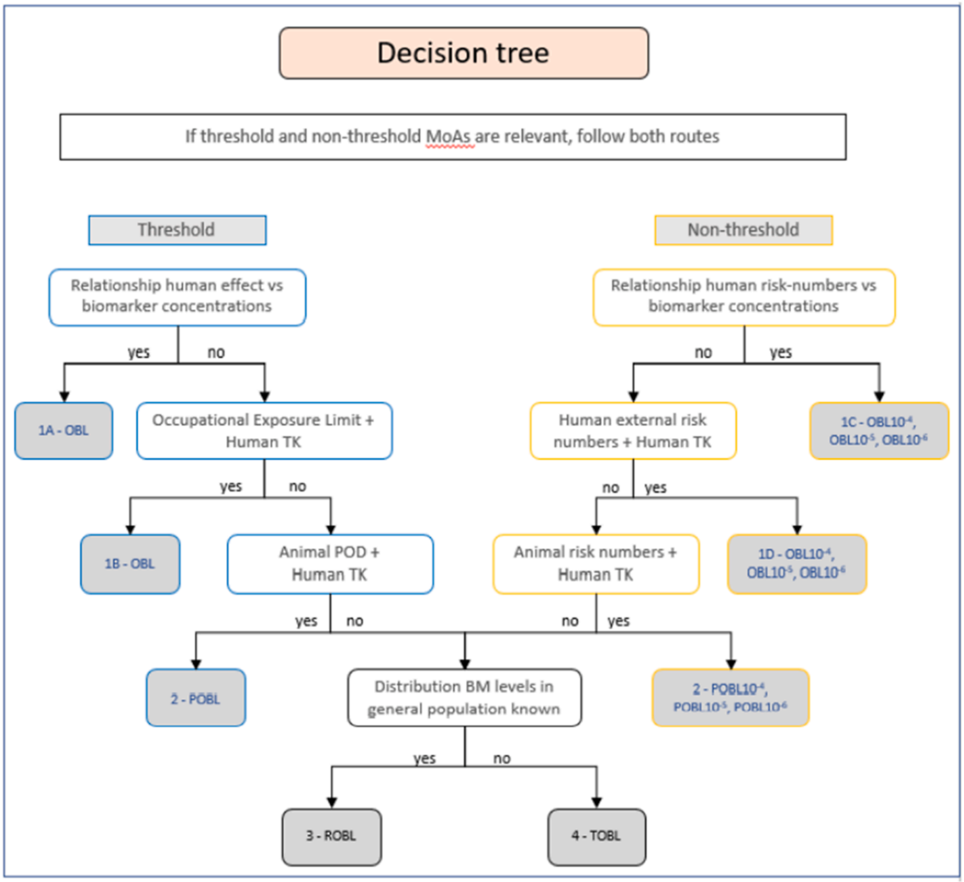

Fig. 4. Decision tree for derivation of Occupational Biomonitoring Level (OBL).

previous biomonitoring assessment values for workers related to their increased lung cancer risk of 4/1000 workers of 40-year exposure. This is leading to OBL values in the range of 1.2–1.8 μg Cr (VI) /g creatinine, which are under discussion. The finalization is expected for 2024.

Again, omitting the human studies, we derived three POBLs. Precautionary POBL derivation with a $DNEL_{oral}$ of 0.019 μg/kg/d based on a LOAEL of 2.5 mg/m^3 after inhalation exposure for nasal irritation, mucosal atrophy, impaired lung function in 104 workers. This resulted in a POBL of 0.76 μg/L. The POD was partially relevant for lung function. A balanced POBL derivation with a NOAEL of 0.01 mg/m^3 after inhalation exposure for increased lung weights in rats after 13 weeks gave a $DNEL_{oral}$ of 0.38 μg/kg/d resulting in a POBL of 15.2 μg/L. The POD was partially relevant for lung function. A relaxed POBL derivation with a LOAEL of 4.3 mg/m^3 after inhalation exposure for epithelial necroses after 18 months in rats gave a $DNEL_{oral}$ of 10.98 μg/kg/d resulting in a POBL of 439 μg/L. The POD was not relevant. Sensitivity of different POBL and OBL approaches was assessed as the ratio between the POBL (0.76 μg/L) and OBL (2.5–10 μg/L) and was for chromium between 3 and 13.

