The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Human biomonitoring after short-term exposure or accident-related events

Assessment Values in Biological Material – Translation of the German version from 2021

T. Jäger[1]
M. Bader[1]
T. Göen[2]
H. Drexler[3,*]
A. Hartwig[4,*]
MAK Commission[5,*]

1 *BASF SE, Corporate Health Management FEH/CB-H 306, Carl-Bosch-Straße 38, 67056 Ludwigshafen, Germany*

2 *Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University (FAU) Erlangen-Nürnberg, Henkestraße 9–11, 91054 Erlangen, Germany*

3 *Head of the working group "Assessment Values in Biological Material" of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University (FAU) Erlangen-Nürnberg, Henkestraße 9–11, 91054 Erlangen, Germany*

4 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

5 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *email: H. Drexler (hans.drexler@fau.de), A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords

human biomonitoring; sampling time; short-term exposure; accident-related events

Abstract

Human biomonitoring (HBM) is a well-established tool in occupational medicine, particularly for the prevention of health effects after chronic exposure. However, there are also exceptional short-term exposures or accident-related events which require a toxicological risk assessment. The German Permanent Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area deliberated and summarised basic information and recommendations on human biomonitoring after acute exposure. The design and implementation of sampling procedures, e. g. the choice of the sampling time, biological material and target biomarkers, must be carried out with special attention to validity and interpretability of the analytical results. Since no specific assessment values for HBM results after acute short-term exposure are currently available, the medical-toxicological evaluation and communication could use the established assessment values for long-term exposure as a rough benchmark. But this approach requires the additional consideration of specific toxicokinetics of the hazardous substance and the target biomarker as well as of the exposure situation, i. e. duration and route of exposure.

Citation Note:
Jäger T, Bader M, Göen T, Drexler H, Hartwig A, MAK Commission. Human biomonitoring after short-term exposure or accident-related events. Assessment Values in Biological Material – Translation of the German version from 2021. MAK Collect Occup Health Saf. 2021 Sep;6(3):Doc069.
DOI: https://doi.org/10.34865/bbgeneralegt6_3or

Manuscript completed:
16 Mar 2020

Publication date:
30 Sep 2021

1 Introduction

In general, risk assessment for workers in an occupational setting relies on the assumption of relatively uniform or at least regularly recurring exposure situations. However, there are also exceptional short-term exposures or accident-related events which require a toxicological risk assessment. While at least the inhalation exposure of employees during short-term activities (e. g. repair and maintenance work) can be monitored and assessed with appropriately planned measurements in the air at the workplace, this is usually difficult in the case of accidental events. For the exposure and risk assessment of such events, the use of biomonitoring is explicitly recommended (AfAMed 2014, 2016; HBM-Kommission 2006; Müller et al. 2014; Scheepers et al. 2014). However, it must be noted that fundamental requirements for an occupational medical and toxicological assessment of human biomonitoring results after short-term or accident-related exposure are often lacking. Since the biological tolerance values (BAT values) and biological guidance values (BLW) are usually derived for chronic exposures and take into account a 40-hour working week, these values can be used only as a rough benchmark for the assessment of short-term exposures. Furthermore, the planning and implementation of sampling in such cases must be carried out in deviation from the usual rules.

2 Sampling time

For human biomonitoring, the sampling time is critical for the validity and interpretation of the analytical results. Most hazardous substances are excreted via the kidneys or the bile after systemic uptake with half-lives of less than 24 hours; volatile substances are usually also largely exhaled via the respiratory tract within a few hours. Highly volatile and polar substances, such as aliphatic hydrocarbons, BTEX (benzene, toluene, ethylbenzene, xylene) aromatics, ethers, low-molecular alcohols and ketones, which are exhaled or excreted unchanged, tend to have shorter half-lives, which in extreme cases can be in the two-digit minute range (e. g. toluene). Substances that are first metabolised or distributed to deeper compartments usually have longer half-lives. In addition, a steady-state is usually not reached after accident-related events. Especially after dermal absorption, delayed systemic availability must also be considered (Griffin et al. 1999; Viau et al. 1995; Woollen et al. 1992).

