Int Arch Occup Environ Health (2008) 82:139–142
DOI 10.1007/s00420-008-0331-3

SHORT COMMUNICATION

Biological tolerance values: change in a paradigm concept from assessment of a single value to use of an average

Hans Drexler · Thomas Göen · Karl Heinz Schaller

Received: 29 April 2008 / Accepted: 29 April 2008 / Published online: 17 June 2008

Abstract Since 1981 biological tolerance values for occupational exposure (BAT values) have been published in the List of MAK and BAT Values of the Deutsche Forschungsgemeinschaft (DFG). In 2007 the list includes threshold limit values for more than 90 substances. The BAT value was defined as the maximum permissible quantity of a chemical substance or its metabolites or the maximum permissible deviation from the norm of biological parameters induced by these substances. The biological limit values derived by other commissions (ACGIH, SCOEL) are to be understood as averages, which may well be exceeded individually, in contrast to the BAT values that were defined as ceiling values and thus did not allow an excess of values in the individual employee. The DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has now revised the concept of biological limit values. The BAT value describes the concentration of a chemical substance, of its metabolites or of an effect indicator in appropriate biological material derived by occupational medical and toxicological criteria, at which the health of an employee is usually not affected, even after repeated or long-term exposure. In this case, derivation of the BAT value is based on the average internal exposures. With this redefinition of the German BAT value, it will be possible to better harmonize the values with those provided by other commissions, which are also based on an average concept.

This paper has originally been published in German in: Drexler H, Göen T, Schaller KH (2007) Arbeitsmed Sozialmed Unweltmed 42:514–516.

H. Drexler (✉) · T. Göen · K. H. Schaller
Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine at the University of Erlangen-Nuremberg, Schillerstr. 25 and 29, 91054 Erlangen, Germany
e-mail: hans.drexler@rzmail.uni-erlangen.de

Keywords New definition of biological tolerance values · Biological monitoring · Biological limit values

Introduction

As for the health hazard posed by xenobiotics, exclusively the quantity of uptake, i.e. the body burden, is of significance in the case of toxic substances with systemic effects. This is the reason why already in 1970 the Working Group "Analyses of Hazardous Substances in Biological Materials" was founded by the Deutsche Forschungsgemeinschaft (DFG) Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, followed by the foundation of the Working Group "Setting of Threshold Limit Values in Biological Materials" in 1979. Since 1981 biological tolerance values for occupational exposure (BAT values) have been published in the German List of MAK and BAT Values of the DFG. By doing so, Germany was the first country worldwide to have established biological threshold limit values for workers exposed to hazardous substances. In 2007 the German List of MAK and BAT values includes threshold limit values for more than 90 substances and thus still represents the most comprehensive list of threshold limit values in biological material worldwide. The list is published in German and English and shows a widespread international distribution.

The original concept behind the BAT values is the principle of individual protection of employees exposed to hazardous chemical compounds (Lehnert 1980). The exposure–effect model, which is based on the stress–strain concept known from the fields of physiology and psychology, was used to infer which biological or health effects resulting from exposure to hazardous substances should be

considered to be tolerable. Tolerable effects appear to be those which also on a long-term basis:

1. do not, after regular exposure, result in a disturbance in the sequence of functions or in the ability to compensate exposure effects,
2. are reversible after the end of exposure,
3. do not increase the sensitivity of an organism to other external influences, especially physical, chemical and biological ones,
4. do not endanger progeny.

The BAT value was defined as the maximum permissible quantity of a chemical substance or its metabolites or the maximum permissible deviation from the norm of biological parameters induced by these substances. The BAT value was established on the basis of currently available scientific data which indicate that these concentrations generally do not affect the health of the employee adversely, even when they are attained regularly under workplace conditions.

At the time this definition was elaborated, only relatively few investigations existed that systematically dealt with the relationship of internal exposure and the thereby induced effects. The first BAT values evaluated were of such an order of magnitude that, after this value had been exceeded, adverse effects could be expected to occur occasionally, and this means that these values were in the range of the LOEL (lowest observed effect level). The first limit values on this basis (lead, trichloroethene, toluene) were published by Angerer et al. (1981), Bolt (1981) and Schaller and Valentin (1980) and therefore made available for discussion by experts. Moreover the critical data evaluations of all BAT values were published in a serial edition of the Deutsche Forschungsgemeinschaft (1983–2007). Since 1994 the critical data evaluations are also available in English (DFG 1994–2005). With an increasing amount of data becoming available and the ongoing discussion about no longer tolerable effects, more precise parameters and their deviations from the norm were considered to be decisive for the determination of the limit value, a fact which necessarily led to a continuous lowering of the BAT values. Lauwerys (1994) had recorded the problems of deducing biological tolerance values as early as in 1994. These generally known difficulties lie in the assessment of epidemiological studies, i.e. in the selection bias and here especially in the "healthy worker effect" or in the "observer bias". Very often, study collectives are too small and control collectives are lacking. In studies carried out to answer toxicological questions, an exact exposure monitoring is only available for the current exposure in most of the cases; exposures that occurred long ago have to be estimated. In addition, exposure to a single substance at the workplace is surely the exception, the rule being exposure to a mixture of various chemical compounds either simultaneously or in succession. Another problem that must not be negated is that of uncertainties in the assessment of the parameters (i.e. analytical and pre-analytical reliability, biological relevance and relevance of the findings for health, diagnostic sensitivity and specificity) (Zielhuis and Verberk 1974).

