J Occup Health 2005; 47: 22–48

Journal of Occupational Health

Review

Biological Monitoring of Exposure: Trends and Key Developments

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Abstract: Biological Monitoring of Exposure: Trends and Key Developments: Marek JAKUBOWSKI, *et al.* Nofer Institute of Occupational Medicine, Poland—The concept of biological monitoring (BM) has gained the special interest of individual scientists and international organizations. Today, when analytical problems have almost ceased due to new laboratory techniques and quality assurance systems, the methods for interpretation of results have become the most important issue. There are important discrepancies regarding the role of biological monitoring of occupational exposure between Europe and the United States. BM has been an important tool of medical health surveillance in the European countries. In the United States it belongs rather to the field of occupational hygiene. It seems that both the approaches can be accepted. More attention should be paid to the development of the truly health-based biomarkers of exposure based on the dose-effect and dose-response relationships. New areas of application of BM of occupational exposure include determination of DNA and protein adducts, unchanged volatile organic compounds in urine, monitoring of exposure to pesticides, antineoplastic drugs, hard metals, and polycyclic aromatic hydrocarbons. In the general environment BM is the most valuable tool for acquiring knowledge of current levels of internal exposure to xenobiotics, identifying the hot spots and developments in trends of exposure. BM can provide policy makers with more accurate information on the control measures undertaken. At present, the main areas include heavy metals, persistent organic pollutants and pesticides. BM of chemical exposure has become increasingly important in the assessment of the health risk in occupational and environmental medicine. Therefore it would be worthwhile to include BM in the curricula for the training of occupational hygienists.
(J Occup Health 2005; 47: 22–48)

Key words: Biological monitoring, Occupational exposure, Environmental exposure

Received July 14, 2004; Accepted Oct 29, 2004
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The view has been commonly shared among scientists that the likelihood of adverse health effect(s) of exposure to chemicals depends on its magnitude. Measures of exposure have been developed independently in various areas of environmental toxicology. Therefore, environmental toxicologists have worked out procedures for the risk assessment of adverse health effects that were based on the daily intake of a given chemical. The reference values, such as the reference dose (RfD) published by the Environmental Protection Agency (USA) (US EPA), or the Provisionally Tolerated Weekly Intake (PTWI) published by the World Health Organization—Food and Agricultural Organization (WHO-FAO), reflect the levels of exposure that should prevent humans from suffering adverse effects of environmental exposure. Moreover, guidelines for the concentrations of chemical substances in the air or drinking water are also published by international organizations[1, 2] or local authorities in different countries. Industrial toxicologists have developed guidelines for interpreting the concentrations of chemicals in the air of industrial enterprises. These values have been published either as recommendations[3, 4] or as official lists of admissible concentrations.

The setting of acceptable exposure limits is based on the assumption that there is no appreciable risk at levels below these limits for all or almost all the persons exposed. Although the recommended daily intake or admissible concentration in environmental media or in the workplace atmosphere have been commonly used and accepted at the governmental level in different countries, it has become clear that various factors can affect exposure. These include additional absorption through the skin; differences in individual uptake which can, for instance, be age-dependent; differences in individual behavior in the general environment and poor working practice; different uptake at the same air concentrations, due to different workload during the shift; and the use and effectiveness of personal protection devices.

In view of the possible influence of these individual factors, the concept of biological monitoring of exposure was developed in the mid fifties[5, 6] of the 20th cent. This concept originates from industrial toxicology as a method

for estimating individual exposure to single compounds, but the researchers noted that large individual variation in results could be found for the same exposure levels. This variation was on the one hand due to the impact of some physiological factors, and on the other, to the low precision of measurements carried out in the past. To take account of both these factors, the idea of collective exposure tests was put forward. Then the concept of biological monitoring started gaining interest among individual scientists and international organizations. Apart from a large number of reports on the results of studies employing biological monitoring, there were many articles[7–13] as well as textbooks[14–19] on the general aspects of the method. The complete scientific documentation of Biological Exposure Indices (BEI) in the USA[20] and Biologische Arbeitstofftoleranzwerte (BAT) values[21–23] in Germany is available.

Biological monitoring of exposure is presently applied to environmental and occupational toxicology as well as epidemiological studies on the dose-response relationship between internal exposure and adverse health effects of exposure to chemicals.

The aim of the present paper is to evaluate:

1. The usefulness of available biomarkers for occupational exposure assessment, taking account of the decreasing trend in occupational exposure levels.
2. The usefulness of biological monitoring for environmental exposure assessment
3. Identification of the new biomarkers of exposure.
4. Interlaboratory quality assurance systems and reference materials for daily quality control within the laboratory.

Definitions

Exposure assessment can be performed with ambient air monitoring and biological monitoring. The term 'biomarker' is a general term for specific measurements of an interaction between a biological system and an environmental agent. According to the International Program of Chemical Safety (IPCS)[24], three classes of biomarkers can be identified:

biomarker of exposure—an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism;

biomarker of effect—a measurable biochemical, physiological, behavioral or other alteration within an organism that, depending on the magnitude, can be recognized as associated with an established or possible health impairment or disease;

biomarker of susceptibility—an indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific xenobiotic substance.

It has been commonly accepted that determining the first two kinds of biomarkers can be recognized as a part of more complex prophylactic activities in the occupational setting. However, the practical application of biomarkers of susceptibility at present gives rise to serious doubts. Genetic screening can be applied both as an indicator of susceptibility to occupational hazards or a predictor of future health. Inborn genetic characteristics that determine the relatively increased susceptibility to particular diseases include the host characteristics that modify the effect of exposure to environmental agents (genes affecting the metabolic capacity and repair capacity e.g. cytochrome P450, glutathione S-transferase, N-acetyltransferase), host susceptibility to occupational diseases e.g. chronic beryllium disease, occupational asthma, or susceptibility to diseases that are not related to work but affect the rate of absence. Consequently, an employer might wish to use such information to deploy workers in the areas appropriate to their particular genetic make-up or to exclude them from employment.

Testing genetic susceptibility for the prevention of occupational diseases is, at present, likely to be irrelevant due to its low predictive value. According to the opinion expressed by the European Group on Ethics in Science and New Technologies to the European Commission on 28 July 2003[25]: "The legitimate duties and rights of employers concerning the protection of health and the assessment of ability can be fulfilled through medical examination but without performing genetic screening. Thus, employers should not in general perform genetic screening or ask employees to undergo tests".

In view of the above, the biomarkers of susceptibility will not be discussed in the present paper.