Substance-specific information on the sampling time after regular or chronic exposure can be found in the List of MAK and BAT Values (DFG 2020) and relevant information on the biological half-life is provided in the respective MAK and BAT Value Documentations in the section “Metabolism and Kinetics”. These can be used as a guide for the interpretation of the biomonitoring results.

Müller et al. (2014) recommend approximate time windows for sampling and specify, for example, a sampling interval of one to two days for metabolites of hazardous substances **in urine**. However, if the elimination of such metabolites in urine is considered as a model assuming first-order kinetics, it becomes clear that already for target parameters with a half-life of six hours, only about 6% of the maximum concentration is found in the urine after one day. Even metabolites with longer half-lives have largely been excreted after 24 hours (Figure 1). As time progresses, the concentration of the biomarker in the biological material decreases and the result is more strongly influenced by toxicokinetic variability and analytical uncertainty. This also reduces the reliability of a biomonitoring study with regard to a back-extrapolation to the original exposure and to the risk assessment. Due to the above-mentioned influencing factors, it is recommended that sampling for human biomonitoring be carried out as soon as possible after the accident-related event.

In addition to considering the half-life of a substance, it must be taken into account that renally excreted substances only enter the urine through diuresis and that a suitable volume of urine must be released into the urinary bladder before the biomarker can be detected and quantified. Approximately 60 ml of urine is released into the urinary bladder per hour (mean daily volume 1500 ml/24 hours). Furthermore, the dilution of the biomarker concentration by the urine that was already in the bladder before exposure has to be considered. It also seems sensible for practical reasons (preparation of a human biomonitoring programme, implementation, communication, coordination of the agencies involved) to choose a sampling strategy that ensures a timely and thus meaningful examination.

While sampling can take place immediately following the activity or event in the case of exposure over several hours, after a short-term exposure for one hour or less, an interval of 30 to 60 minutes should be passed before sampling, during which the target compounds are eliminated into the urinary bladder. It is reasonable to carry out the sampling within the first to maximum second half-life of the target parameter. For most biomarkers, sampling should therefore take place up to a maximum of 16 hours after the end of exposure.

