

# Guidance values for the biomonitoring of occupational exposure. State of the art

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## KEY WORDS

Biological monitoring; guidance value; speciation

## SUMMARY

*Biomonitoring was developed for the assessment of the health risks from exposure to chemicals at work, and the approaches and concepts of biomonitoring are derived from such exposures. At present, biomonitoring is increasingly used also to assess exposure from the environment. Biomonitoring and assessment of external exposure are complementing activities, where the exposure assessments are much more widely applied, especially when the number of chemicals concerned is considered; environmental analysis also offers the distinct advantage of speciation analysis – which is very poorly developed for biomonitoring. Biomonitoring on the other hand provides information on exposure from all sources, and via all absorption routes, and considers also accumulation of the chemical in the body. Biomonitoring using exposure biomarkers thus consider interindividual differences in the absorption, while use of effect biomarkers ideally also considers interindividual differences in sensitivity. Few effect biomarkers, however, have been validated. The major challenges of biomonitoring are the development of monitoring methods, which are inexpensive enough to be applied at a frequency that makes possible meaningful biomonitoring of chemicals with a short half-time; development of exposure biomarker guidance values specific to individual species of different metals; expansion of the repertoire of validated effect biomarkers; and validation and application to effect monitoring of the omic technologies. Another major challenge is a reconsideration of the basis of biomonitoring action limits to reflect the change in the work place. Biomonitoring should be adapted to assist in the generation of a healthy workplace, which is capable of attracting workers, and assist them to perform their work effectively – rather than just to guarantee absence of serious health effects.*

*l'accumulo dell'agente chimico nel corpo. Inoltre, il monitoraggio biologico, attraverso gli indicatori di esposizione, considera le differenze interindividuali nell'assorbimento, mentre l'utilizzo di indicatori di effetto idealmente permette di considerare la variabilità individuale di sensibilità. Anche se pochi sono gli indicatori di effetto validati. Le sfide principali del monitoraggio biologico sono (i) lo sviluppo di metodi di controllo che siano sufficientemente economici da essere applicati con una frequenza tale da rendere possibile un monitoraggio efficace di agenti chimici con un breve tempo di dimezzamento; (ii) lo sviluppo di valori guida di indicatore di esposizione specifico per le singole specie di metalli differenti; (iii) l'ampliamento del repertorio di indicatori di effetto validati; e (iv) la validazione e l'applicazione al monitoraggio degli effetti delle tecnologie "omiche". Un'altra importante sfida è la riconsiderazione delle basi dei limiti di azione del monitoraggio biologico nel riflettere i cambiamenti negli ambienti di lavoro. Il monitoraggio biologico deve essere adatto al fine di aiutare la creazione di un posto di lavoro sano, che sia capace di attrarre i lavoratori, di favorirli nello svolgere il loro lavoro in maniera efficace, piuttosto che garantire solo l'assenza di seri danni alla loro salute.*

## INTRODUCTION

The first paper on biomonitoring - on the use of the analysis of lead in urine in exposed workers as means of diagnosing lead-induced industrial disease - was published in 1927 (6). We thus approach the 80<sup>th</sup> anniversary of biomonitoring. Biomonitoring has its origins and widest area of application in the assessment of exposure to chemicals at work, but it has made important contributions also to the assessment of health hazards from environmental exposure, and at present an extensive programme on environmental biomonitoring is in progress in the US (<http://www.cdc.gov/exposurereport/>) and another is planned in Europe ([http://www.euro.who.int/eehc/implementation/20051017\\_1](http://www.euro.who.int/eehc/implementation/20051017_1)). Widely publicized results of analyses of environmental chemicals in the blood and urine of populations have raised concerns, when the interpretation and limitations of the results have not been clear (<http://today.reuters.com/News/CrisesArticle.aspx?storyId=L05670176>).

