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Mini-review

Biological monitoring and Biological Limit Values (BLV): The strategy of the European Union

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Abstract

Occupational standards concerning allowable concentrations of chemical compounds in the ambient air of workplaces have been established in several countries worldwide. With the integration of the European Union (EU), there has been a need of establishing harmonised Occupational Exposure Limits (OEL). The European Commission Directive 95/320/EC of 12 July 1995 has given the tasks to a Scientific Committee for Occupational Exposure Limits (SCOEL) to propose, based on scientific data and where appropriate, occupational limit values which may include the 8-h time-weighted average (TWA), short-term limits/excursion limits (STEL) and Biological Limit Values (BLVs). In 2000, the European Union issued a list of 62 chemical substances with Occupational Exposure Limits. Of these, 25 substances received a "skin" notation, indicating that toxicologically significant amounts may be taken up via the skin. For such substances, monitoring of concentrations in ambient air may not be sufficient, and biological monitoring strategies appear of potential importance in the medical surveillance of exposed workers. Recent progress has been made with respect to formulation of a strategy related to health-based BLVs.

Keywords: Biological exposure limits; Biological monitoring; European Union; Occupational Exposure Limits

Contents

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1. Introduction

Since several decades, the setting of occupational standards for chemical compounds in the ambient air at workplaces has been developed as a preventive tool in occupational hygiene and medicine. Early scientific roots date back to Lehmann (1886) who was the first to perform systematic studies on workers exposed to some occupational toxicants. By 1938, occupational exposure standards had been established in Germany for about 100 substances (Henschler, 1985). In the United States, a provisional list of eight compounds was compiled in 1942, and the first official list of threshold limit values (TLV) was issued in 1946 (Cook, 1985).

In 1953, Oettel intended to establish a unified European list of standards, but failed (Henschler, 1985). As a consequence, most European countries started to use the American TLV list. In 1958, Germany started to develop an own list of MAK values which was later used, either as a whole or in parts, together with the TLV list, also by other European countries (Austria, Switzerland, The Netherlands and Nordic countries). However, differences in the industrial, social and constitutional structure of European countries prevented an early establishment of a unified European list of occupational standards (Henschler, 1985).

2. Biological exposure values—initial developments

Progress in analytical chemistry, toxicokinetics and toxicodynamics opened new possibilities of monotoring toxicants in biological media. A first official reference to biological exposure limits has been made in the preface of the 1974 edition of the TLV booklet. It was noted that measurements may be made of substances to which the worker is exposed, based on analysis of blood, urine, hair, nails, body tissues, fluids and exhaled breath, or the amount of metabolites in tissues and fluids (Cook, 1985). In Germany, a first set of three Biological Limit Values (BLV) (lead, toluene and trichloroethylene) was introduced with the MAK list 1981 (“Biological Tolerance Values”, BAT), and another six compounds were added in 1982 (i.e., cadmium, mercury, dichloromethane, halothane and perchloroethylene). More recently, a comprehensive compendium of the strategy of biological monitoring in general was issued (Lehnert and Schaller, 2000), and future perspectives were highlighted (Deutsche Forschungsgemeinschaft, 2000).

The first American Biological Exposure Indices (BEI) was published by ACGIH in 1984. At that time, a broad international discussion on biological standard setting had been initiated, as evidenced by contributions from Belgium, Denmark, Italy, Poland, Sweden, Switzerland and the USA at an ACGIH/WHO Symposium in April 1985 (ACGIH, 1985). These discussions also led to the development of guidelines for biological monitoring (Lauwerys and Hoet, 2001).

The present list of BEI values contains 41 entries (ACGIH, 2004) and the German BAT value list has evaluated 78 compounds (Deutsche Forschungsgemeinschaft, 2004), visualising the considerable potential of biological monitoring strategies.

3. Development of Occupational Exposure Limits in the European Union

With the growing integration of the European Union (EU), there was a need of harmonising national workplace standards, backed by the EU policy to remove trade barriers between its member states (Thier and Bolt, 2001).