According to the review undertaken by the Scientific Committee on Occupational Exposure Limits (SCOEL), the biological monitoring (BM) methods that are currently used to assess workplace exposure fall into three main categories[26]:

- determination of a substance or its metabolite in a biological medium (biological exposure monitoring)
- measurement of reversible, non-adverse biological effects (biological effects monitoring)
- measurement of the amount of substance interacting with a target (biological monitoring of effective dose)

The present application of biomarkers of occupational exposure

The concept of BM has been given special consideration on the part of individual scientists and international organizations. The biological monitoring of exposure thus far has been applied to environmental and occupational toxicology as well as epidemiological studies to evaluate the dose-response relationship between internal exposure and adverse health effects of exposure to chemicals.

Presently, biological monitoring plays but a complementary role in industrial hygiene practice. There are several reasons for that. Firstly, this attitude used to

be commonly accepted as something obvious. Then BM was thought to be more expensive than environmental monitoring (EM), the worker could not, for ethical reasons, serve as an individual sampler, and the collection of blood samples has not been generally approved.

Moreover, it is not clear whether BM actually belongs to occupational hygiene or occupational medicine. Consequently, BM recommendations are not considered to represent legal standards, as is the case of EM in most countries.

Today, when the analytical problems have almost ceased due to new laboratory techniques and quality assurance systems, the methods for interpretation of results have become the most important issue. And these are much more difficult to understand for the legislative bodies than the methods used in environmental monitoring where the rules are relatively simple.

The problem of the selection of a sampling strategy is much more difficult than in EM because of the different toxicokinetics of unchanged compounds and their metabolites in different media (blood, urine, exhaled air). There are also problems in expressing the results of determinations of chemical substances or their metabolites excreted in urine (these can be calculated for creatinine, specific gravity or rate of excretion).

There are two basic ways that the data for interpretation can be obtained. They can be either health-based or constitute an equivalent to the air concentration of a given chemical. The latter can be gained as the outcomes of a human volunteer study under controlled experimental conditions or of a field study where the workload and the possible additional absorption through the skin are difficult to control.

The true health-based values have been obtained mostly via epidemiologic studies, on the basis of the dose-effect or dose-response relationships. These values make it possible to directly evaluate the health risk based on the determination of chemical agents or their metabolites in biological material. These are the most valuable indicators. Unfortunately, in occupational exposure their number is limited to lead in blood, cadmium in blood and urine, mercury in urine, fluorides in urine, carboxyhemoglobine, methemoglobine, and the decrease in cholinesterase activity in erythrocytes, and to some extent also the arsenic concentration in urine.

The American Conference of Governmental Industrial Hygienists (ACGIH) and the Deutsche Forschungsgemeinschaft (DFG), the two main organizations involved in the setting of BM reference values differ in their approach to and definitions of these values.

ACGIH BEI values represent the levels of analytes that are most likely to be observed in specimens collected from a healthy worker who has been exposed to chemicals to the same extent as a worker with inhalation exposure at the TLV (Threshold Limit Value) level. BEIs are understood as advisory levels that may be exceeded by individuals in the observed group. Industrial hygienists are expected to reduce the exposure if BEI values are exceeded for a longer period of time or if a BEI is exceeded for a substantial group within the exposed population. ACGIH[3] has already published BEI values for 37 substances or groups of substances.

The DFG BAT values are defined as "the maximum permissible quantity of a chemical substance or its metabolites, or the maximum possible deviation from the norm for biological parameters induced by these substances in exposed humans. The BAT values are considered the ceiling values for healthy individuals". They are intended to protect the workers from work-related health impairments. DFG has so far determined BAT values for 50 substances or groups of substances. For 14 carcinogenic substances, exposure equivalents for carcinogenic materials (EKA) have been established[4].

Previously, an analysis of the criteria for biological limit values developed in Germany and the US and a comparison of the BEI and BAT values was undertaken by Morgan and Schaller[13]. The changes in the BAT and BEI values that have been made since the latter publication are shown in Tables 1 and 2. According to these data, both DFG and ACGIH were very active in the field of BM and these activities were aimed at extending the respective lists as well as updating the existing values. As regards the ACGIH listing, the most important changes refer to n-hexane and methyl n-butyl ketone, where the specific determination of 2,5-hexanodione without hydrolysis made it possible to eliminate the influence of background levels, as well as styrene, for which the number of parameters has been considerably reduced. In the DFG classification, 24 new substances have been added (e.g. manganese) and what is important the BAT for lead in blood (Pb-B) has been reduced from 700 $\mu g/l$ to 400 $\mu g/l$ for men and from 300 $\mu g/l$ to 100 $\mu g/l$ for women <45 yr old.

There are 33 compounds with BAT values that are not included in the BEI list. Only three compounds have BEI values without a counterpart in the BAT list. In many cases, there are discrepancies between the exposure indices recommended by these two organizations. Moreover, different concentrations in biological material have been recommended for the same indices.

In the United Kingdom (UK), biological exposure indices have been established for 64 compounds. They are based mostly on the ACGIH values but six of them were proposed by the UK Health and Safety Executive[27] (Table 3). These belong to the health guidance values (HGV) and the benchmark guidance values (BGV). The health guidance values are set at a level at which there is no indication from the scientific evidence available that the substance being monitored is likely to be injurious to

Table 1. Changes in DFG recommendations made since 1999

Categories of DFG recommendations	Substances added	Substances removed	Changes in BAT values		
			Substances and indices	1999	2003
1. BAT	n-Butyl alcohol, Cumene, Cyclohexane, 1,2-Dichlorobenzene N,N- Dimethyl acetamide Ethylene glycol monobutyl ether, Ethylene glycol monobutyl ether acetate, Ethylene glycol monethyl ether, Isopropyl alcohol, Manganese, 4,4-Methylene diphenyl isocyanate (MDI)	2-Butoxyethanol 2-Butoxyethylacetate δ-Aminolevulinic acid 1,4-Dichlorobenzene Dichloromethane Diphenylmethane-4,4'-diisocyanate 2-Ethoxyethanol Propanol Phenol	Lead (B)(a)	700 μg/l 300 μg/l (women)	400 μg/l 100 μg/l (women 45yrs)
			Chlorobenzene	70 mg/g creat.(d)	35 mg/g creat. (d)
			Total 4-chlorocatechol (U)	300 mg/g creat. (b)	175 mg/g creat. (b)
			Dimethyl formamide N-Methyl formamide (U)	15 mg/l (b)	35 mg/l (b)
			Carbon tetrachloride (B)	70 μg/l (c,b)	3,5 μg/l (c,b)
			Tetrahydrofurane (U)	8 mg/l (b)	2 mg/l (b)
2. EKA	Dichloromethane Tetrachloroethylene Trichloroethylene				
3.Carcinogenic substances without EKA	Antimony and its inorganic compounds, Berylium, Dichlorobenzene Ethylbenzene, Mercury, organic compounds, Methyl bromide	Tetrachloroethylene Trichloroethylene			
4. BLW	Arsenic and inorganic compounds Cresol, Methyl bromide, Phenol				