8.3. *Case study 3 – HDI*

Respiratory sensitization is the critical effect of HDI exposures. There are no data on the relationship between adverse effects and the corresponding urinary diamine (U-HDA) biomarker, which is a metabolite of HDI (method 1 Table 2). There is no respiratory sensitization threshold, therefore it should be noted that the existing OBLs for HDI were derived for irritation effects and do not fully account for respiratory sensitization (TLV and MAK, see (Leng, 2017). Developments in how to handle this type of health endpoint is currently being discussed for diisocyanates and a dose-response between air concentrations of the "NCO (functional isocyanate group) group" and the occurrence of asthma has recently been proposed (ECHA, 2020). The excess risk approach used for carcinogen can also be used for respiratory sensitization.

There is some information on the association between of HDI air and U-HDA concentrations in occupationally exposed workers. An OBL was derived using correlation equations (method 2 Table 2) with OELs of 0.034 (TLV) and 0.035 (MAK) mg/m^3 giving the corresponding U-HDA concentration of 15 μg/g creatinine in post-shift samples (Maître et al., 1996). Although, the dataset was small with only 19 occupationally exposed individuals, the air – urine relationship was supported by other data finding U-HDA concentrations of 11 μg/g creatinine corresponding to 0.034 mg/m^3 (Gaines et al., 2010; Gaines et al., 2011). Excess risk over a working lifetime was 1 % for bronchial hypersensitivity calculated for HDI concentrations of 0.11 μg/m^3 and 5 % at greater than 0.67 μg/m^3 expressed as reactive isocyanate (NCO) groups. These values are 50 times lower than the current OELs based on irritation. Evaluating this excess risk by assuming that 1 % is considered an "acceptable" risk level, then it is not possible to use the available correlation equation to calculate U-HDA because this equation does not cover sufficiently low concentrations. In addition, the correlation was established between air HDI monomer and U-HDA concentrations while at work, prepolymers of HDI are used in coating applications. The difference in HDI monomers and prepolymer can result in an underestimation of exposure to reactive NCO groups coming from HDI prepolymer exposures because they are not reflected as elevated U-HDA concentrations.

The POBL derivation was conducted for the HDI scenario without human data. A precautionary POBL derivation with a LOEC for hyaline degeneration of the respiratory epithelium in rats of 0.035 mg/m^3 gave a $DNEL_{oral}$ of 0.089 μg/kg/d resulting in a POBL of 0.93 μg/L HDA. The POD was for sensitization. A balanced POBL derivation with a NOAEL for adaptations in nasal epithelium in a 2-year chronic rat study

Table 5
Interpretation and perspective for action following compliance vs exceedance of the Occupational Biomonitoring Level (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 and safe handling or proper use of personal protective equipment (PPE) and other risk mitigation measures (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. Consider OBL derivation.	Mitigation of personal exposure indicated. E.g., safe handling or proper use of personal protective equipment and other risk mitigation measures. Consider additional biomonitoring, also other workers might be exposed. Suggest discussing the situation with OHPs.
	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 measures to reduce exposure	
	Compliant	No exposure above the lowest technically achievable exposure	

(because of missing adversity of adaptations the reported LOAEL was interpreted as a NOAEL) of 0.005 mg/m^3 gave a $DNEL_{oral}$ of 0.27 µg/kg/d resulting in a POBL of 2.79 µg/L HDA. The POD was partially relevant and related to sensitization. A relaxed POBL derivation with a LOEC for maternal toxicity and fetotoxicity in rats of 3.5 mg/m^3 gave a $DNEL_{oral}$ of 8.87 µg/kg/d resulting in a POBL of 93.14 µg/L HDA. The POD was not related to sensitization. Sensitivity was assessed as the ratio between the POBL (0.93–2.79 µg/L) and OBL (15 µg/L) and was for HDI between 5 and 16.