In particular, the Council Directive 80/1107/EEC (European Union, 1980), amended by Council Directive 88/642/EEC (European Union, 1988), introduced the objective of establishing Occupational Exposure Limits (OEL). This Directive considered two types of Occupational Exposure Limits: Binding Limit Values and Indicative Limit Values (ILVs). The latter were intended to be the more common type of limit, reflecting evaluations based on scientific data.

The first set of ILVs was introduced by Commission Directive 91/322/EEC (European Union, 1991); these ILVs for 27 chemicals (or groups of chemicals) were proposed by the Commission and agreed by member states on the basis of pre-existing national positions. At the same time, the Commission assembled an advisory group of experts in the disciplines of toxicology, epidemiology, occupational medicine, occupational hygiene and analytical chemistry. This “Scientific Committee on Occupational Exposure Limits” (SCOEL, formerly called the “Scientific Expert Group”, SEG) had as its major remit the role of examining appropriate scientific documentations, usually in the form of criteria documents, on the toxicological and other relevant properties of chemicals and to recommend to the Commission values for substance-specific Occupational Exposure Limits (SCOEL, 1998). In 2000, the European Union issued a list of 62 chemical substances with Occupational Exposure Limits.

At that time, it had been recognised that biological monitoring, entailing the measurement of substances,

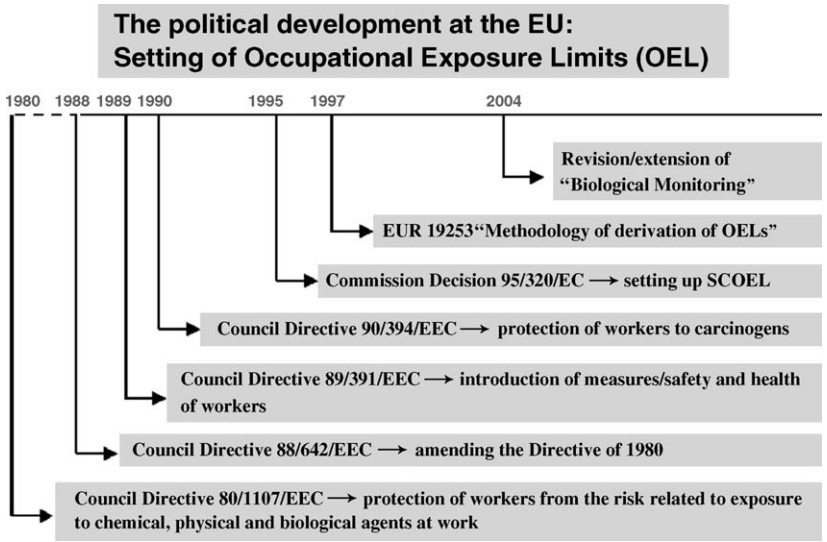

Fig. 1. Time sequence of steps towards an official implementation of biological monitoring by the European Union.

metabolites or adducts in biological media, or the measurement of non-adverse biological effects induced by the substance, was an important means to protect the health of workers. Details of the procedures used in deriving both OELs (analysis of substances in ambient workplace air) and Biological Limit Values (use of biological media) were communicated (SCOEL, 1999). A key compound, with respect to general issues of biological monitoring and Biological Limit Values, has been lead for which a BLV of 30 μg/100 ml blood has been proposed (SCOEL, 2003).

The time sequence of implementation steps by the European Union is visualised in Fig. 1.

4. Skin notation and consequences for biological monitoring

Skin penetrating compounds may exert systemic toxic effects, which cannot efficiently be prevented on the basis of analytical control of the workplace air alone. Lists of Occupational Exposure Limits include designations of such compounds ("S" for skin, "H" for Haut or huid, etc.). In Germany, for such compounds (marked "H") the use of biological monitoring strategies has been officially recommended (Anon., 1996), and an official Technical Guidance Note issued by the Federal Ministry of Labour and Social Affairs gave indications of the legal and organisational frame for biological monitoring (Anon., 2000).

5. Biological monitoring—the strategy of the European Union

Scientific advances in biological monitoring of chemical exposures have led to progress in establishing legal frameworks (Bolt, 1999).

