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ORIGINAL ARTICLE

Biological reference values for chemical compounds in the work area (BARs): an approach for evaluating biomonitoring data

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Abstract Biological monitoring is a routine method that has been applied in occupational medical practice for many years. A requirement for its application is the availability of criteria suitable for evaluating biomonitoring data. Health-based threshold values are particularly useful as a criterion, yet only for substances for which effect thresholds can reliably be determined. For substances for which the concept of health-based threshold values is not applicable, the Working Group *Setting of Threshold Limit Values in Biological Materials* of the *DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area* has recently established "Biologische Arbeitsstoff-Referenzwerte" (BARs, Biological Reference Values for Chemical Compounds in the Work Area) as an approach for evaluating biomonitoring data. The BAR represents the upper reference concentration of a biomarker in the general adult population without occupational exposure to the agent. It is derived from biomonitoring data of a sample of a defined population group. In general, a BAR corresponds to the 95th percentile of the sample distribution. Ideally, national environmental surveys including human biomonitoring results are used as basis for deriving BARs. The influence of age, sex, social status, residential area and life style factors on background exposure is considered in the evaluation of these values. Because tobacco smoking is the most frequent influencing factor, several BARs have been determined for non-smokers only. To date, BARs for 17 substances or substance groups are listed in the *List of MAK and BAT Values 2011*. BARs for another five substances have been discussed, but have not been established because of the insufficient scientific database. Establishing the BARs aims to facilitate the evaluation of human exposure to chemical compounds for which no health-based threshold values can be derived but an adequate assessment of exposure is required due to their toxicity. The application of BARs does not permit a toxicological evaluation, but does allow the occurrence and the extent of occupational exposure to hazardous substances to be proved.

Keywords Biological monitoring · Occupational exposure limits · Occupational and environmental medicine

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Introduction

Biological monitoring (biomonitoring), i.e., the repeated recording of the concentration of a hazardous substance, its metabolites or of an induced biological effect in human biological materials (urine, blood, plasma), is a routine procedure that has been applied in occupational medical practice for many years. Nevertheless, biomonitoring can accomplish its purpose only if reliable analytical procedures as well as suitable reference values for evaluating biomonitoring data are available.

For a number of decades, research teams worldwide have developed analytical procedures for the quantitative determination of biological exposure and effect markers in workers occupationally exposed to chemicals (for review see Fiserova-Bergerova and Ogata 1990). In Germany, such procedures have been published since 1972 by the Working Group *Analyses of Hazardous Substances in*

Biological Materials of the *DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area*, initially in German, and for more than 25 years also in English (DFG 1985–2004, 2005–2010a). This Working Group not only develops biomonitoring methods or adopts them from other research groups, but also controls experimentally each of these methods for its reproducibility and reliability (Göen et al. 2011). An outstanding feature of the analytical guidelines published by this Working Group is that they can be adopted in appropriately equipped laboratories without any difficulties if the reliability criteria are considered.

In general, health-based threshold values are used as criteria for evaluating biomonitoring data, and many organizations worldwide have developed and published such values (ACGIH 2011; Bolt and Thier 2006; Cocker et al. 2007; DFG 2011; Jang et al. 1993; JSOH 2010; Kiilunen 1999). Nevertheless, such health-based threshold values cannot be properly derived for many chemicals, and therefore, additional evaluation criteria have to be established.

Health-based threshold values for biomonitoring data

In Germany, the *DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area* has derived and published Biological Tolerance Values (BAT) since 1981 (DFG 1994–1998, 2005–2010b, 2011). For that purpose, a specific Working Group called *Setting of Threshold Limit Values in Biological Materials* was founded in 1979 as a subgroup of the *DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area* (Lehnert 1980; Lehnert and Schaller 1995). Thus, Germany was the first country in the world that introduced biological threshold values for occupational medical examinations of workers exposed to hazardous substances (Drexler 2007; Drexler et al. 2008). In addition, the Committee of the American Conference of Governmental Industrial Hygienists (ACGIH®) has published Biological Exposure Indices (BEI) since 1982 (Morgan and Schaller 1999; Morgan 1998). Groups with similar tasks have been established in other countries, such as Finland (Kiilunen 1999), the UK (Cocker et al. 2007), Japan (Omae et al. 1999) and South Korea (Jang et al. 1993). Since 2000, the Scientific Committee for Occupational Exposure Limits (SCOEL) of the European Union has also been concerned with threshold values in biological materials (Bolt and Thier 2006).