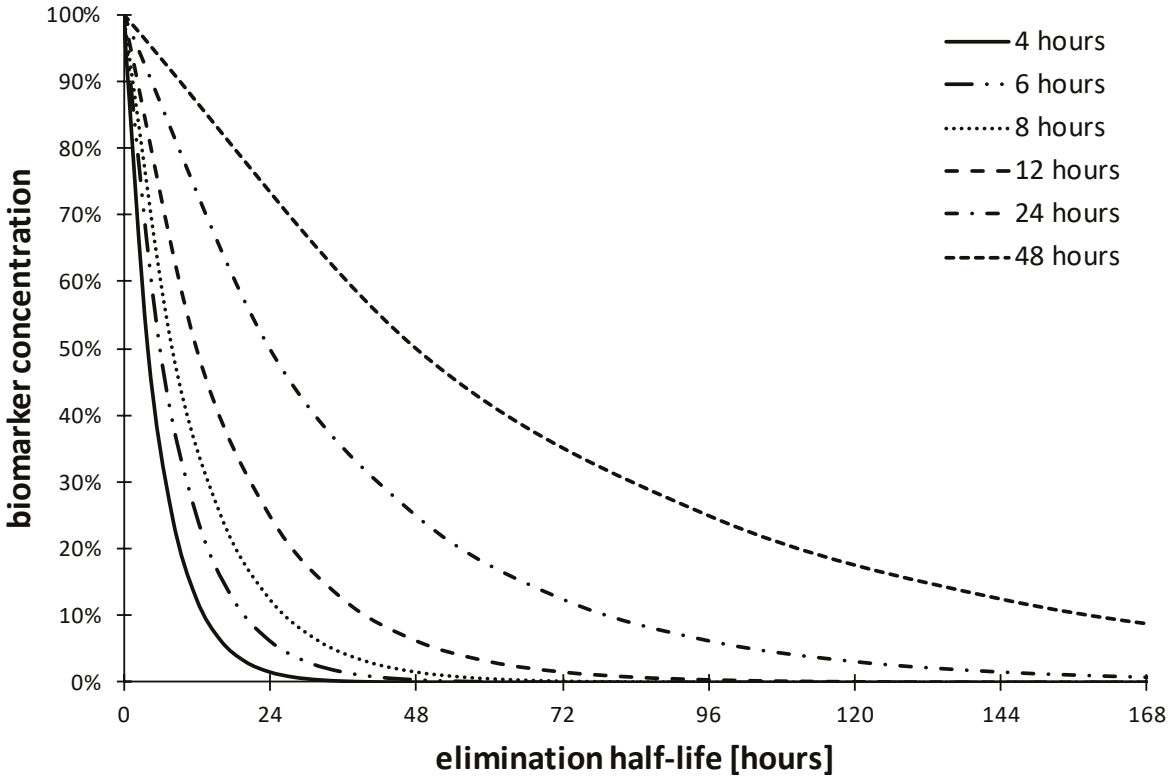

Fig. 1 Effect of elimination half-life on biomarker concentration (assuming 1st order kinetics)

Other matrices, such as blood and plasma can also be examined depending on the half-life of the substance or metabolite of interest in the respective biological matrix. Peak exposures that are associated with an increased risk can often be better detected **in blood**. It must be taken into account that the half-lives in the blood compartment, with the exception of persistent compounds, are usually shorter than in urine and thus pose special challenges for timely sampling.

Rather uncritical with regard to the sampling time are substances for which human biomonitoring can be carried out by means of haemoglobin adducts. Due to the long circulation time of the erythrocytes of approx. 120 days and the associated slow decline of the adduct concentration, a follow-up examination can be carried out even after an exposure that took place some time ago. Table 1 provides an overview of various biomarkers and the corresponding time periods in which human biomonitoring can usefully be carried out in connection with an accident-related event.

Tab. 1 Limits of sampling

Examination parameters	Possible sampling period after exposure
Blood, plasma, urine metabolites	Depending on the half-life - between up to 1 hour and 2 days for non-persistent compounds - within maximum 2 half-lives
Protein adducts	up to a maximum of 50% of the lifetime of the protein - haemoglobin ~ 60 days - serum albumin ~ 15 days
DNA adducts	up to 20 days

As already mentioned, due to the limited knowledge about the exposure conditions, the initial maximum concentration can be back-extrapolated only by accepting large error intervals.

If no information on exposure time or period is available, repeated sampling several hours apart from the initial sampling (e. g. 4, 8, 16, 24 hours) may help to improve back-calculations and exposure estimation. Furthermore, it is recommended to record on the sample container or a standardised accompanying questionnaire both the sampling time and the time or end of exposure as well as other exposure conditions (e. g. possible skin contact, ingestion) in order to be able to retrospectively estimate the maximum biomarker concentration, if necessary. In the case of an event with several potentially exposed persons, it is recommended to perform the sampling at the same time, if possible, to ensure better comparability of the human biomonitoring results.

3 Sampling, storage and transport

In addition to the optimal sampling time, requirements for sample collection, storage and transport to the laboratory must also be taken into account. Particularly in the case of accident-related events and unclear side conditions, attention must be paid to good sampling practice. Guidance on this can also be found in Occupational Medical Rule 6.2 Biomonitoring (AfAMed 2014). Contamination must be avoided when collecting blood and urine samples (change of clothing, cleaning of hands, sampling in an uncontaminated environment). Samples must then be sent immediately to the laboratory or, if possible, preserved at a minimum of –18 °C. Blood samples are more problematic for storage than urine samples due to haemolysis. Depending on the nature of the hazardous substance, further requirements may be placed on the sampling vessel (e. g. airtight lancing ampoules for headspace analysis in the case of volatile substances). It is therefore recommended to contact the biomonitoring laboratory promptly to discuss specific requirements for the respective biomarker.

4 Toxicological evaluation and communication

In the medical-toxicological assessment and communication of human biomonitoring results, it must be taken into account that currently no specific assessment values are available for acute short-term exposure or after accident-related events. Assessment values based on occupational (biological limit value (BGW), BAT value, BLW, exposure equivalents for carcinogenic substances (EKA)) and environmental medicine (HBM-I, HBM-II values) usually refer to chronic exposures over longer periods of time and thus cannot be used to assess the health hazard without taking into account the duration of exposure, the time interval between exposure and sampling, and the kinetics of the hazardous substance or of the parameter that can be used to assess the health hazard after a single exposure (exceptions are hazardous substances with acute toxic effects such as carbon monoxide or acetylcholinesterase inhibitors). Usually, assessment values derived from occupational medicine and toxicology for chronic exposures are far below the threshold values for acute effects (Bäcker et al. 2018). Nevertheless, these assessment values can be used as a benchmark to relate human biomonitoring results after a single exposure to a chronic exposure, and thus support risk communication.