Groups: 1. -BAT values; 2. -Exposure equivalents for carcinogenic materials (EKA); 3. -Carcinogenic substances for which EKA cannot be evaluated; 4. -BLW; the amount of a chemical substance or its metabolites or the deviation from the norm of biological parameters induced by the substance in exposed humans which serves as an indicator for necessary protective measures. (U)-urine, (B)-Blood, Time of sample collection: (a) - not fixed, (b) - end of exposure or end of shift, (c) - end of workweek, (d) - at the beginning of the next shift. creat. - creatinine

Table 2. Changes in ACGIH recommendations made since 1999

Substances and/or indices added	Substances and/or indices removed	Indices or values changed		
		Substances and indices	1998	2004
Aniline: Aniline (U) Aniline released from hemoglobin in blood	Styrene: Mandelic acid (U) Phenylglyoxylic acid (U)	Arsenic elemental and soluble inorganic compounds (U)	50 μg/g creat. (c).	35 μg/g creat.(c)
Benzene t,t-Mucomic acid in urine	Styrene (B) prior to next shift		30 μg/g creat. (b,c)	25 μg/g creat.(b,c)
Cyclohexanol 1,2-Cyclohexane diol (U) Cyclohexanol (U) Cyclohexanone (U) 1,2-Cyclohexanediol (U) Cyclohexanol (U)		Chromium Total chromium (U)	5 mg/g creat. (with hydrolysis) (b,c)	0.4 mg/*l* * (b,c)
Methyl n-Butyl ketone 2,5-Hexanodine (U)*		n-Hexane 2,5 -hexane dion (U)		
Styrene Mandelic acid + phenylyoxylic acid (U).				
Tetrahydrofurane (U)				

*- without hydrolysis, U-urine, B-Blood, Time of sample collection: (b) -end of exposure or end of shift, (c) -end of workweek, creat. - creatinine.

Table 3. United Kingdom biological monitoring guidance values[28)]

Substance	Health guidance value HGV	Sampling time	Benchmark guidance value BGV	Sampling time
Butan-2-one*	70 μmol butan-2-one/*l* in urine	Post-shift		
2-Butoxyethanol	240 mmol butoxyacetic acid/mol creatinine in urine	Post-shift		
N,N-Dimethylacetamide	100 mmol n-methylacetamide/mol creatinine in urine	Post-shift		
Lindane			35 nmol/*l* (10 μg/*l*) of lindane in whole blood (equivalent to 70 nmol/*l* of lindane in plasma	Random
MbOCA (2,2'dichloro-4,4'-methylene dianiline)			35 nmol total MbOCA/ mol creatinine in urine	Post-shift
Mercury	20 μmol mercury/mol creatinine in urine	Random		
4,4'-Methylenedianiline (MDA)			50 μmol total MDA/mol creatinine in urine	Post-shift for inhalation and pre-shift next day for dermal exposure
4-Methylpentane-2-one	20 μmol 4-methylpentan-2-one/*l* in urine	Post-shift		
Carbon monoxide	30 ppm carbon monoxide in breath, equivalent to 5% COHb	Post-shift		

*Non included in the H&S Guidance on Laboratory Techniques in Occupational Medicine[27)] in 2002.

health. The values not greatly in excess of an HGV are unlikely to produce serious short- or long-term effects on health. The health guidance values are therefore health-based and are equivalent in terms of health protection to the occupational exposure standards. The benchmark guidance values are not health based; they are the practicable, achievable levels set at the 90th percentile of available biological monitoring results collected from a representative sample of workplaces with good occupational hygiene practice. A result greater than a BGV does not necessarily mean that ill health will occur, but it does indicate that the control of exposure may be inadequate[28].

In Finland, the BM practice is well established. The booklet published every year by the Finnish Institute of Occupational Health contains 74 recommended values[29]. In Italy, there are 44 compounds with biological exposure indices. They are based mostly on the ACGIH BEI values. Considering some of the regression curves published in literature, the so-called Biological Equivalent Exposure Limits (Limite Biologico Equivalente) for unchanged volatile organic compounds (VOCs) in urine have been proposed in Italy for seven substances (benzene, n-hexane, methylchloroform, methylethylketone, styrene, toluene and xylene)[30]. In Poland, BM recommendations have been published for 20 substances[31].

Where no biological monitoring guidance values have been set, it may be appropriate for employers to consider setting "in-house" values[32].

In general, in spite of the decrease in occupational exposure limits, the currently published BATs and BEIs can be used as the reference values for evaluating exposure or health risk. Nevertheless, specific and sensitive analytical methods of instrumental analysis are required, such as gas chromatography (GC), and high pressure liquid chromatography (HPLC) and in some cases possibly with mass detectors (MS or MS-MS) for organic compounds and flame (FL-ASA) or flameless atomic absorption spectrometry for metals. High quality of determinations is necessary and this can be ensured through the laboratory's participation in external quality assurance systems. Obviously, the quality assurance issues apply also to the measurements of toxic substances in the air.

The usefulness of biological monitoring for environmental exposure assessment

In the biological monitoring of population exposure, two different kinds of criteria can be applied: (a) health-based, and (b) used for the evaluation of the magnitude of exposure against the reference values or to compare the levels and trends of exposure in different regions or countries.

The health-based recommendations can be obtained for substances that are deposited in the organism. Unfortunately, for a majority of environmental toxins there are no appropriate and well-designed epidemiological studies. Furthermore, it is at present difficult to find groups within the general population that have been substantially exposed to environmental toxins to study the dose-effect and dose-response relationships between the levels of biomarkers and early health effects and to determine the Lowest Observed Adverse Effect Level (LOAEL) or the No Observed Adverse Effect Level (NOAEL) values.

1. Health-based recommendations

To date, well-documented health-based recommendations after the results of epidemiologic studies have been formulated for three substances: inorganic lead, inorganic cadmium and methylmercury.

Cadmium

Kidneys are the critical organs in a long-term occupational or environmental exposure to cadmium. A wide range of tests of different sensitivity and significance have been used among cadmium-exposed populations to assess cadmium nephrotoxicity.

The results of several studies performed on populations environmentally exposed to cadmium indicate that changes in sensitive renal biomarkers may occur at lower urinary cadmium levels than those found in adult male workers.