The definitions of health-based threshold values proposed by the various committees are quite similar. For example, the BAT value describes the toxicologically derived concentration of a substance, its metabolites or of an effect parameter in the corresponding biological material, at which the health of a worker is in general not adversely affected, even after repeated and long-term exposure. BAT values are based on the relationship between external and internal exposure or between internal exposure and the resulting toxic effect (DFG 2011). The concept for the derivation and application of BAT values has recently been revised. It is now based on individual average values as detailed by Drexler et al. (2008).

The *List of MAK and BAT Values 2011* comprises BAT values for 50 substances or substance groups and provides documentations for another eleven for which a BAT value could not be established. Nevertheless, the concentrations of far more hazardous substances and/or of their metabolites can be determined by using modern analytical methods. The Working Group *Analyses of Hazardous Substances in Biological Materials* has published biomonitoring procedures for more than 250 chemical compounds and/or their metabolites (Hartwig 2008).

Non-health-based assessment values for biomonitoring data

The concept of health-based threshold values is not applicable to substances for which an effect threshold cannot or only insufficiently be determined. This applies particularly to genotoxic and carcinogenic substances. In addition to their carcinogenic potential, such substances frequently show other critical toxic effects for which thresholds do exist. The Working Group *Setting of Threshold Limit Values in Biological Materials* derives so-called Biologische Leitwerte (BLWs) for these substances (Hallier et al. 2001). Most toxic effects will be avoided if BLWs are observed; however, a carcinogenic risk may still remain. The BLW of 50 µg arsenic/l urine for arsenic and inorganic arsenic compounds and that of 550 pmol N-(2-carbonamideethyl)valine/g globin for acrylamide are examples for the derivation of BLWs. While the development of neurotoxic effects might be avoided if one adheres to the threshold values of these compounds (DFG 2011), the induction of cancer demonstrated in humans for arsenic and inorganic arsenic compounds or in animal experiments for acrylamide might still occur. The BEIs published by ACGIH® must also be assigned to this category of partially health-based threshold values, if they have been evaluated for carcinogenic substances, as in the case of benzene, for example (ACGIH 2011; see also Table 1).

BLWs are also established for some substances, even if there is a relatively small toxicological data base, allowing the derivation of threshold values only with some degree of uncertainty. In these cases, the BLWs can be tentatively

Table 1 National and international values for the assessment of biomonitoring data

Assessment categories	Recognized threshold values (country of origin)
Health-based threshold values	BAL (FIN)[a]; BAT (D); BEI (US)[a]; BLV (EU); BLW (D)[a]; BMGV (UK)[a]; OEL-B (J) and others
Partially health-based threshold values	BEI (US)[a]; BLW (D)[a]
Equivalents of external and internal exposure	EKA (D)
Values based on good practice	BAL (FIN)[a]; BMGV (UK)[a]
Reference values for background exposure	BAR (D); BGV (EU)

[a] Threshold values assigned to different categories according to substance

applied, similarly to BAT values, despite the insufficient data base (Hallier et al. 2001). The *List of MAK and BAT Values 2011* contains BLWs for eight substances or substance groups, and documentations for another five for which BLWs could not be derived.

Apart from the application of BLWs, there are other ways for assessing exposure to hazardous substances for which no health-based threshold value can be established. For example, exposure to carcinogenic substances can be deduced from the relationship between exposure level and the resulting increment of cancer risk. However, epidemiological studies in which both cancer incidence and exposure level have been determined are necessary to describe the exposure–risk relationship. As only the exposure to ambient air is usually measured in such studies, the relationship between biomarker level and the level of the carcinogenic substance in the workplace air must be known. Since 1984, the Working Group *Setting of Threshold Limit Values in Biological Materials* has been evaluating so-called "Expositionsäquivalente für krebserzeugende Arbeitsstoffe" (EKAs, Exposure Equivalents for Carcinogenic Substances) based on the correlations between external and internal exposure. Biomarker concentrations can be derived from EKAs for inhalative exposure to carcinogenic substances (DFG 2011). The *List of MAK and BAT Values 2011* includes EKA correlations for 24 substances or substance groups and provides documentations for another six for which EKAs could not be established. In Germany, the AGS ("Ausschuss für Gefahrstoffe bei der Bundesanstalt für Arbeitsschutz und Arbeitsmedizin", Committee for Hazardous Substances of the German Ministry of Labor and Social Affairs) defines specific cancer risks as socially tolerable or acceptable (AGS 2008). Such risk-based values can also be used to interpret biomonitoring results.