In risk assessment of metal exposures, indicators of effects and indicators of exposure have been considered in several consensus documents, published since the 1970:s by the Scientific Committee on the Toxicology of Metals of the International Commission of Occupational Health (ICOH) (7, 9, 21, 22). Authoritative reviews on different aspects of biological monitoring, including analytical methods, reference values, and guidance values, have been published by IPCS, WHO and others (1, 4, 10, 11, 13-15, 23, 24). The term "Biological Monitoring" (synonym Biomonitoring) has been

used for a long time and more widely during the last two decades (8, 9) to describe exposure and internal dose of metals by measurements in biological samples such as blood and urine and other human tissues and fluids.

A *biomarker* is an indicator signalling an event or condition in a biological system or sample, giving a measure of exposure, effect or susceptibility (17).

A *Biomarker of exposure* relates exposure to a xenobiotic (*i.e.*, a metal or metal compound) to the levels of this substance or its metabolite, or of the product of an interaction between the substance and some target molecule or cell that can be measured in a compartment within an organism (13, 17).

A *biomarker of effect* is a biomarker that, depending on its magnitude, can be recognised as associated with an established or possible health impairment or disease (13, 17).

There are some examples of useful *biomarkers of early (critical) effects*. One such example is the detection of early damage to the kidney tubules by cadmium using urinary levels of low molecular weight proteins such as beta-2-microglobulin, protein HC and the enzyme N-acetylglucosaminidase.

## INTERPRETATION OF BIOMONITORING RESULTS

A prerequisite of a meaningful interpretation of biomonitoring results is an accurate chemical analysis. Although analytical techniques have developed dramatically in the last few years, the ana-

lytical quality still is of major concern, and an efficient external quality control such as those provided by e.g. the German Society for Occupational and Environmental Medicine, Erlangen, Germany (<http://www.g-equas.de/>), Finnish Institute of Occupational Health ([http://www.ttl.fi/search/MsmGo.exe?grab\\_id=149&page\\_id=11534848&query=quality+assurance&hiword=assurance+quality+](http://www.ttl.fi/search/MsmGo.exe?grab_id=149&page_id=11534848&query=quality+assurance&hiword=assurance+quality+)), United Kingdom National External Quality Assessment Service (<http://www.ukneqas.org.uk/anage/overview.htm>), Robens Institute of Industrial and Environmental Health, Guildford, UK (<http://www.surrey.ac.uk/SBMS/eqas/index.html>) and Toxicology Centre, Québec, Canada (<http://www.ctq.qc.ca/ctqintre.html>), should be a part of all biological monitoring programmes.

A feature that distinguishes biomonitoring of chemicals from e.g. clinical chemistry analyses, is the dependence of the concentration of the chemical of the kinetics and exposure pattern: At work, the exposure is at most for a period of 8 hours daily, and very often is limited to only short periods of time within the working hours. Some chemicals or their metabolites have a very short half time in the body, especially in blood, and thus the concentration drops very rapidly immediately after the exposure – and the concentration measured may reflect more the time lapse between exposure and sample collection than the actual original concentration while the exposure takes place. This will lead to badly distorted assessment of the exposure – and of the risk involved, and even to the conclusion that there is no exposure when in fact there was exposure but by the time the sample was collected all chemical has disappeared from the blood. While the excretion in the urine functions as a buffer and the problem thus is not equally conspicuous, all biomonitoring requires knowledge of the timing of the sample collection, and of the kinetics of the analyte measured in that matrix.

Biomarkers of exposure may be used to identify exposed individuals or groups, quantify the exposure, assess the health risks, or to assist in diagnosis of (environmental or) occupational disease. The first two depend on a comparison of the results with reference values, the latter two to a comparison to biomonitoring action limits.