For these reasons, both the American Conference of Governmental Industrial Hygienists (ACGIH), the American counterpart of the German Commission, and the Scientific Committee on Occupational Exposure Limits (SCOEL), the corresponding body of the EU, have argued that biological limit values do not permit a distinction to be made between a hazardous and a non-hazardous exposure. The biological values derived by these commissions are therefore to be understood as averages, which may well be exceeded individually, in contrast to the BAT values that were defined as ceiling values and thus did not allow value transgression in the individual employee. Reference has been made a number of times to the resultant discrepancies in limit values in biological material in various countries and to the misinterpretations of these discrepancies (Morgan and Schaller 1999; Omae et al. 1999; Wilson 1999).

The DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has now reviewed the concept of biological limit values (Drexler et al. 2007). The following arguments convinced the DFG commission of the fact that the concept of the biological tolerance value used to date has to be revised:

1. A biological limit value does not permit a sharp distinction to be made between hazardous and non-hazardous exposure. The reasons for this include the intra-individual variability both with regard to the resulting internal exposure, for example from the daily varying conditions of occupational hygiene, varying physical activity, varying amounts of additional non-occupational exposure, or from influences on the renal excretion behaviour and also with regard to the resulting adverse effects on health.
2. From an analytical point of view each measured value has a method-related variance attached. The parameter concentrations to be recorded during biological monitoring are, as a rule, in the analytical trace or ultra-trace range and can thus vary, even if only to a relatively marked extent.
3. The scientific literature on which derivation is based as a rule refers to the averages of collectives, without taking adverse effects on health occurring from extreme values into special consideration, nor describing them in a differentiated manner.

In addition, there are also intra-individual differences due to the individual susceptibility as conditioned by genetic enzyme disposition, age, sex, previous illnesses, life style and a varying physical constitution. Irrespective of these

difficulties in deriving values for the evaluation of occupational medical and toxicological measured data, the DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area is of the opinion that the concept of using biological monitoring as an instrument of individual prevention is nevertheless to be retained. A concept based on a collective average alone would push the advantages of biological monitoring into the background. The decisive fact is not whether a BAT value at the workplace is observed by a collective of several employees, but rather to what extent an individual worker has been exposed.

Against this background, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the Deutsche Forschungsgemeinschaft has decided to work out a new definition for the BAT values and BLWs.

Definition

The Commission establishes BAT values (''Biologische Arbeitsstoff-Toleranzwerte'': biological tolerance values for occupational exposures) and BLWs (''Biologische Leitwerte'') with the aim of being able to assess an individual health risk resulting from exposure to a particular chemical substance at the workplace.

The BAT value describes the concentration of a chemical substance, of its metabolites or of an effect indicator in appropriate biological material derived by the occupational medical and toxicological criteria, at which the health of an employee is usually not affected, even after repeated or long-term exposure. BAT values are based on a relationship between external and internal exposure or between internal exposure and the effect of the substance caused by such an exposure. In this case, derivation of the BAT value is based on the average internal exposures.

The BAT value is exceeded if the average concentration of the parameter in one person is above the BAT value after several investigations; values exceeding the BAT value must be evaluated on an occupational medical and toxicological basis. If the BAT value is exceeded only once, an adverse effect on health cannot necessarily be inferred.

In the case of carcinogenic substances and substances with insufficient database, BLWs, which are also defined as mean values, are derived wherever possible.

Explanations on definition

The introductory section of the definition pointed out that it is the individual health risk that is to be primarily assessed. In terms similar to those of clinical medicine (e.g. via determination of the LDL cholesterol, arterial blood pressure, etc.) it should be possible, using the results of biological monitoring, to assess the risk of an exposure to chemical substances. This takes account of the fact that biological monitoring is a method of individual prevention used by the physician which, among other factors, is subject to full medical discretion.

Just as stated in the original definition of the BAT value, the worker should be protected even during life-long exposure. There was also no need of change with regard to tolerable deviations of workplace-related exposure-specific effects. What is new, however, is the statement that the derivation of the BAT value is based on average exposures. Therefore, the average value of reference is for the first time explicitly mentioned in the new definition. In the past, however, it had already often been necessary to base BAT derivations on average values, since the literature used as a basis has often not allowed for other statements to be made.