The number of well-performed environmental studies on the influence of cadmium on kidney functions is limited. Several markers of renal tubular dysfunction, including β_2-microglobulin (β_2M), retinol binding protein (RBP) and N-acetyl-β-D-glucosamidase (NAG), were positively associated with urinary excretion of cadmium. There was a 10% probability of the values being higher than the cut-off level when cadmium excretion exceeded $2 \div 4$ μg/24 h[33]. Schütz and Elinder[34] noted urinary excretion of α_1-microglobulin (HC) above the cut-off level in 10% of the investigated population with cadmium in urine (Cd-U) concentrations about 1 μg/g creatinine. The results obtained recently by Noonan *et al.*[35] and Trzcinka-Ochocka *et al.*[36] revealed that the urinary excretion of early biomarkers of kidney dysfunction can be increased at cadmium levels in urine of about 2.0 μg/g creatinine.

It has been postulated that for the general population the Cd-U levels should be below 2.5 μg/g creatinine[37].

Lead

Biological monitoring is used for the assessment of total exposure from different sources. In the case of environmental exposure to lead, health effects can be referred to blood lead levels.

Children constitute the highest risk group and the central nervous system (CNS) is the critical organ in environmental exposure to lead. A wide range of behavioral tests have been performed on lead-exposed

populations to assess the influence of lead on CNS functions. A meta-analysis of the results of epidemiological studies carried out mainly in the US, Australia and Europe was published by IPCS in 1995[38].

The WHO Air Quality Guidelines for Europe recommended that at least 98% of the population exposed in the general environment should have Pb-B below 100 μg/*l*, and the median blood lead level should not exceed 54 μg/*l*. The Centers for Disease Control[39] (CDC) recommended that the Pb-B values in children should be below 100 μg/*l*. Nevertheless, according to the recently published results of studies by Canfield *et al*.[40], blood lead concentrations, even those below 100 μg/*l*, are inversely associated with children's IQ scores at three and five years of age, and associated declines in IQ are greater at these concentrations than at higher levels.

The geometric mean values published recently in different countries imply that in women and children the Pb-B levels are approaching the range of 10–30 μg/*l* considered as "baseline" of minimal anthropogenic origin[41–45].

Methyl mercury

The effects of methylmercury on the adult differ both in quantitative and qualitative terms from the effects observed after prenatal or, possibly, postnatal exposure. The critical organ is the nervous system and the critical effects include developmental neurologic abnormalities in human infants, and paraesthesia in adults. The foetus is at particular risk. Prenatal exposure leads to psychomotor retardation in infants. Developmental neurologic abnormalities are considered the critical effects in the infant population.

Hair is a biomarker of long-term exposure to methylmercury. Once mercury is incorporated into hair, it remains unchanged. The level of mercury in hair (Hg-H) is dependent on fish consumption.

The dose-response relationship between maternal hair concentration and the frequency of health effects in children was used by the IPCS for the purpose of risk assessment[46]. At peak mercury levels in maternal hair at above 70 μg/g, there is a high risk (more than 30%) of neurological disorder in the offspring, and a 5% risk may be associated with a peak mercury level of 10–20 μg/g in maternal hair.

Recently, benchmark dose calculations have been performed for methylmercury-associated delays on evoked potential latencies in two cohorts of children from the Faroe Islands and Madeira[47]. The obtained benchmark dose (BMDL 5%) of approximately 10 μg/g maternal hair was similar to that calculated for other neurological variables[48] in the Faroese children and in the New Zealand population[49].

The present background level of Hg-H, associated with no or low fish consumption or a low fish methylmercury concentration, amounts to from 0.25 μg/g to 0.8 μg/g[50–52]. Much higher Hg-H levels result from the consumption of large amounts of fish or sea mammals. The mean Hg-H levels in the Faroe Island population amounted from 1.6 μg/g (one fish meal per week) to 5.2 μg/g (four fish meals per week)[51]. In the Madeira fishermen and their families, it amounted to 38.9 μg/g in men and 10.4 μg/g in women[53].

2. The German approach to human biological monitoring values for environmental toxins

Two kinds of values are recommended by the Commission on Human Biological Monitoring of the German Federal Environmental Agency established in 1993: (a) reference values and (b) human biological monitoring values (HBM values)[54, 55]. The HBM values

Table 4. Human Biological Monitoring Values (HBM) - values recommended by the German Commission on Human Biological Monitoring (Status: March 1999)

Analyte	Group	HBM I	HBM II
Lead in blood	Children ≤12 yr and females in the reproductive age	100 μg/*l*	150 μg/*l*
	Males and females <45 yr	150 μg/*l*	250 μg/*l*
Cadmium in urine	Children, males and females <25 yr	1 μg/g creat.	3 μg/g creat.
	Adults >25 yr	2 μg/g creat.	5 μg/g creat.
Mercury in urine	Children and adults	5 μg/g creat.	20 μg/g creat.
Mercury in blood	Children and adults	5 μg/*l*	15 μg/*l*
Pentachlorophenol (PCP) in serum	Children and adults	40 μg/*l*	70 μg/*l*
Pentachlorophenol (PCP) in urine	Children and adults	25 μg/*l*	40 μg/*l*
		20 μg/g creat.	30 g/g creat.

HBM—The concentration of an environmental toxin in human biological material, below which there is no risk of advance health effects. HBM II—The concentration above which there is increased risk of adverse health effects in susceptible individuals in the general population. creat. - creatinine

have been derived from human toxicology and epidemiology studies and are intended as a basis for a health-related evaluation of human biological monitoring data. Usually, the Commission recommends two different HBM values: HBM I, the concentration of an environmental toxin in human biological material below which there is no risk of adverse health effects, and HBM II, the concentration above which there is an increased risk of adverse health effects in susceptible individuals in the general population. The HBM values are shown in Table 4.

3 Centers for Disease Control and Prevention (CDC, USA)

On March 21, 2001, the U.S. Centers for Disease Control and Prevention released the National Report on Human Exposure to Environmental Chemicals with preliminary data on biological monitoring of a large U.S. population. The Report provided summary analyses for blood and urine samples obtained in 1999 from the National Health and Nutrition Examination Survey (NHANES 99+) and enhanced information from previous NHANES. This report described the results for 27 environmental chemicals, including several metals, several phthalate metabolites, a nicotine metabolite, and six organophosphate metabolites.

