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Requirements for suitable human biomonitoring parameters

Assessment Values in Biological Material – Translation of the German version from 2023

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area describes requirements for suitable human biomonitoring parameters, regarding specificity, sensitivity, intraindividual variability, kinetics, sampling time, pre-analytical criteria and reliable analytical determination, in order to be able to derive assessment values in biological material, which protect workers from hazards when handling harmful substances at the workplace.

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Introduction

Human biomonitoring of harmful substances involves the quantitative determination of the substances themselves, their metabolites or exposure parameters in biological material. In order to be able to assess the hazard to workers when handling harmful substances at the workplace, suitable exposure or effect indicators (human biomonitoring parameters), are required, which should fulfil defined criteria.

Conditions for the suitability of a parameter as a useful exposure or effect indicator

Specificity

A biological human biomonitoring parameter should be as specific as possible for the substance in question, i.e. it should be able to reliably indicate exposure to that substance without the risk of a false positive result. This is also important with regard to decreasing levels of exposure at the workplace. Usually this criterion is fulfilled if the unchanged substance is determined in biological material, unless it can also be formed by the metabolisation of other substances.

There are metabolites that are formed exclusively or almost exclusively from one specific substance and thus have a high specificity (e.g. *S*-phenylmercapturic acid in the case of benzene exposure). Non-specific metabolites, which can be formed in the metabolism of various substances or also endogenously, are suitable as exposure indicators of a harmful substance only to a limited extent or only under certain circumstances (exact knowledge of the exposure) (e.g. *trans*,*trans*-muconic acid is formed during exposure to benzene, but also from sorbic acid (food preservative)).

Hazardous substances can affect physiological processes in the organism in the sense of effects. Therefore, in addition to parameters indicating exposure to a substance, also biological markers indicating effects are used for biomonitoring. Here, too, it is preferable to select effect indicators that are influenced as specifically as possible by the hazardous substance under consideration and are modulated as little as possible by general physiological processes. A possible effect indicator for exposures to hazardous substances is, for example, the inhibition of acetylcholinesterase (biological guidance value (BLW): reduction of the acetylcholinesterase activity to 70% of the reference value in the case of exposure to acetylcholinesterase-inhibiting substances such as pesticides (including parathion)).

Sensitivity

In order to reliably detect and assess exposure differences, the parameter must be sufficiently sensitive to avoid false negative results. This means that its concentration or its deviation is changed in a sufficiently sensitive manner at least at the level of the assessment value or is sufficiently high to be able to detect increased or critical exposures reliably.

Association with the toxic effect

The concentration of an exposure parameter in the biological material ideally correlates with its effect in the sense of a dose-response relationship, i.e. there is a relationship between the concentration of the parameter and the strength of the adverse health effects. If the actual toxic metabolite cannot be determined, a metabolite is used that mirrors the exposure well. In the absence of data on the relationship between biomonitoring parameter and health effects, either a reliable quantitative relationship between external exposure to the substance and internal exposure to the human biomonitoring parameter (correlation to MAK value) or the derivation from an animal NOAEL (no observed adverse effect level) via human toxicokinetic modelling can be used.

The hazardous substance itself may have a direct toxic effect and may serve as an exposure indicator. The use of a metabolite of the substance as exposure indicator is particularly recommended if the metabolite is specific for the substance in consideration and if the toxic effect of the substance occurs via this metabolite or via products of its metabolism (toxicity after metabolic activation).

Intraindividual variability/influence of gender

The current physiological condition, the day-night rhythm, etc. can influence parameters intraindividually. Therefore, parameters with a low intraindividual variability are preferred.

The influence of gender-specific factors on possible human biomonitoring parameters is usually not sufficiently studied, but already within the sexes there is a considerable range of variation in toxicokinetics (Bolt 2021; e.g. creatinine excretion). Some parameters may be influenced by physiological differences between the sexes, such as the reference value for lead in blood.

Kinetics and sampling time

Sampling should take place when the parameter is in steady state. It should be noted that even in the case of non-persistent hazardous substances or non-accumulating parameters, the concentration or deviation of the parameter does not react immediately to external exposure because these only build up after absorption and distribution processes and possibly after metabolism. This is especially true for metabolites formed via several phase I reactions or a combination of phase I and phase II reactions, such as *N*-acetyl-*S*-(*N*-methylcarbamoyl)cysteine, a metabolite of *N*,*N*-dimethylformamide (Mráz and Nohová 1992). For exposure indicators that do not require extensive distribution processes and for which metabolism plays a minor role, such as aromatics or halogenated hydrocarbons in blood, the steady state can already be reached after a few minutes. On the other hand, the steady state for the concentration of metabolites in urine is often reached only after several hours. Alternatively, another time point can be set as sampling time according to the kinetics (e.g. sampling before the next shift).