In order to justify the demand that biological monitoring has to remain an instrument of individual prevention, it has been specified in the definition of the BAT value that this value is exceeded if, after subjecting a person to several examinations, the average parameter concentration is above the BAT value. This constitutes a decisive difference to the definition of the BEI (Biological Exposure Indices) of the American Conference of Governmental Industrial Hygienists (ACGIH) and of the BLV (Biological Limit Value) of the European Scientific Committees for Occupational Exposure Limits (SCOEL). According to its definition, biological monitoring comprises repeated measurements of a substance or its metabolites in biological materials (Zielhuis 1984). The individual remains the aim of protection even after redefinition of the BAT value. In the German concept it is still required that only a physician specialized in occupational medicine is in a position to interpret the measured values. Measured values above the BAT value have to be assessed on the basis of occupational medical and toxicological criteria. The assessment also has to specify how the time intervals of control examinations and the measures for exposure reduction are established and proved.

The hereby introduced new definition again leads to the fact that a BAT value cannot be established for carcinogenic substances for which no threshold concentrations can be derived. However, the Working Group "Setting of Threshold Limit Values in Biological Materials" tries to evaluate BLWs (Biologische Leitwerte) for carcinogenic substances, if this appears to be meaningful, based on the data available for the non-carcinogenic effects of chemical substances. Otherwise, in the case of stochastic damage, which can be expected with a concentration-dependent probability, the legislator is requested to determine the risk acceptable to society.

With this redefinition of the German BAT value, it will be possible to better harmonize the values with those provided by other commissions, which are also based on an average concept, without having to give up the concept of individual prevention. According to the Guidelines for Occupational Medical Examinations of the German Social Accident Insurance (DGUV 2007) biological monitoring is clearly characterized as an occupational medical instrument that is exclusively within the responsibility of the physician. Here too, it seems to be helpful to view the results of biological monitoring more as a measure of risk and less as rigid limit values. From a legal point of view, it is not the responsibility of physicians employed in industry to change exposure conditions. However the knowledge obtained by the company physician from biological monitoring, among other things, should be used in advising the employer according to occupational health measures without violating professional secrecy.

References

Angerer J, Behling K, Lehnert G (1981) Biologische Arbeitsstoff-Toleranz-Werte: BAT-Wert für Toluol. Arbeitsmed Sozialmed Präventivmed 16:161–164

Bolt HM (1981) Biologische Arbeitsstoff-Toleranz-Werte: BAT-Wert für Trichloräthylen. Arbeitsmed Sozialmed Präventivmed 16:116–121

Deutsche Forschungsgemeinschaft (DFG): biological exposure values for occupational toxicants and carcinogens. Critical Data Evaluation for BAT and EKA Values, vols. 1–4. Wiley, Weinheim (1994–2005)

Deutsche Gesetzliche Unfallversicherung (DGUV): Prophylaxis in occupational medicine. Guidelines for occupational medical examinations. Gentner, Stuttgart (2007)

Drexler H, Göen T, Schaller KH (2007) Biologischer Arbeitsstoff-Toleranzwert (BAT-Wert). Ein Paradigmenwechsel von der Einzelwert-betrachtung zum Mittelwert-konzept. Arbeitsmed Sozialmed Unweltmed 42:514–516

Lauwerys RR (1994) Health-based occupational exposure levels to chemicals: interpretation of human data. Appl Occup Environ Hyg 9:689–692

Lehnert G (1980) Biologische Arbeitsstoff-Toleranz-Werte: Ein Konzept zur Individualprävention bei Exposition gegenüber gesundheitsschädlichen Arbeitsstoffen. Arbeitsmed Sozialmed Präventionsmed 80:266–220

Morgan MS, Schaller KH (1999) An analysis of criteria for biological limit values developed in Germany and in the United States. Int Arch Occup Environ Health 72:195–204. doi:10.1007/s004200050362 Medline

Omae K, Takebayashi T, Sakurai H (1999) Occupational exposure limits based on biological monitoring; the Japan Society for Occupational Health. Int Arch Environ Health 72:271–273. doi:10.1007/s004200050372

Schaller KH, Valentin H (1980) Biologische Arbeitsstoff-Toleranz-Werte: BAT-Werte für Blei und seine anorganischen Verbindungen. Arbeitsmed Sozialmed Präventivmed 15:277–287

Wilson KH (1999) Biological monitoring values for occupational exposure: a United Kingdom perspective. Int Arch Occup Environ Health 72:274–278. doi:10.1007/s004200050373 Medline

Zielhuis RL, Verberk MM (1974) Validity of biological tests in epidemiological toxicology. Int Arch Arbeitsmed 32:167–190. doi:10.1007/BF00539335 Medline

Zielhuis RL (1984) Recent and potential advances applicable to the protection of workers' health—biological monitoring. In: Berlin A, Yodaiken RE, Henman BA (eds) Assessment of toxic agents at the workplace—roles of ambient and biological monitoring. Commission of the European Communities, Brüssel, pp 84–94