Defining standards for adequate occupational hygiene and establishing biomarker levels that can be observed under conditions of good occupational hygiene are another approach to control exposure to substances for which no threshold values exist. Such occupational hygiene threshold values have been used by occupational physicians in the chemical industry for decades (Zober and Will 1996) and have been established as valid national values for the assessment of biomarker data in a number of countries such as the UK (Cocker et al. 2007) and Finland (Kiilunen 1999). In Germany, the concept of "Technische Richtkonzentrationen" (TRKs, Technical Exposure Limits), applied up to the end of 2004 (DFG 2004), was based on an occupational hygiene assessment model that allowed the use of biological monitoring via the EKA.

A generally applicable approach to assess occupational exposure is the comparison of the exposure level detected in the worker with the general background levels in individuals without occupational exposure to the chemical compound (Apostoli 1999). Such an assessment requires the establishment of values representative for the general exposure of the adult population that are at least valid at the national level (Aitio 2006).

Concept of the "Biologischer Arbeitsstoff-Referenzwert" (BAR)

One important requirement for introducing the reference value concept is that the concentrations of hazardous substances in biological materials have frequently been measured in order to differentiate between workplace- and environment-related exposures. Because of the increased sensitivity and specificity of modern analytical methods, a large number of hazardous substances and/or their metabolites in biological materials can be measured in the occupationally non-exposed population. Many of the analytical methods published by the Working Group *Analyses of Hazardous Substances in Biological Materials* can be used to assess background exposure (Göen et al. 2011).

If the concentration of a hazardous substance or of one of its metabolites in the biological material exceeds the quantification limit, the question arises in cases of occupational exposure, whether the exposure is caused by the general environmental conditions or by occupational exposure. If the latter applies, it is of interest to know its relative contribution. Unfortunately, the laboratory-specific reference values often vary from one laboratory to another. As a consequence, the individual laboratories provide assessments of the occupational contribution to exposure that deviate from each other.

In light of this situation, the Working Group *Setting of Threshold Limit Values in Biological Materials* has taken steps to establish "Biological Reference Values for Hazardous Substances" starting in the 1990s. First, the Working Group identified exogenous and endogenous background exposures (Lewalter and Neumann 1996a), then it collected quantitative data on the background exposure of a larger number of substances and, eventually, discussed its importance for the interpretation of biomonitoring results (Lewalter and Neumann 1996b). Also in 1996, the HBM-UBA ("Kommission Human-Biomonitoring des Umweltbundesamtes", Human Biomonitoring Commission of the Federal Environment Agency) in Germany started to derive and publish reference values for the application in environmental medical examinations. In contrast to the Working Group, the Human Biomonitoring Commission often considers the specific conditions of children and the elderly, i.e., of population groups not in the age of the labor force, when evaluating reference values (Ewers et al. 1999; Schulz et al. 2011).

In recent years, the importance of background exposure for the assessment of occupational biomonitoring data has grown, because both the number of biomarkers and the availability of methods for their determination at background levels have distinctly increased. Therefore, the *DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area* has initiated the evaluation of reference values for the general population of working age, the so-called "Biologische Arbeitsstoff-Referenzwerte" (BARs). BARs describe the exposure of individuals of a reference population of working age to a substance to that they are not occupationally exposed, and which is found in their body at a specific point in time. Reference values for a substance or its metabolites in biological material are derived from a sample of a defined population group by means of the measured values. The BARs correspond to the 95th percentile without referring to health effects.

The validity of the reference values primarily depends on the size of the investigated population. Ideally, environmental surveys at the national level can be used as basis, such as those carried out in Germany by the UBA ("Umweltbundesamt", Federal Environment Agency) or in the USA by the *Centers for Disease Control and Prevention* (CDC 2009; Schulz et al. 2007). The reference values should be based on a broad database constituted of representative random samples and evaluated according to the corresponding guidelines of the respective scientific organization, e.g., the *International Union of Pure and Applied Chemistry, Clinical Chemistry Division, Commission on Toxicology* (Poulsen et al. 1997). If a BAR is derived for a substance for which no representative data are available, the evaluation protocol includes a description as to how the reference value has been derived and from which database.

For some biomarkers, the available studies do not have the ability to detect the biomarker in a reasonable number of samples and therefore do not allow an estimation of the reference value. In these cases, reference values are specified as below the detection limit of the study (see Table 2).

Influencing factors and regional validity of the BARs

When BARs are evaluated, the influence of age, sex, social status, residential area and life style must be considered among other factors on background exposure. Tobacco smoking is the most important influencing factor to be taken into account. As tobacco smoke contains a large number of substances in relatively high concentrations, particularly carcinogenic compounds such as aromatic amines, cadmium, polycyclic aromatic hydrocarbons and alkylating agents, smoking can result in significantly higher concentrations of biological exposure markers. Therefore, BARs are exclusively derived for non-smokers and are thus strictly applicable only for them. Specific reference values for smokers cannot be derived, because the exposure to the various compounds in tobacco smoke depends on the type and quantity of the tobacco consumed. Nevertheless, references to empirical values in smokers are provided in the occupational medical and toxicological documentations of the BAR, as far as available (DFG 1994–1998, 2005–2010b; see also Table 2). If known, the influence of passive smoking on reference values for non-smokers is also addressed in the BAR documentation.