## IDENTIFICATION OF EXPOSED PEOPLE

For the identification of the exposed, the analytical results are compared to the reference interval for the element in the matrix studied. Reference intervals are derived from reference values observed in a reference population, usually as the 95th percentile – meaning that 1 out of 20 non-exposed will give a result outside the reference range. As the reference values are different in different geographic locations (mainly because of variation in exposure via the diet), reliable identification of exposure crucially depends on reference values determined in the area of analysis, and is up-to-date. There is considerable variation among countries depending on a combination of geological factors, dietary habits and anthropogenic exposures that may affect a whole country (18). Examples are mercury levels in blood and hair which are much dependent on the fish consumption in the population studied (19, 20). Cadmium levels are higher in Japan than in other countries, probably due to a low level contamination of rice which originates from a combination of geological factors and mobilisation of Cd into the environment by human activities (12). Year-by-year fluctuations in selenium levels have been recorded in the Finnish population related to the wide distribution of selenium-rich imported wheat some years when the local crops were insufficient (5). While dietary exposure to the chemical is the main component of the reference values, factors such as smoking also have to be considered: reference values of cadmium in blood and urine, and also of benzene /its metabolites, or toluene in blood, are different for smokers. The main obstacle for biomonitoring of platinum is the platinum derived from dental prostheses, which overshadows any occupational or environmental exposure.

As discussed above false negative results will be obtained if the timing of the specimen collection is not appropriate.

A biomarker level above the reference limit does not tell anything of a possible health hazard – it simply means that the individual has been exposed to a greater extent than the reference population.

Reference values are intended to identify exposed individuals; if biomarker concentrations are

available for several members of a group, a more appropriate assessment of the exposure situation of the group is obtained from a statistical comparison of the exposed group and the reference population.

### QUANTITATION OF EXPOSURE

In occupational settings, quantitation of exposure usually refers to a comparison of the amount absorbed in the body at an exposure equivalent to the occupational exposure limit rather than to the derivation of a dose *e.g.* in mg/kg body weight. The situation is quite complicated in environmental biological monitoring, there is not similar point of reference, and the assessment of the dose is done by modelling; data required for the modelling is only available for few chemicals.

Quantitation of exposure relies on knowledge on the relationship between the exposure, usually measured the time-weighted average concentration of the chemical in the air, and the concentration at a specified time, of the biomarker in the blood or urine - or in rare cases, other biological media.

The robustness of different biomarkers as quantitative indicators of exposure varies: for some, such as mandelic/phenylglyoxalic acid in urine in exposure to styrene, thiothiazolidine carboxylic acid in urine in exposure to carbon disulphide, or chromium in urine in manual metal arc welding, or methylmercury in blood or hair in dietary exposure, the relationship is well known, and several studies give similar results. On the other hand, while for some chemicals individual studies show a relationship between exposure and the biomarker level, individual studies give different results - such as dimethylformamide, hexane, or cobalt. For some further chemicals, only very limited database is available and thus there is a major uncertainty - such as benzene or toluene in blood or urine, or the arsenic metabolites in exposure to arsenic trioxide.

As discussed above, consideration of the kinetics and appropriate timing of specimen collection are prerequisites of accurate exposure assessment. If the half-time is shorter than say 6 hours, it may be impossible to do any quantitative biomonitoring. Concentration in the urine is related to the time-

weighted average concentration in blood (or actually to the free concentration in plasma). Thus for elements with a short half-time in the blood, it may be kinetically advantageous to analyse the urine rather than blood

For many chemicals, the disappearance from the blood exhibits several consecutive half-times, and thus by an appropriate sampling strategy, an idea of exposure over different time periods may be obtained: *e.g.*, concentration of chromium in the urine of manual metal arc welders on Friday afternoon reflects mainly exposure over that day, that in a Monday morning urine specimen, exposure over the preceding week (3).

Quantitation of exposure in itself does not give an indication or prediction of adverse health effects. However, for several chemicals, follow-up studies among exposed worker populations - in which the level of exposure is known - allow assessment of the risk. If in addition. The relationship between the biomarker levels and the exposure is known, an indirect estimation of health risks may be achieved from biomonitoring data; this is the case for *e.g.* styrene, carbon disulphide, and dimethylformamide.