In January 2003, CDC released the Second National Report on Human Exposure to Environmental Chemicals[56, 57]. Chemicals and their metabolites were measured in blood and urine samples from selected participants in the National Health and Nutrition Examination Survey. This report presents exposure information on 116 chemicals in people who had blood and urine samples taken during 1999 and 2000. The provided 95th-percentile levels mean that 95 percent of the serum or urine concentrations in the population are below that level.

4. Evaluation of the magnitude of exposure against the reference values and comparison of the levels and trends of exposure in different regions or countries

The so-called reference values, mainly for metals and persistent organic pollutants, have been published by different organizations[57–62], but such data are of limited value on the international scale. They may be influenced by environmental exposure levels in a given country, the confounding factors (smoking, kind of food consumed), changes due to reduced emission (e.g. lead), improved control of the contamination that may occur during sampling[63], better analytical procedures and internal or external quality control of the determinations. Nonetheless, these data may be useful at a local level. For example, in Germany, the reference values are intended to indicate the upper margin of the current background exposure of the general population and to identify subjects with an increased level of exposure[55].

The results of biological monitoring can be used for evaluating the background contamination or the trends regarding contamination in different countries. On the international level, they were used to compare internal exposure to organochlorine compounds[63] or the trends in the concentration of dioxins in breast milk in the European countries[64]. The application of biological monitoring can also confirm the effectiveness of the technical solutions aimed at reducing environmental exposure on the local scale in a country as was the case for lead blood levels in children. For example, in the U.S., the geometric mean of the Pb-B concentration in children, during the consecutive phases of NHANES II, III and IV in 1976–80 ; 1988–91 and 1991–94, amounted to 150 $\mu g/l$; 36 $\mu g/l$ and 27 $\mu g/l$, respectively[45]. In Sweden, the geometric mean of the Pb-B concentration in schoolchildren has decreased from about 60 $\mu g/l$ in 1978 to about 25 $\mu g/l$ over a period of 15 yr[65].

The main prospective areas for application of biological monitoring of occupational exposure

1. Unchanged VOCs in urine

For volatile organic compounds (VOCs), the biological monitoring of exposure is based mainly on the determination of specific metabolites in urine. This approach has been developing since biological monitoring started to be applied and most of the recommendations[3, 4, 27] on exposure assessment concern the level of metabolites in urine.

Nevertheless, in the occupational settings, VOCs are almost as a rule present in mixtures[66] and for a large number of them, the critical effect consists of a depressive action on the central nervous system[3]. The necessity to perform numerous determinations of different metabolites in urine may be the main reason why biological monitoring is rarely used in practice, unlike for e.g. metals, for the evaluation of VOCs exposure. It can be reliable in some cases involving exposure to a single compound, e.g. styrene, during the production of laminated constructions, or compounds with specific toxicity, such as the carcinogenic benzene or strongly neurotoxic n-hexane.

Relevant literature reports mainly on two methods for a simultaneous screening and quantitative determination of VOCs in biological material, but the determinations of unchanged compounds in blood and exhaled air have not gained wide acceptance mainly because the first one is invasive, and in the second one the sampling is difficult. What is more, the half-life of the first phase of VOCs elimination from blood and expired air is very short and the concentration can decrease by half within several minutes after exposure termination. There are recommendations that blood samples should be collected before the shift next day[3] but then the concentrations are

low.

VOCs are eliminated from the organism through the kidneys as metabolites; a certain percentage of absorbed solvents is eliminated unchanged through the lungs. After occupational exposure the proportion of the solvent excreted in urine to the amount absorbed is not high. It may vary, depending on the hydrophobicity, from 1.5% for methanol to 0.001% both for 1,1,1-trichloroethane and toluene, and to even less for hexane[67]. This small amount of solvent dissolved in urine collected in the bladder tends to reach a pressure equilibrium with alveolar air and arterial blood[68]. Therefore, following Ghittori *et al.*[69], the end-of-exposure urinary concentration of the unmetabolized amount can be seen as the outcome of the natural integration over time of a rather fast partition between air and arterial blood and between arterial blood and urine, with the bladder serving as a collection and mixing vessel.

The determination of unchanged VOCs in urine was recommended mostly for short-chain alcohols and ketones[3, 4]. They possess a high to medium water solubility and are easily excreted in urine without metabolism, by a simple diffusion process (into acetone, methyl isobutyl ketone and methanol).

This method has been recommended by several research teams also for the biomonitoring of other chemical classes of VOCs. Ghittori *et al.*[69] proposed what they called the biological equivalent exposure limit for nine solvents (acetone, 2-cyclohexane, 1,2-dichloropropane, n-hexane, methyl-ethyl ketone, perchloroethylene, styrene, toluene and 1,1,1-trichloroethane). This study was performed in an occupational setting. High correlation (r=0.87–0.96) was found between the concentration of these solvents in the air and the concentration of unchanged compounds in urine samples collected during the first four hours of the work shift. There were also attempts to use the determination of unchanged VOCs in urine for the evaluation of exposure to low concentrations of the components of gasoline vapours during the unloading of tankers and railway wagons[70], during tank lorry loading[71] and in road tanker drivers[72]. During the unloading[70], the concentrations of VOC vapours were very low. For benzene, toluene, xylenes, trimethylbenzenes, methyl tert-butyl ether (MTBE) and methyl tert -amyl ether (MTAE), the geometric mean concentrations amounted to 0.10; 0.61; 0.68; 0.50 0.69 and 0.27 mg/m^3, respectively. In spite of the very low exposure, the correlation coefficients for the concentrations in the breathing zone and in urine samples collected at the end of shift amounted to from 0.411 to 0.981. Vainiotalo *et al.*[71] and Saarinen *et al.*[72] found a correlation between MTBE and methyl tert - amyl ether (TAME) concentrations in the breathing zone and the excretion of unchanged compounds in urine collected after the shift. Determinations of unchanged toluene[73], toluene and xylenes[74] or tetrachloroethylene[75] were also performed, showing a correlation between the concentration of these compounds in the air and in urine samples collected at the end of exposure.

The conditions concerning urine sampling and sample storage were investigated and general conclusions have been reached[67, 76]. The determination can be performed by means of gas chromatography after VOCs' separation from urine by means of traditional 'head space' (HS) or head space solid phase microextraction (HS-SPME)[76, 77].

Based on some of the regression curves published in literature, the so-called Biological Equivalent Exposure Limits (Limite Biologico Equivalente) for unchanged VOCs in urine have been proposed in Italy for benzene, n-hexane, methylchloroform, methylethylketone, styrene, toluene and xylene[30].

Generally, the results reported in literature show that the measurement of urinary excretion of unchanged solvents provides a highly sensitive and specific exposure index. This method can be applied to the biological monitoring of occupational exposure to low levels of solvents or, what is more important, to solvent mixtures.