8.4. Case study 4 – DEHP

DEHP is a plasticizer that has been shown to exert antiandrogenic effects resulting in adverse reproductive effects (Hlisníková et al., 2020). There are no available data showing direct correlation between urinary DEHP metabolite concentrations with adverse health nor with DEHP air concentrations in exposed workers. PBK models including inhalation and skin uptake, commonly observed in occupational exposure, are also absent.

A urinary mass balance approach (method 4 in Table 2) has been used to set an OBL for DEHP corresponding to an OEL of 2 mg/m^3 (MAK). The toxicity studies used to derive this OEL was based on extrapolation from oral studies. The lowest NOAEL was 3.7 mg DEHP/kg bw/d in a 90-day rat study and a LOAEL (vacuolization of Sertoli cells) was 38 mg/kg bw/d. A conversion factor was used to extrapolate from animals to humans. These extrapolations gave a "low" confidence in the derived OBL. The OBL was set as the sum of four metabolites (represents the steady state); MEHP + 5-OH-MEHP + 5-oxo-MEHP + 5-cx-MEPP to 4 mg/g creatinine (BLW) (Rettenmeier et al., 2019). The urine collection time for long-term exposures was set at the end of shift after several shifts. Another OBL was derived based on the same toxicological data and again, using the urinary mass balance approach. This OBL was for 5-cx-MEPP and set to 0.62 mg/g creatinine (HBM GV from HBM4EU). This OBL was based on fertility effects (onset of aspermatogenesis) (David et al., 2000) with a POD of 5.8 mg/kg bw/d (NOAEL). Here too, the OBL confidence was judged as "low" (Lange et al., 2021).

POBL derivation for DEHP omitting the human studies: A precautionary POBL derivation with a LOAEL for dysgenesis of genitalia in rat of 3 mg/kg bw/d has a $DNEL_{oral}$ of 0.01 mg/kg/d resulting in a POBL of 0.15 mg/L for two metabolites: 5-oxo-MEHP and 5-OH-MEHP. A balanced POBL derivation with a NOAEL for reproduction toxicity in rats of 4.8 mg/kg bw/d gave a $DNEL_{oral}$ of 0.096 mg/kg/d resulting in a POBL of 1.44 mg/L for two metabolites: 5-oxo-MEHP and 5-OH-MEHP. A relaxed POBL derivation with a NOAEL for bilateral aspermatogenesis reprotoxicity of 5.8 mg/kg/d gave a $DNEL_{oral}$ of 0.116 mg/kg/d resulting in a POBL of 1.74 mg/L for two metabolites: 5-oxo-MEHP and 5-OH-MEHP. Sensitivity was assessed as the ratio between the POBL (0.15–1.44 mg/L) and OBL (4.52 mg/L) and was for DEHP between 3 and 30.

9. Conclusion and outlook

This methodology reflects current state of knowledge in occupational biomonitoring. It provides detailed harmonized approaches for deriving health based human biomarker guidance or limit values called Occupational Biomonitoring Levels (OBLs). Furthermore, this concept combines international knowledge and offers a harmonized approach consisting of four widely accepted OBL deriving methods along with their accompanied confidence assessments. Assessing the confidence during the OBL derivation eliminates redundant risk assessment work, encourages knowledge transfers, and enhances transparency as well as defensibility. This confidence assessment may reduce the potential for quality-related debates when implementing OBLs. We recommend using these globally harmonized methods for deriving the health based OBLs and POBLs for hazardous and relevant chemicals already on the market as well as new chemicals and for the harmonized application of occupational biomonitoring (Hopf et al., 2024). Harmonizing the OBL derivation should encourage the use of biomonitoring in chemical risk assessments on national and international levels. Finally, we provide a tiered approach and a decision tree for deriving OBLs. The OBL derivation is guided by strength of scientific evidence and their practical application in occupational exposure assessment and occupational health risk management. In addition to the provided harmonized methodology for the derivation and interpretation of OBLs in occupational exposure biomonitoring, we describe the basis and outlook for including effect biomonitoring in occupational risk assessment. Effect biomarker biomonitoring is part of an ongoing OECD activity to address health risks resulting from combined chemical exposures.