One of the areas where biomonitoring has traditionally been considered as best justified is the assessment of exposure of chemicals that are mainly absorbed through the skin, as traditional industrial hygiene measurements are not very informative. However, biomonitoring also has problems in this area: although it may measure the exposure very well, the result does not automatically render itself to interpretation, the question being, what does this result represent in terms of absorbed amount (or health risk). The answers must be sought from experimental exposure studies, comparisons between exposure exclusively via inhalation, and via the dermal route - but especially for very toxic, or carcinogenic chemicals, such experiments may not be possible to carry out. An important step forward, originally proposed by the British Health and Safety Executive, was to use levels observed in work places with good hygiene as the basis for determining, what is an acceptable biomonitoring result in these situations: they set the biomonitoring action limit to a level achieved in 90% of the #good work places.

## ASSESSMENT OF HEALTH RISK

Assessment of health risk of health risk from biomonitoring may be achieved if the relationship between the effects and the biomarker concentrations is known. This is the case for lead in blood, cadmium in blood and urine, methylmercury in blood and hair, and inorganic mercury in urine, and to a more limited extent, for arsenic in urine, carbon monoxide in blood, and fluoride in urine. For these elements, epidemiological studies are available, which have studied the relationship between the biomarker level and long-term health effects. In fact, for methylmercury, cadmium, and lead, the risk assessment is primarily based on biomonitoring. Such studies are difficult to carry out, and often the study results are not very consistent.

For some chemicals (styrene, carbon disulfide), an assessment of health risks may also be obtained indirectly from the relationship between health effects and external exposure (concentrations in the air) and that between the biomarker concentration and the concentration in the inhaled air.

## BIOMONITORING IN CLINICAL DIAGNOSIS

Chemically-induced adverse health effects or diseases usually are not different from the same disease induced by other causes, and thus a causal diagnosis, "etiognosis" depends on the clinical picture plus history of exposure considered sufficient to cause the disease. In the assessment of the history of exposure, biomonitoring when available is probably the best means as it provides direct information of the exposure of the individual.

## BIOMARKERS OF EXPOSURE AND INDUSTRIAL HYGIENE MEASUREMENTS

Biomonitoring most widely applied in occupational health, and thus has a similar objective as industrial hygiene measurements, assessment of exposure through measurement of the concentration in the air. While it is clear that for most chemicals, industrial hygiene measurements are the best and

often the only way of assessing exposure, the two approaches complement each other as their scope and performance are not identical.

Air is a homogeneous and relatively simple matrix, and therefore, sample preparation is often simple and straightforward, and analytical methods relatively easy. When the air-borne concentration of the chemical is low, the amount of air collected on the filter may be increased, and thus the sensitivity of the analysis improved. As air measurements also have a long tradition, established methods exist for the large majority of industrial chemicals. For several elements, fractionation and speciation analysis methods are available and thus important qualitative information on the exposure may be gained from such analyses.

On the other hand, concentrations of chemicals in workplace air are seldom stable but fluctuate with time and are different in different locations. The amount of a chemical that reaches the alveolar region of the respiratory tract is directly related to the volume of respiration and thus to the work load. Exposure peaks often coincide with increased workloads caused by e.g., the malfunctioning of a closed process. Several chemicals are absorbed also via the dermal route and the absorption via the skin is generally not related to the concentration in the air. Even when the exposure takes place mainly by inhalation, the bulk of the actual absorption may be via the gastrointestinal tract (notably aerosols with particle sizes too large to lead to deposition in the alveolar region). Personal working habits vary, and individuals may absorb different amounts of chemicals in apparently similar conditions. Protection afforded by personal protection devices varies depending on the user and on the condition of the device. Furthermore, biomarker, in contrast to industrial hygiene measurements, reflects the accumulation of the chemical in the body. Biomarkers of exposure, which reflect all this variation in exposure - and at the same time, exposure from all sources - are thus closer than industrial hygiene measurement to the toxicologically important concentration of the chemical at the target site (1).

Biomarkers of exposure do not consider inter [or intra]-individual differences in the toxicodynamics of the chemical - which are covered in an ideal case

of effect biomarkers. Biomarkers do not differentiate between sources of exposure and in order to decrease the risk from the chemical, it may be necessary to consider (and analyse) separately, from where the exposure is derived, from work or from e.g. hobbies, or environment.