But, according to the opinion of the ACGiH[20], there is insufficient information at present on the kinetics of e.g. toluene excretion in urine. If the kinetics is similar to that for toluene in expired air and blood, the end-of-shift specimens would be reflective of exposure only for the last two hours of the shift. The lack of experimental data concerning the toxicokinetics of unchanged VOCs excreted in urine refers to all the other compounds as well. Also the linearity of the regression curve between the concentration in the air and in urine was studied for a limited range of exposure levels. For example, the results obtained by Kawai *et al.*[73] indicate that this relation can be curvilinear since for the air toluene concentrations of 10, 25, 50 and 100 ppm, the respective urine concentrations of toluene amounted to 16, 26, 40 and 67 $\mu g/l$.

All the problems concerning the kinetics of urinary excretion of unchanged compounds with different octanol: water partition coefficients and the resulting sampling strategy, or the linearity within the relatively large range of concentrations, can be resolved only with the aid of a well-designed experimental study. The arguments for the use of this method are the noninvasive specimen collection, the possibly minor kinetic influence in comparison with VOC levels in blood, and the simultaneous quantification of mixture compounds in a single urine sample. The arguments against include the small percentage of lypophilic VOCs excreted in urine, increased analytical requirements, probability of VOCs loss during the pre-analytical phase, and more complex sample handling. It has been estimated that the concentrations of toluene, xylene and tetrachloroethylene in blood can be about ten times as high as in urine samples collected at the same time[11].

2. Polycyclic aromatic hydrocarbons (PAH)

PAHs are a large group of compounds which consist of two or more fused aromatic rings made entirely from carbon and hydrogen. In an occupational setting, PAHs uptake is through the respiratory tract and the skin as a result of contact with PAHs-containing materials.

Metabolites in urine

Several methods have been developed to assess internal exposure to PAHs after exposure in workplaces. In most studies, PAHs metabolites were measured in urine. The metabolites measured in urine and feces include urinary thioethers, 1-naphtol, β-naphtylamine, hydroxy phenanthrenes and 1-hydroxypyrene (1-HP)[78].

No difference in thioether excretion in urine was observed between the controls and coke oven workers or workers at coke and graphite-electrode-producing plants. It was concluded that the determination of thioethers in urine was of little value, since smoking is a strong confounding factor[79–81]. Becher and Bjorseth[82] developed an analytical procedure to measure PAHs in human urine after reducing metabolites to parent compounds. Total PAHs were higher than the levels for nonsmokers, but when individual PAHs were examined, there was no significant difference. Further application of this method to the analysis of urine samples from workers at an aluminum plant[83] and from coke oven workers[84] did not show differences between the exposed workers and controls in PAH levels in urine.

1-HP, a pyrene metabolite, was introduced as a biomarker of exposure to PAHs by Jongenellen *et al*.[85] and has been widely used as such since that time. Its advantage lies in that pyrene is present in all PAHs mixtures in relatively high concentrations. Pyrene is metabolized predominantly to 1-HP. In contrast to other PAHs metabolites, which are excreted mainly in feces, 1-HP is excreted mostly in urine.

When 1-HP was used as a biomarker for PAHs exposure, the oral, dermal and inhalation routes were all shown to be important. Furthermore, low levels of exposure could also be determined. A great advantage is that the determination of urinary 1-HP is quick and easy and thus well suited for use in large-scale epidemiological studies.

The determination of 1-HP in urine can be used today to trace the trends of exposure in a given enterprise and to evaluate the effectiveness of prophylactic measures undertaken. For example, the use of dermal protection in the form of impermeable polyvinyl chloride suits led to a substantial decrease in the urinary concentrations of 1-HP[86]. Frequent changes of work clothes and underclothes reduced 1-HP excretion by 37–55%[87, 88].

The comparison of different work environments may, however, be difficult because the proportion of pyrene as compared to that of benzeno [*a*] pyrene (BaP) and other potentially carcinogenic PAHs, may vary. For example, the creosote oil used in a wood impregnation plant contained about 3.4% pyrene and less than 0.0004% BaP. The levels of 2–10% pyrene and 0.4–0.6% BaP are found in coal-tar that is the main PAH contaminant in the coke industry, in primary aluminum industry, and during road paving with tar. Polluted ambient air contains about 6.5% BaP and 1.8–2.7% pyrene[78].

Several authors tried to establish admissible levels of 1-HP in urine for specific exposures. According to Jongenellen[89], in coke-oven workers, the urinary concentration of 1-HP of 4.4 μg/g creat. reflects the concentrations of coal tar pitch and BaP in the air of 0.2 mg/m^3 and 2 μg/m^3, respectively. A similar value, of 4 μg/g creat., was proposed by Levin *et al*.[90] A higher value of 6.1 μg/g creat. was suggested by Van Roij *et al*.[91] In the study on workers at an aluminum reduction plant, Tjoe Ny *et al*.[92] assumed that exposure to 0.2 mg/m^3 of coal tar pitch or 5 μg/m^3 of BaP will result in a urinary concentration of 1-HP of 8.6 μg/g creat.

Based on the logistic regression between the prevalence of abnormal high frequency cells (HFC) in peripheral lymphocytes and PAHs in the air or 1-HP in postshift urine of nonsmoking workers exposed to PAHs, Buchet *et al*.[93] concluded that the concentrations of PAHs in the air and 1-HP in urine should be kept below 6.4 μg/m^3 and 2.7 μg/g creat., respectively.

Recently Jongenellen[94] proposed a three-level benchmark guideline for urinary 1-hydroxypyrene as a biomarker of occupational exposure to PAHs. The reference value, as a 95th percentile in non-occupationally exposed controls, is 0.24 μmol/mol creat (0.46 μg/g creat.) and 0.76 μmol/mol creat. (1.44 μg/g creat.) for nonsmokers and smokers, respectively. This is the first level of the benchmark guideline. A no biological effect level of 1-hydroxypyrene in exposed workers was found at 1.4 μmol/g creatinine (2.66 μg/g creatinine). It is the lowest reported level at which no genotoxic effects were found (the second level of the benchmark guideline). The correlation between airborne concentrations and urinary 1-HP in coke oven workers and workers in the primary aluminum industry was used to estimate the level of urinary 1-HP corresponding to the current occupational exposure limit (OEL) of PAH. The concentration of 1-HP in urine, equal to the OEL, is 2.3 μmol/mol creat. (4.37 μg/g creat.) and 4.9 μmol/mol creat. (9.31 μg/g creat.), respectively, in these two industries, but the scattering of results in this case is substantial and these values represent the lowest reported estimate for the concentration equal to the OEL.