At least as important as the formation kinetics (including the dynamics of effects) is the elimination kinetics of the exposure indicator. This applies in particular to parameters that show extremely rapid elimination (elimination half-life < 1 hour), because in this case, sampling immediately at the end of exposure is mandatory. An example of this is the determination of most highly volatile hazardous substances in the blood, because these are exhaled via the respiratory tract efficiently with short half-lives. In addition, the assessment of such exposure indicators is complicated by the frequently varying exposure situations at the workplace, whereby the (acute) exposure immediately before sampling may not reliably represent the average exposure during the entire working day.

Persistent substances, that successively accumulate during chronic exposure in the body and accordingly in human biological material, such as polychlorinated biphenyls and perfluorinated compounds, deserve special consideration. The same applies to parameters that also accumulate, such as haemoglobin adducts.

When investigating the parameters, the half-life of the respective parameter must be taken into account, especially after intermittent periods without exposure, e.g. holidays.

Multiple human biomonitoring parameters for one substance

Several human biomonitoring parameters for the same substance can provide different information and allow the assessment of different exposure conditions and exposure periods such as (i) current shift or day, (ii) exposures on previous days or during the previous week, (iii) accidental exposures, etc. For different parameters for the same substance, different matrices, sampling times and analytical methods used may have to be taken into consideration.

Pre-analytical criteria

Human biomonitoring parameters should be determinable in easily accessible biological matrices such as blood or urine, the sampling of which is well standardised, and possibly also in alveolar air and should be measurable with reliable methods. This is currently not the case for faeces, hair, saliva, adipose tissue, etc. If exposure indicators can be measured in blood and urine with equal quality in terms of specificity, sensitivity, validated analytical method and existing assessment values, the urine matrix should be preferred because of the non-invasive sampling.

During transport and storage of the sample until analysis, the stability of the parameter in the sample must be ensured. Depending on the stability of the analyte, the determination of the respective parameter may have to be carried out timely after sampling. In the case of highly volatile substances, airtight sealed sample containers must be used.

Sampling must be reasonable for workers (minimally invasive, preferably without inconvenience or risks) and practicable for physicians (compatible with routine monitoring).

To be able to interpret the human biomonitoring parameters, the respective sampling times must be considered.

Contamination of the sample, e.g. by the substance itself, by contamination of the skin or by contaminated sample collection vessels, must be avoided. Generally, the risk of contamination during sampling is reduced in the case of determination of metabolites.

To get valid and reliable test results for the respective parameters, appropriate information should be obtained in advance regarding possible special characteristics of sampling such as sampling time, contamination risk or special collection vessels (e.g. by contacting the commissioned laboratory).

Reliable analytical determination

Analyses should only be carried out under the conditions of statistical quality assurance according to the guidelines of the German Medical Association for quality assurance of laboratory medical examinations (Bundesärztekammer 2023) and the Occupational Medicine Rule 6.2 Biomonitoring (AfaMed 2014). Validated analytical methods that are sufficiently specific and sensitive to answer the questions at hand should be used to determine the human biomonitoring parameters. Validated and verified methods of the Commission's Working Group “Analyses in Biological Material” can be found in The MAK Collection for Occupational Health and Safety (https://series.publisso.de/en/pgseries/overview/mak/dam/allContents/alphabetical/BI, https://repository.publisso.de/resource?query%5B0%5D%5Bfacets%5D%5BcreatedBy%5D%5B0%5D=335&query%5B0%5D%5Bterm%5D=biomonitoring+methods).

Quality assurance

For the assessment of the quality of laboratories with regard to comparability and accuracy in the determination of the human biomonitoring parameter, external quality assurance is required, in particular through interlaboratory comparisons. As a rule, there is an offer for external quality assurance for established parameters (see also biomonitoring information system of the German Federal Institute for Occupational Safety and Health (BAuA 2023)).

Assessment values

The legal prerequisite for occupational biomonitoring in Germany is the existence of assessment values in biological material as a standard of assessment (AfaMed 2014; BMAS 2008). Assessment values may be health-based and risk-based limit values or reference values. Alternatively, an internal control collective can be examined for certain questions.

An overview of the assessment values in biological material derived by the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) for biomonitoring parameters as well as validated and tested analytical methods can be found in the MAK Collection for Occupational Health and Safety

(https://series.publisso.de/en/pgseries/overview/mak/dam/allContents). It contains documentation for biological tolerance values (BAT), biological guidance values (BLW), biological reference values (BAR) and the exposure equivalents for carcinogenic substances (EKA), also published annually online in the List of MAK and BAT Values (DFG 2023). The biological limit values (BGW) of the German Committee for Hazardous Substances (AGS) can be found in the Technical Rule for Hazardous Substances (TRGS) 903 (AGS 2023 a), the equivalent values for the acceptance and tolerance concentration of the exposure-risk relationships (ERR) in TRGS 910 (AGS 2023 b).

A detailed presentation of other assessment values and analytical methods available for biomonitoring in biological material, including links to the available online documents, can be found in the biomonitoring information system of the German Federal Institute for Occupational Safety and Health (BAuA 2023).

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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