Reference values reflect the background exposure of a certain population and may in part only attain regional validity. If background exposure varies regionally, region-specific BARs must be derived, or attention must be drawn to the possibly specific exposure conditions. Up to now, relevant regional variances in background exposure have only occasionally been revealed and only for larger regions. Examples are the diverging selenium exposure in Germany, the USA, Finland and Central Asia (Lippman et al. 2009; Moreno-Reyes et al. 1998; Salonen et al. 1984; Schaller et al. 2008), the differing mercury exposure in Germany and East Asia (Schulz et al. 2007; Son et al. 2009) or manganese body burden in different regions of the world (Triebig et al. 2005). Exposure to uranium varies particularly widely from region to region. The disparate geological occurrence of this element in various parts of Germany results in great differences of exposure via the drinking water, and thus, in the internal exposure of the German population (Kemper et al. 2004). Therefore, the Working Group *Setting of Threshold Values in Biological*

Table 2 BARs established at present (based on the *List of MAK and BAT Values* 2011)

Substance [CAS number]	Skin designation	Carcinogen category by DFG	Parameter	BAR	Assay material	Sampling time
Acrylamide [79-06-1]	H	2	N-(2-Carbonamideethyl)valine	50 pmol/g globin[a]	Erythrocytes fraction of whole blood	a
			N-Acetyl-S-(2-carbonamide ethyl)cysteine	100 μg/g creatinine[a]	Urine	b
Acrylnitrile [107-13-1]	H	2	N-(2-Cyanoethyl)valine	0.3 μg/l[a]	Erythrocytes fraction of whole blood	a
4-Aminobiphenyl [92-67-1]	H	1	4-Aminobiphenyl (released from the hemoglobin conjugate)	15 ng/l[a]	Erythrocytes fraction of whole blood	a
Arsenic [7440-38-2] and inorganic arsenic compounds (apart from arsine)		1	Inorganic arsenic and methylated metabolites	15 μg/l	Urine	c
Barium compounds, soluble (calculated as Ba [7440-39-3])			Barium	10 μg/l	Urine	c, b
Benzidine [92-87-5]	H	1	Benzidine adducts	Not established	Erythrocytes fraction of whole blood	a
			Benzidine	Not established	Urine	c, b
Beryllium [7440-41-7] and its inorganic compounds		1	Beryllium	0.05 μg/l	Urine	c, b
Cadmium [7440-43-9] and its inorganic compounds	H	1	Cadmium	1.0 μg/l[a]	Whole blood	a
			Cadmium	0.8 μg/l[a]	Urine	a
Chromium [7440-47-3] and its compounds	H	2	Total chromium	0.6 μg/l	Urine	b
4,4′-Diaminodiphenylmethane [101-77-9]	H	2	4,4′-Diaminodiphenylmethane	<0.5 μg/l	Urine	b
			4,4′-Diaminodiphenylmethane (released from the hemoglobin conjugate)	<5 ng/l	Erythrocytes fraction of whole blood	a
Manganese [7439-96-5] and its inorganic compounds			Manganese	15 μg/l	Whole blood	c, b
2-Naphthylamine [91-59-8]	H	1	2-Naphthylamine	Not established	Urine	b
			2-Naphthylamine adducts	Not established	Erythrocytes fraction of whole blood	a
Nickel [7440-02-0] and its compounds		1	Nickel	3 μg/l	Urine	c
Polychlorinated biphenyls [1336-36-3]	H	3B	PCB 28	0.02 μg/l	Plasma/serum	a
			PCB 52	<0.01 μg/l	Plasma/serum	a
			PCB 101	<0.01 μg/l	Plasma/serum	a
Propylene oxide [75-56-9]	H	2	N-(R,S)-(2-Hydroxypropyl)valine	10 pmol/g globin[a]	Erythrocytes fraction of whole blood	a
			N-Acetyl-S-(2-hydroxypropyl) cysteine	25 μg/g creatinine[a]	Urine	b, c
o-Toluidine [95-53-4]	H	1	o-Toluidine	0.2 μg/l[a]	Urine	b