CRediT authorship contribution statement

Nancy B. Hopf: Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization. **Robert Pasanen-Kase:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Conceptualization. **Radu Corneliu Duca:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Jos Bessems:** Writing – review & editing, Conceptualization. **Tiina Santonen:** Writing – review & editing, Conceptualization. **Susana Viegas:** Writing – review & editing, Conceptualization. **Ludwine Casteleyn:** Writing – review & editing, Conceptualization. **Devika Poddalgoda:** Writing – review & editing, Conceptualization. **Farida Lamkarkach:** Writing – review & editing, Conceptualization. **Thomas Göen:** Writing – review & editing, Methodology, Conceptualization. **Maryam Zare Jeddi:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Michael Koller:** Writing – review & editing, Conceptualization. **Christophe Rousselle:** Writing – review & editing, Conceptualization. **Kate Jones:** Writing – review & editing. **Kaspar Schmid:** Writing – review & editing, Conceptualization. **Rex FitzGerald:** Writing – review & editing, Methodology, Conceptualization. **Michael Bader:** Writing – review & editing, Writing – original draft, Methodology. **Koki Takaki:** Writing – review & editing, Methodology. Patience Browne: Writing – review & editing, Methodology. **Virpi Väänänen:** Writing – review & editing, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

All authors have provided a Conflict-of-Interest Statement. No external funding was received for this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxlet.2024.12.006.

Data availability

No data was used for the research described in the article.

References

Angerer, J., Aylward, L.L., Hays, S.M., Heinzow, B., Wilhelm, M., 2011. Human biomonitoring assessment values: approaches and data requirements. Int J. Hyg. Environ. Health 214 (5), 348–360. https://doi.org/10.1016/j.ijheh.2011.06.002.

ANSES (French Agency for Food, Occupational and Environmental Health & Safety) (2017), Valeurs limites d'exposition en milieu professionnel. Évaluation des indicateurs biologiques d'exposition et recommandation de valeurs biologiques pour le chrome VI et ses composés. Rapport d'expertise collective. Only available in French and available on request.

Apel, P., Rousselle, C., Lange, R., Sissoko, F., Kolossa-Gehring, M., Ougier, E., 2020. Human biomonitoring initiative (HBM4EU) - strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. Int J. Hyg. Environ. Health 230, 113622. https://doi.org/10.1016/j.ijheh.2020.113622.

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

Boogaard, P.J., Hays, S.M., Aylward, L.L., 2011. Human biomonitoring as a pragmatic tool to support health risk management of chemicals – Examples under the EU REACH programme. Regulatory Toxicology and Pharmacology 59, 125–132.

Chen, J.-L., Guo, Y.-L., Tsai, P.-J., Su, L.-F., 2002. Use of inhalable Cr+ 6 exposures to characterize urinary chromium concentrations in plating industry workers. J. Occup. Health 44 (1), 46–52. https://doi.org/10.1539/joh.44.46.

Commission., G.H. (1996). *Konzept der Referenz- und Human-Biomonitoring-Werte (HBM) in der Umweltmedizin Bundesgesundheitsbl.*

David, R.M., Moore, M.R., Finney, D.C., Guest, D., 2000. Chronic toxicity of di(2-ethylhexyl)phthalate in rats. Toxicol. Sci. 55 (2), 433–443. https://doi.org/10.1093/toxsci/55.2.433.

ECHA. (2020). *Committee for Risk Assessment RAC: Opinion on scientific evaluation of occupational exposure limits for Diisocyanates. ECHA/RAC/A77-O-0000006826-64-01/F.* ⟨https://echa.europa.eu/fi/oels-activity-list/-/substance-rev/41207/term⟩.

ECHA (2012), Guidance on information requirements and chemical safety assessment. V.2,2 Chapter R.8.1.2.7 (page 10), Appendix R.8-5 and Appendix R.8-15 Chapter 6. A.2 (page 158). Available at : https://echa.europa.eu/documents/10162/17224/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258 (last access at 17.12.2024).

Fedak, K.M., Bernal, A., Capshaw, Z.A., Gross, S., 2015. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg. Themes Epidemiol. 12 (1), 14. https://doi.org/10.1186/s12982-015-0037-4.