Biomarkers of exposure reflect the amount of the chemical in the systemic circulation and models have been developed to predict concentrations in other compartments in the body. However, a major obstacle in the interpretation of biomonitoring data involves concentration and effects at the site of entry, such as the lungs after exposure to particulates containing metals: concentrations in the urine or even blood of nickel tell little of the concentrations or the health risks in the lungs after exposure to soluble or insoluble nickel. Similarly, irritation - a mainly concentration-related effect - is not easily assessed from exposure biomonitoring data.

### BIOMARKERS OF EFFECT

Biomarkers of effect have the intrinsic advantage that they may take into account differences in individual sensitivity to the chemical. Thus e.g. in exposure to cadmium, assessment of low-molecular weight protein in urine may be used to identify individuals who are exceptionally sensitive, i.e., develop adverse health effects at levels of exposure, at which individuals with normal sensitivity remain healthy. However, cadmium and its renal effects are practically the only case, where such an advantage can be achieved; no other biomarker of effect has been truly validated as a predictor of health effects, although a large variety of biomarkers of effect have been described for neurotoxicity, lung toxicity, and genotoxicity (2, 4).

### SPECIATION IN BIOMONITORING

With few exceptions, routine biomonitoring is dependent on the analysis of the total content of an element as the biomarker, rather than a speciation analysis. For some elements, this simplistic ap-

proach is well sufficient; this is notably the case when the key effect of the element on the health is systemic and the relationship between the total element concentration and the effect is known. Thus most of the time in occupational exposure, a reliable prediction of long-term health effects may be made from (total) lead in blood, (total) mercury in blood or urine, and total cadmium in blood or urine. However, in exposure to tetraethyl lead, or in exposure to methylmercury from diet, these analyses may be very much misleading. This error may be even more marked, when there is concomitant exposure to different species of the same metal. The toxicity, including mutagenicity and carcinogenicity of several metals is very much dependent on the identity of the elemental species - e.g. the oxidation state, inorganic vs. organic compounds of the same element. To overcome these problems, speciation analysis is an important aspect in biomonitoring now and in the future. Speciation in biomonitoring may be approached with three different strategies: analysis of specific element species (as of now, practically limited to arsenic), fractionation by chemical analytical means to organic vs. inorganic species (mercury, lead in blood mainly), or application to the analysis of information on the differences in the distribution of different species of an element (mercury in plasma, blood cells, urine; chromium in erythrocytes / plasma (15)).

Even when the total concentration of an element is measured, exposure indices of the individual species to which the population is exposed should be developed and used, when appropriate (15).

### FUTURE TRENDS

The major challenges of biomonitoring include the development of monitoring methods, which are inexpensive enough to be applied at a frequency that makes possible meaningful biomonitoring of chemicals with a short half-time; development of exposure biomarker guidance values specific to individual species of different metals; expansion of the repertoire of validated effect biomarkers; and validation and application to effect monitoring of the omic technologies.

A further major challenge is a reconsideration of the basis of biomonitoring action limits: Until today, they have been derived from consideration of serious health effects. With the demographic development in industrialized countries, and looming or already prevailing shortage of work force, there is an increasing pressure to generate workplaces that are able to attract people, and chemical exposures thus must be kept low enough to guarantee not only health but also work environment that stimulates the work force to high productivity. Work place attractivity thus has to be tailored in to the biomonitoring action limits – and such a paradigm does not exist today.

As of today, biomonitoring action limits (like their model, industrial hygiene guidance values) have been mostly developed as point estimates of the highest concentration likely not to induce serious health effects. Thus the approach is quite different from the modern risk assessment practices, where a no-effect level is first developed, than the uncertainty of the assessment is considered, and the final figure of acceptable concentration is developed through the application of an uncertainty factor. Therefore, the biomonitoring action limits/workplace air standards differ from the guidance given to the general population often much more than what would be expected from the difference between the two populations (working population vs. general population including children and sensitive individuals).

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