Furthermore, a comparison of the human biomonitoring results with biological reference values (BAR) or reference values of the Human Biomonitoring Commission of the Federal Environment Agency can be used to distinguish between exposed and unexposed persons. This approach allows a more targeted medical follow-up of individual acutely exposed persons. If necessary, additional considerations are required to assess the plausibility of acute effects.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

References

AfAMed (Ausschuss für Arbeitsmedizin) (2014) Arbeitsmedizinische Regel (AMR 6.2). Biomonitoring. BAuA, Dortmund. https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/AMR/pdf/AMR-6-2.pdf?__blob=publicationFile&v=2, accessed 29 Apr 2021

AfAMed (Ausschuss für Arbeitsmedizin) (2016) Arbeitsmedizinische Regel (AMR 11.1). Abweichungen nach Anhang Teil 1 Absatz 4 ArbMedVV bei Tätigkeiten mit krebserzeugenden oder keimzellmutagenen Gefahrstoffen der Kategorie 1A oder 1B. BAuA, Dortmund. https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/AMR/pdf/AMR-11-1.pdf?__blob=publicationFile&v=2, accessed 29 Apr 2021

Bäcker S, Jäger T, Busch H, Conzelmann T, Bader M (2018) Human-Biomonitoring und klinische Beobachtungen nach akuter dermaler oder inhalativer Exposition gegenüber Benzol oder benzolhaltigen Gemischen. In: Letzel S, Nesseler T (eds) 58. Wissenschaftliche Jahrestagung der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM). Gentner Verlag, Stuttgart, 158

DFG (Deutsche Forschungsgemeinschaft) (ed) (2020) List of MAK and BAT Values 2020. Maximum Concentrations and Biological Tolerance Values at the Workplace. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, report 56. German Medical Science, Düsseldorf. DOI: https://doi.org/10.34865/mbwl_2020_eng

Griffin P, Mason H, Heywood K, Cocker J (1999) Oral and dermal absorption of chlorpyrifos: a human volunteer study. Occup Environ Med 56(1): 10–13. DOI: https://doi.org/10.1136/oem.56.1.10

HBM-Kommission (Kommission „Human-Biomonitoring“ des Umweltbundesamts) (2006) Empfehlungen zum Einsatz von Human-Biomonitoring bei einer stör- oder unfallbedingten Freisetzung von Chemikalien mit Exposition der Bevölkerung. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 49(7): 704–712. DOI: https://doi.org/10.1007/s00103-006-1298-4

Müller M, Schmiechen K, Heselmann D, Schmidt L, Göen T (2014) Human biological monitoring – A versatile tool in the aftermath of a CBRN incident. Toxicol Lett 231(3): 306–314. DOI: https://doi.org/10.1016/j.toxlet.2014.09.017

Scheepers PTJ, van Brederode NE, Bos PMJ, Nijhuis NJ, van de Weerdt RHJ, van der Woude I, Eggens ML (2014) Human biological monitoring for exposure assessment in response to an incident involving hazardous materials. Toxicol Lett 231(3): 295–305. DOI: https://doi.org/10.1016/j.toxlet.2014.03.002

Viau C, Carrier G, Vyskocil A, Dodd C (1995) Urinary excretion kinetics of 1-hydroxypyrene in volunteers exposed to pyrene by the oral and dermal route. Sci Total Environ 163(1–3): 179–186. DOI: https://doi.org/10.1016/0048-9697(95)04494-l

Woollen BH, Marsh JR, Laird WJ, Lesser JE (1992) The metabolism of cypermethrin in man: differences in urinary metabolite profiles following oral and dermal administration. Xenobiotica 22(8): 983–991. DOI: https://doi.org/10.3109/00498259209049904