Table 2 continued

Substance [CAS number]	Skin designation	Carcinogen category by DFG	Parameter	BAR	Assay material	Sampling time
2,4-Toluylene diamine [95-80-7]	H	2	2,4-Toluylene diamine (after hydrolysis)	Not established	Urine	b
2,4-Toluylene diisocyanate [584-84-9]		3A	2,4-Toluylene diamine (after hydrolysis)	Not established	Urine	b
Trichloroethylene [79-01-6]	H	1	Trichloroacetic acid	0.07 mg/l	Urine	c, b
2,4,6-Trinitrotoluene [118-96-7] (and isomers in technical mixtures)	H	2	4-Amino-2,6-dinitrotoluene	<1 µg/l	Urine	b
			2-Amino-4,6-dinitrotoluene	<4 µg/l	Urine	b
Uranium [7440-61-1] and its inorganic compounds	H	2/3B	Uranium	Not established	Urine	b
Vinyl chloride [75-01-4]		1	Thiodiglycolic acid	1.5 mg/l	Urine	d

Sampling time (legend): (a) not fixed, (b) end of exposure or end of shift, (c) for long-term exposures: after several shifts, (d) at the beginning of the next shift

[a] Other values apply for smokers

Materials has not established a BAR for the uranium concentration in urine.

Individuals in different regions of the world have different levels of exposure. This is particularly important for the evaluation of the internal exposure of immigrants to biological persistent chemicals compounds. For example, Schmid et al. (1997) showed that organochlorine concentrations in blood samples of people seeking asylum in Germany often differed significantly from those of people raised in Germany. Both higher concentrations, e.g., of DDT, and in part lower concentrations, e.g., of polychlorinated biphenyls, were found in immigrants.

The biological persistence of hazardous substances is also the reason why different age groups exhibit varying levels of internal exposure. A familiar example is the exposure to particularly persistent polychlorinated biphenyl congeners. Data from population studies show that the concentrations of PCB 138, PCB 153 and PCB 180 (Ballschmiter nomenclature) in human blood increase with age (Becker et al. 2002). Specific reference values for different age groups have to be established for substances with this feature (Schulz et al. 2011).

Basically, the concentration of a hazardous substance measured in biological samples collected from the general population reflects environmental exposure. The hazardous substance enters the human body either directly via consumer products or indirectly via the diet and drinking water. Yet environmental exposure may vary with time as shown for some hazardous substances. For example, environmental lead pollution and, subsequently, exposure of humans to this metal have decreased in recent decades as a result of the introduction of lead-free fuel and the catalytic converter (Wiesmüller et al. 2007). The dynamic nature of the environmental exposure implies that reference values are only temporarily valid. Consequently, reference values must be revised after a certain period of time, and new values must be established if necessary.

Application of the BARs in occupational medical practice

The comparison of biomonitoring values in occupationally exposed persons by means of BARs allows the determination of the extent of occupational exposure. In contrast to the assessment of background exposure, the sampling time cannot be randomly assigned to record the occupational exposure of a worker, but must be based on the half-life of the biomonitoring parameter and on the time-related exposure profile of the worker. These two reasons in particular require reference values valid for the working population, specified as "Biologische Arbeitsstoff-Referenzwerte" (BARs).

The *DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area* published the first BARs for chromium and its inorganic compounds as well as for 2,4,6-trinitrotoluene together with the BAR definition in the *List of MAK and BAT Values 2008* (DFG 2008). BARs for 17 substances or substance groups are listed in the present *List of MAK and BAT Values 2011* (DFG 2011). BARs for additional five substances have been discussed, but have not been established because of the insufficient data base (see Table 2).

Meanwhile, the concept of using data on background exposure to assess occupational exposure has been adopted

by other organizations. The *Scientific Committee on Occupational Exposure Limits of the European Commission* (SCOEL) has recently started to evaluate so-called Biological Guidance Values (BGVs) based on the background exposure of the European working population (SCOEL 2009).

In general, the varying parts of the exposure routes (inhalative, dermal, by diet and drinking water) responsible for the background levels of the biomarkers are unknown. Considering the different resorption rates and kinetics of the different exposure routes, the estimation of the amounts of external exposure from the reference value is unfeasible hence in the most cases.

Establishing the BARs aims to facilitate the evaluation of human internal exposure to chemical compounds for which no health-based threshold values can be derived but an adequate assessment of exposure is required due to their toxicity. The application of BARs does not permit a toxicological evaluation, but does allow the occurrence and the extent of occupational exposure to hazardous substances to be proved. Thus, it can be decided whether further interventions are indicated to reduce the exposure level of workers to carcinogenic substances (substitution of the chemical compound, technical measures of reducing exposure, personal protection measures) or to counteract any increased risk by introducing additional occupational medical surveillance examinations.

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