Gaines, L.G., Fent, K.W., Flack, S.L., Thomasen, J.M., Ball, L.M., Richardson, D.B., Ding, K., Whittaker, S.G., Nylander-French, L.A., 2010. Urine 1,6-hexamethylene diamine (HDA) levels among workers exposed to 1,6-hexamethylene diisocyanate (HDI). Ann. Occup. Hyg. 54 (6), 678–691. https://doi.org/10.1093/annhyg/meq041.

Gaines, L.G., Fent, K.W., Flack, S.L., Thomasen, J.M., Whittaker, S.G., Nylander-French, L.A., 2011. Factors affecting variability in the urinary biomarker 1,6-hexamethylene diamine in workers exposed to 1,6-hexamethylene diisocyanate. J. Environ. Monit. 13 (1), 119–127. https://doi.org/10.1039/c0em00122h.

Göen, T., Schaller, K.H., Drexler, H., 2012. Biological reference values for chemical compounds in the work area (BARs): an approach for evaluating biomonitoring data. Int Arch. Occup. Environ. Health 85 (5), 571–578. https://doi.org/10.1007/s00420-011-0699-3.

Hadrup, N., Sørli, J.B., Jenssen, B.M., Vogel, U., Sharma, A.K., 2024. Toxicity and biokinetics following pulmonary exposure to aluminium (aluminum): A review. Toxicology 506, 153874. https://doi.org/10.1016/j.tox.2024.153874.

Hlisníková, H., Petrovičová, I., Kolena, B., Šidlovská, M., Sirotkin, A., 2020. Effects and mechanisms of phthalates' action on reproductive processes and reproductive health: a literature review. Int J. Environ. Res Public Health 17 (18). https://doi.org/10.3390/ijerph17186811.

Holst, E., Christensen, J.M., 1992. Intervals for the description of the biological level of a trace element in a reference population. J. R. Stat. Soc.: Ser. D. (Stat.) 41 (2), 233–242. https://doi.org/10.2307/2348256.

Hopf, N.B., Rousselle, C., Poddalgoda, D., Lamkarkach, F., Bessems, J., Schmid, K., Jones, K., Takaki, K., Casteleyn, L., Zare Jeddi, M., Bader, M., Koller, M., Browne, P., FitzGerald, R., Viegas, S., Göen, T., Santonen, T., Väänänen, V., Duca, R.C., Pasanen-Kase, R., 2024. A harmonized occupational biomonitoring approach. Environ. Int 191, 108990. https://doi.org/10.1016/j.envint.2024.108990.

Klotz K.M.-B.M., van Thriel C., Pallapies D., Nasterlack M., Letzel S., Roßbach B., Triebig G., & Weistenhöfer W, D.H., Hartwig A. & MAK Commission (2021). (2019). Addendum to Aluminium [BAT value documentation]. The MAK-Collection for Occupational Health and Safety (eds). Retrieved from https://doi.org/10.1002/3527600418.bb742990vere2419.

Lange, R., Apel, P., Rousselle, C., Charles, S., Sissoko, F., Kolossa-Gehring, M., Ougier, E., 2021. The European Human Biomonitoring Initiative (HBM4EU): Human biomonitoring guidance values for selected phthalates and a substitute plasticizer. Int J. Hyg. Environ. Health 234, 113722. https://doi.org/10.1016/j.ijheh.2021.113722.

Leng, G. (2017). *Hexamethylene Diisocyanate (HDI)*. The MAK-Collection of Occupational Health and Safety 2017, BAT Value Documentations, DFG, *Deutsche Forschungsgemeinschaft*.

Lindberg, E., Vesterberg, O., 1983. Monitoring exposure to chromic acid in chromeplating by measuring chromium in urine. Scand. J. Work Environ. Health 9 (4), 333–340. https://doi.org/10.5271/sjweh.2406.

Maître, A., Berode, M., Perdrix, A., Stoklov, M., Mallion, J.M., Savolainen, H., 1996. Urinary hexane diamine as an indicator of occupational exposure to hexamethylene diisocyanate. Int Arch. Occup. Environ. Health 69 (1), 65–68. https://doi.org/10.1007/bf02630741.

Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

Rettenmeier, A.W., Drexler, H., Hartwig, A., & Commission, M. (2019). Di-(2-ethylhexyl) phthalat (DEHP) [BAT Value Documentation in German language, 2018]. In The MAK-Collection for Occupational Health and Safety (pp. 878-893). https://doi.org/https://doi.org/10.1002/3527600418.bb11781d0023.

Riihimäki, V., Aitio, A., 2012. Occupational exposure to aluminum and its biomonitoring in perspective. Crit. Rev. Toxicol. 42 (10), 827–853. https://doi.org/10.3109/10408444.2012.725027.

Santonen, T., Porras, S.P., Bocca, B., Bousoumah, R., Duca, R.C., Galea, K.S., Godderis, L., Göen, T., Hardy, E., Iavicoli, I., Janasik, B., Jones, K., Leese, E., Leso, V., Louro, H., Majery, N., Ndaw, S., Pinhal, H., Ruggieri, F., Scheepers, P.T.J., 2022. HBM4EU chromates study - Overall results and recommendations for the biomonitoring of occupational exposure to hexavalent chromium. Environ. Res 204 (Pt A)), 111984. https://doi.org/10.1016/j.envres.2021.111984.

Schulz, C., Wilhelm, M., Heudorf, U., Kolossa-Gehring, M., 2011. Update of the reference and HBM values derived by the German Human Biomonitoring Commission. Int J. Hyg. Environ. Health 215 (1), 26–35. https://doi.org/10.1016/j.ijheh.2011.06.007.

SCOEL. (2006). *Recommendation from the Scientific Committee on Occupational Exposure Limits for 2-Methoxyethanol and 2-Methoxyethyl Acetate. SCOEL/SUM/120, September, 2006*. Retrieved from ⟨http://ec.europa.eu/social/BlobServlet?docId= 3865&langId=en⟩ (last access at 26.01.2022).

SCOEL. (2017). Methodology for derivation of occupational exposure limits of chemical agents. The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL) 2017. Available at: ⟨https://op.europa.eu/en/publication-detail/-/publication/3c8ef3e0-48fc11e8-be1d-01aa75ed71a1⟩ (last access at 17.08.2021.

Solberg, H.E., 1983. The theory of reference values Part 5. Statistical treatment of collected reference values. Determination of reference limits. J. Clin. Chem. Clin. Biochem 21 (11), 749–760.

Terry, A.L., Chiappa, M.M., McAllister, J., Woodwell, D.A., Graber, J.E., 2024. Plan and operations of the national health and nutrition examination survey, august 2021-august 2023. Vital.-. Health Stat. 1 (66), 1–21.

Viegas, S., Martins, C., Bocca, B., Bousoumah, R., Duca, R.C., Galea, K.S., Godderis, L., Iavicoli, I., Janasik, B., Jones, K., Leese, E., Leso, V., Ndaw, S., van Nieuwenhuyse, A., Poels, K., Porras, S.P., Ruggieri, F., Silva, M.J., Verdonck, J., Hbm

Eu Chromates Study, T., 2022. HBM4EU chromates study: determinants of exposure to hexavalent chromium in plating, welding and other occupational settings. Int J. Environ. Res Public Health 19 (6). https://doi.org/10.3390/ijerph19063683.
Vogel, N., Conrad, A., Apel, P., Rucic, E., Kolossa-Gehring, M., 2019. Human biomonitoring reference values: Differences and similarities between approaches for identifying unusually high exposure of pollutants in humans. Int J. Hyg. Environ. Health 222 (1), 30–33. https://doi.org/10.1016/j.ijheh.2018.08.002.
Weistenhöfer, W.G., T., Drexler, H., Hartwig, A., MAK Commission, 2023. Requirements for suitable human biomonitoring parameters. Assessment values in biological material – Translation of the German version from 2023. MAK Collect Occup. Health Saf. 8 (4) https://doi.org/https://doi.org/10.34865/bbgeneralegt8_4ad.