Mutagenicity in urine

The mutagenicity in urine from persons exposed to PAHs has been assayed by the Ames' test in a number of studies. Tobacco smoking was found to be mutagenic. No increase in mutagenic activity was found in most studies of workers exposed in occupational settings such

as coking, coal tar distillation, aluminum plants, anode plants or graphite electrode plants[78]. Only a heavy exposure to coal-tar formulations in patients with psoriasis[95, 96] and in coke oven workers[97] resulted in mutagenic urine.

The Ames' test, therefore, appears not to be sensitive enough to detect the presence of urinary mutagens due to occupational exposure to low levels of PAHs.

Current recommendations

At present, only ACGIH[3] in their notice of intended changes mentioned the measurement of 1-hydroxypyrene as a possible BEI but with Nq notation which means that biological monitoring should be considered, but a specific BEI could not be determined due to insufficient data.

3. Pesticides

Pesticides comprise a large group of chemical compounds designed specifically for the control of pests, weeds and plant diseases. In the United States, there were about 620 pesticidal active ingredients which were formulated into approximately 20,000 different products registered with the Environmental Protection Agency (EPA)[98].

Unlike other man-made chemicals, exposure to pesticides may affect a large part of the human population, including workers involved in their industrial manufacture, formulation and application either in agriculture or public health, and a part of the general population who may experience exposure through domestic use and consumption of contaminated food and water.

In the case of pesticides for which occupational exposure, mainly in agriculture, fluctuates in time and the skin is a significant route of absorption[99], biological monitoring constitutes an important tool for obtaining information on exposure and possible early health effects.

Unfortunately, biological monitoring of occupational exposure to pesticides is not always carried out for routine field activities. At present, the number of biological exposure indices recommended by ACGIH[3] is limited to organophosphorous pesticides (OP) (measurements of acetylcholinesterase (AchE) activity in red blood cells and p-nitrophenol, a metabolite of parathion in urine) and pentachlorophenol (PCP) in urine and plasma. The German BAT values are available for lindane (blood, serum), for AchE activity and parathion[4]. Biological limit values for dieldrin, endrin, coumarins, 4-chloro-2-methylphenoxyacetic acid (MCPA), and 2,4-dichlorophenoxyacetic acid (2,4-D) were also proposed by the Study Group of the Scientific Committee on Pesticides of the International Commission on Occupational Health[100].

This situation seems to be changing and the biological monitoring of pesticide exposure is gaining more and more attention both in occupational (agricultural) and environmental settings[56, 100].

Considerable progress has been made in the field of analytical methods. Most of the studies are aimed at measuring metabolites or unchanged compounds in urine and/ or blood. The principal groups of pesticides include: organophosphorous compounds, carbamates, organochlorine compounds, pyrethroids, herbicides, fungicides and other compounds. The choice of the method should be based on the objective. For monitoring the general population, the limit of detection (LOD) of the analytical methods must be about 1 $\mu g/l$, higher values apply to the monitoring of occupationally exposed persons. Aprea *et al.*[101] reviewed the analytical methods currently used in this field. In the case of OP compounds it is possible to measure unchanged compounds or their metabolites, mainly alkylphosphates (AP). The most commonly used analytical methods are gas chromatography (GC) with photometric detection (GC-FPD, or mass detection (GC-MS). The LODs are for an AP amount to about 1 $\mu g/l$ of urine. Recently, CDC has developed a scientifically sound GC-MS-MS method to quantify non-specific AP[102]. GC with an electron capture detector (GC-ECD) is used for the measurement of organochlorine pesticides. The LODs for these methods are between 1 ng/l and 1 $\mu g/l$.

There is a rapidly growing body of evidence from biomonitoring studies aimed at the evaluation of exposure, mainly to OP compounds, in pesticide applicators[103–108] and their families as well as in members of the general population (pesticide residues in food and pesticides in indoor environments). A subject of special concern is the necessity for the biological monitoring of environmental exposure of children who, depending on age, may come into contact with dust and soil, and of pregnant women's exposure[109–114].

In the case of biological monitoring of pesticide exposure, the development of analytical methods is much faster than the capacity for interpreting the results of the determinations. Angerer[115] presented the results of studies conducted among 1000 representatives of the general population in Germany. The metabolites of organophosphorous pesticides, dimethylphosphate and dimethylthiophosphate were found in about 80% of the study while diethylphosphate was detected in about 70% of the subjects.

Health-based interpretation of results is lacking as a rule and the biological monitoring is used mainly to assess the absorbed dose, which can be done by a comparison with the pre-exposure levels or reference values. As the LODs of the methods for biological monitoring continue to decrease, the reference doses also become lower. CDC established the reference ranges for several pesticides based on the measurements of their metabolites in urine samples from randomly selected adults in the US population. These data have been successfully used to

evaluate internal pesticide doses of the spouses and children of farmer applicators. For example the 2,4-D levels in the urine of applicators' children clearly exceeded the reference range (<1.0 to 1.8 $\mu g/l$)[98]. Biological monitoring was also used for the calculation of daily intake, which can then be compared with respective recommendations. For example Koch *et al.*[116] determined the concentrations of 3,5,6 -trichloro-2-piridinol (TCPyr), a specific metabolite of OP pesticides, chlorpyrifos (CHP) and chlorpyrifos-methyl (CHPM). The median excretion of 3,5,6-trichloro-2-piridinol (TCPyr) in non-occupationally exposed persons was 1.4 $\mu g/l$, which corresponds to a daily intake of 2.5 μg CHP + CHPM. The acceptable daily intake (ADI) amounts to 10 μg/kg b.w. Similar results were obtained in other countries. A study carried out in the USA[117] yielded a 50 percentile of 3 $\mu g/l$, and an Italian study[101] a geometric mean of 2.8 μg/g creatinine.

4. Cytostatic drugs

There has been a major concern about the potential exposure and subsequent effects in health care workers who handle cytotoxic and antineoplastic drugs. Many of these drugs have mutagenic, teratogenic, or carcinogenic properties, where no threshold dose can be identified. Therefore, exposure to these compounds should be avoided. Any drug absorption in hospital staff is generally assumed to proceed via the skin or mucous membranes, and to a lesser extent by inhalation, but the ward staff may be exposed not only from the spillage of drugs, but also via contact with the patients' body fluids, such as vomit, sweat and urine[118]. Biological monitoring constitutes the best method for determining whether the exposure hazard at the hospital wards where cytotoxic drugs were handled was controlled appropriately.