The European Commission Directive 95/320/EC of July 12, 1995, setting up the aforementioned Scientific Committee for Occupational Exposure Limits, describes the tasks of the Committee as follows [article 2(1) of this Directive]:

> "The Committee shall in particular give advice on the setting of Occupational Exposure Limits based on scientific data and, where appropriate, shall propose values which may include:
>
> - the 8-h time-weighted average (TWA);
> - short-term limits/excursion limits (STEL) and
> - Biological Limit Values" (European Union, 1995).

In 1999, SCOEL has published a Methodology for the Derivation of Occupational Exposure Limits. This included a first definition of Biological Limit Values that was later amended:

> "Biological monitoring entails the measurement of substances and/or metabolites in biological media, and the measurement of biological effects induced by the substance. Biological Limit Values are reference values for the evaluation of potential health risks in the

practice of industrial hygiene. They are established on the basis of currently available scientific data. Exposure concentrations equivalent to the BLV generally do not affect the health of the employee adversely, when they are attained regularly under workplace conditions (8 h/day, 5 days/week). In general, OELs and BLVs are based on similar quantities of internal exposure; in this case, the BLV is related to a group means. In cases of a high health impact of individual peak exposures, a BLV may be conceived as a ceiling value for individual persons, dependent on its justification".

Moreover, details of a biological monitoring strategy have been put forward, as outlined below.

6. Approaches to biological monitoring

Biological methods used to assess exposure and/or risks to health are considered to fall into the following categories:

(1) Determination of the substance or its metabolite in a biological medium (*biological exposure monitoring*). Most methods fall into this category, with the medium of choice usually being blood, urine, or occasionally, exhaled breath. The method may either be specific for a particular substance or general for a group of related substances. The level determined may reflect exposure over widely different time periods, depending on the kinetics of the substance, the medium involved and the time of sampling.
(2) Measurement of biological effects (*biological effects monitoring*). This involves the measurement of parameters of biological response (e.g., erythrocyte cholinesterase activity for organophosphates).

A powerful possibility of biological exposure monitoring is determination of macromolecular adducts of toxicants or their metabolites (e.g., adducts to haemoglobin or to serum albumin). The determination of haemoglobin adducts provides an integrated measure of the effective internal exposure over a longer period of time, due to the life span of erythrocytes.

7. Airborne limits (OELs) and biological limits (BLVs)

BLVs are representative of the levels of determinants, which are observed in workers exposed to the respective chemical, exclusively by inhalation, at the level of the respective OELs.

Exceptions are the BLVs for substances for which the OELs serve as protection against non-systemic effects (e.g., irritation or respiratory disorders) or for substances, which require biological monitoring due to other routes of absorption, in particular, the skin.

BLVs do not indicate a sharp distinction between hazardous and non-hazardous exposures. Due to biological variability, it is possible for an individual's measurement to exceed the BLV without incurring in increased health risk. If, however, measurements in specimens obtained from a worker on different occasions persistently exceed the BLV, or if the majority of measurements of specimens obtained from a group of workers at the same workplace exceed the BLV, the cause of the excessive values must be investigated and proper action taken to reduce the exposure.

BLVs for working schedules other than 8 h exposures, 5 days a week, may be extrapolated on toxicokinetic and toxicodynamic bases. Attention should be paid to determination of the correct sampling time point. In cases of long half-life of toxicants (e.g., lead), or of biological effect monitoring, the sampling time points for biological monitoring are even independent of exposure profiles (as exemplified by Bolt and Rutenfranz, 1988).

The biological monitoring of genotoxic carcinogens requires a separate discussion. When a health-based OEL cannot be derived, the same consequence relates to the BLV. However, biological monitoring procedures can successfully be applied for a number of important industrial carcinogens (Lewalter, 1986). In cases where technically based exposure limits are set, corresponding biological limits may be documented (Deutsche Forschungsgemeinschaft, 2000).

8. Biological media

The choice of biological medium depends on kinetic factors, the convenience of sample collection and the possibility of sample contamination.

(1) *Blood*. Since this is the main vehicle for transport and distribution, most systematically active substances and their metabolites can be found in blood. The medium is useful for inorganic chemicals and for organic chemicals, which are poorly metabolised and have a sufficiently long half-life.
(2) *Urine*. Urine collection is easier, less invasive and more readily accepted by workers. It is usually suitable for water-soluble metabolites of organic substances and for some inorganics.

The concentration of a substance in urine usually reflects the mean plasma level during the period

of urine accumulation in the bladder. End of shift samples is appropriate for rapidly excreted substances, such as solvents; 24-h specimens (although rarely collected) may be more representative in some cases. The concentration of a substance in urine will depend on the rate of urine production, and correction of results on the basis of creatinine concentration or density may be necessary. Contamination during collection can be a source of error.

(3) *Breath*. Exhaled air analysis may be used to estimate exposure to volatile organic substances (solvents), although it is much less frequently used than blood or urine sampling. The method is non-invasive, but involves a risk of external contamination.

Concentrations will vary depending on whether they are measured in "end exhaled" air (alveolar) or in "mixed exhaled" air (normal breathing). Timing of sampling is very critical in determining whether the measurement reflects very recent exposure or exposure during the previous day. Concentrations can also be influenced by a variety of physiological factors.

Whichever medium is chosen, it is important to establish a sampling strategy, based on knowledge of the kinetics of the biological marker in question.

9. Analysis and interpretation of results

Careful attention must be paid to both pre-analytical (sample collection, transport and storage) and analytical methodology and the derivation of the analytical detection limit to ensure accuracy.

Each aspect of biological monitoring should be conducted within an effective quality assurance (QA) programme. The appropriate specimen must be collected, at the proper time, without contamination or loss, and with use of a suitable container. Donor identification, time of exposure, source of exposure and the sampling time must be recorded. The analytical method used by the laboratory must have the accuracy, sensitivity and specificity needed to produce results consistent with the BLV. Appropriate quality control specimens should be included in the analysis, and the laboratory must follow routine quality control rules. The laboratory should participate in an external quality control programme.

Like any results of laboratory investigations, biomonitoring results can only be evaluated given knowledge of the whole situation. As well as the other medical findings, especially

Table 1
Proposals of Biological Limit Values by SCOEL (SCOEL, 1998, 2003)

	OEL	BLV
Carbon monoxide	20 ppm	4% CO–Hb in blood
Lead (inorganic)	0.1 mg/m^3	30 μg Pb/100 ml blood
2-Butoxyethanol	Biological monitoring may be appropriate	
Sulfotep	Biological monitoring recommended	

OEL, Occupational Exposure Limit (for ambient air).

- the dynamics of pathophysiological processes;
- the short-term effects of exposure-free periods;
- the long-term effects of ageing;
- the specific workplace conditions;
- intensive physical activity and unusual conditions of atmospheric pressure and
- any individual background exposures must be taken into account.

As any other clinical laboratory data, biological monitoring data need to be interpreted by a physician.

Some BLVs, referring to urinary excretions, are expressed relative to ceatinine concentrations. In first instance, this refers to compounds for which the relevant studies are only documented, based on urinary creatinine values.

10. Summary and current state

- By decision of 12 July 1995, the European Commission has established the Scientific Committee on Occupational Exposure Limits, with the mandate to give advice on Occupational Exposure Limits and Biological Limit Values.
- SCOEL has proposed a BLV for inorganic lead in blood of 30 μg Pb/100 ml, and there are current discussions on a number of compounds to be assigned with a BLV (Table 1).
- A general strategy related to health-based BLVs has been formulated.
- Compounds with a "skin notation" are viewed as priority candidates for a BLV assignment.
- In general, there is a clear political tendency in Europe from national towards supranational (EU) regulations in the entire field of occupational safety and health.
- Improvements of regulations on chemical substances are receiving high political priority and interest, as exemplified by current discussions on the "New Chemicals Policy" of the European Commission (see: http://europa.eu.int/comm/environment/chemicals/reach.htm).

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