The apparent half lives for urinary excretion are roughly 5 h for methotrexate, 12–24 h for cyclophosphamide and isofosfamide, and 72 h for cisplatin. The urine measurement for these chemicals may be largely influenced by exposure in the preceding 24 h, but for those drugs whose half lives are 24–72 h, the urine measurement may more exactly reflect the level of exposure over the previous week[118].

In order to monitor the possible uptake of these drugs, it is necessary to use sensitive and compound specific detection methods. In recent studies, GC-MS, HPLC-MS-MS, GC -ECD, ELISA, voltametry and inductively coupled plasma with mass spectrometry (IPC-MS) methods were used. The detection limit of these methods (except for GC-ECD) was lower than 1 $\mu g/l$ of urine. The results of the investigations carried out in the Netherlands, Germany, Italy and U.K.[118–122] show that the internal exposure of the personnel involved in the preparation and administration of drugs may depend on the practice applied.

According to the opinion of Ziegler *et al.*[118] the "non-detected" urine measurement result does not signify any exposure or risk. These authors calculated that a continuous uptake of cyclophosphamide commensurate with a detection limit of about 0.25 $\mu g/l$ urine, may represent an annual cancer risk of 3–20 per million.

5. Hard metals

Hard metals are commonly used, mainly because of their resistance to corrosion, temperature, and wear. The most important use is as alloy components. For example, the main components of cemented carbides are tungsten carbide and cobalt metal. Beryllium is used in alloys with other metals (particularly Cu and Ni, and to a lesser extent Co, Cr, Fe and Mg) for improving hardness and resistance to corrosion, wear, vibration, and collision[123]. As a result of the increasing industrial use of beryllium, occupational exposure to the metal may be an important issue.

Occupational exposure to hard metal dust was reported to induce adverse effects on the upper and lower respiratory tract and the skin. Several studies suggested that cobalt is the main aethiological agent for the development of interstitial fibrosis. Soluble tungsten compounds affect the functions of the central nervous system. Chronic pulmonary beryllium disease (CBD) is an immunologically-mediated syndrome, defined as the occurrence of lymphocyte proliferation coupled with the presence of alveolar granulomas[124]. The other well-known effect of occupational exposure to beryllium is cancer (group A1 by IARC).

The recommended levels for biological material are available for cobalt and nickel, but not for tungsten and beryllium. In Germany, the exposure equivalent for carcinogenic materials (EKA) is 30 $\mu g/l$ urinary cobalt for 0.05 mg/m^3 cobalt in air[4]. ACGIH[3] set up two BEIs for cobalt: 15 $\mu g/l$ for urine and 1 $\mu g/l$ for blood samples collected at the end of the shift at the end of the workweek. The reference value for urinary cobalt is 1.5 $\mu g/l$[125]. The EKA value for nickel is 15 $\mu g/l$ urine for 0.10 mg/m^3 nickel in air[34]. The reference value for urinary nickel is 2.2 $\mu g/l$[125].

Kraus *et al.*[125] attempted to evaluate the excretion of tungsten in the urine of workers exposed to different tungsten compounds in a plant producing hard metals. The tungsten analysis was carried out with ICP-MS. The detection limit for urine was 0.05 $\mu g/l$. The mean tungsten concentrations in the urine of non-exposed people (n=33) were 0.31 $\mu g/l$ and 0.30 μg/g creatinine. The reference values (95 percentile) were 0.86 $\mu g/l$ and 1.00 μg/g creatinine. The mean concentrations of tungsten in urine amounted to 94.4 μg/g creatinine in the grinders, 42.2 μg/g creatinine in workers at departments producing tungsten carbide, and 24.9 μg/g creatinine in heavy alloys workers. Due to the low limit of detection, the results

obtained made it possible to differentiate between the renal excretion in the exposed and non-exposed groups. But, due to the different bioavailability of tungsten, increasing in the order: tungsten metal, tungsten carbide, tungstenate, there was no correlation, on a group basis, between tungsten concentrations in the air and urine. This means that a simple solution for biological monitoring of exposure to tungsten compounds is not possible. The authors postulate that only when the data from environmental and biological monitoring are considered in combination, can a valid and effective definition of high risk be derived.

Also the data for biological monitoring of exposure to beryllium are not available because of the small number of working activities involving exposure to this metal, and formerly the lack of appropriate analytical methods. The mean values for urinary beryllium in non-exposed persons as reported in the past amounted to 0.4 $\mu g/l$[126], 0.28 $\mu g/l$[127]. In the studies by Apostoli and Schaller[123] or Wegner *et al*.[128] where beryllium analysis was carried out by the ICP-MS method, the detection limit was 0.03 $\mu g/l$, or 0.06 $\mu g/l$, and beryllium concentrations in the urine samples of persons not occupationally exposed were below these detection limits.

Wegner *et al*.[128] investigated 57 gemstone cutters. For 27 cutters working in contact with beryls for 21 h/wk on average, beryllium could be detected in 17 pre-shift and 12 post-shift urine specimens. The median for the pre-shift urine samples was 0.09 $\mu g/l$ (<0.06 to 0.56 $\mu g/l$) and for the post-shift urine samples <0.06 $\mu g/l$ (<0.06–0.29 $\mu g/l$). No analysis of the correlation between external and internal exposure was carried out.

Apostoli and Schaller[123] examined 65 metallurgic workers in two electric steel plants and two copper alloy foundries. Beryllium concentrations in urine varied from <0.03 to 0.54 $\mu g/l$. A significant correlation was found for the relationship between external and internal exposure. The urinary Be levels were in the range 0.12 to 0.15 $\mu g/l$ whereas the concentrations of Be in inhalable dust were below the recommended threshold limit value–time weighted average (TLV-TWA) of 0.2 $\mu g/m^3$.

6. DNA and protein adducts

Exposure to genotoxic carcinogens results in the formation of covalently bound adducts between the genotoxin and DNA, which if not repaired may lead to a mutation and alteration of gene function. Genotoxic carcinogens also react with many other nucleophilic sites intra- and extra-cellularly (eg. protein, glutathione). Protein adducts are not repaired and are regarded simply as exposure monitors, but DNA adducts may also give further information with regard to the mutagenic significance of exposure.

According to Farmer[129], the sensitivity of the currently available methods (^{32}P postlabelling, HPLC-MS-MS) for adduct measurement has been shown to be sufficient for detecting the background level of DNA and protein damage, i.e. the one observed in non-smoking people without known exogenous exposures to electrophilic carcinogens. It appears that the total extent of adduct formation in normal human DNA (excluding oxidative damage) is at least 1 modification per 10^7 nucleotides, which stands for at least 600 modified nucleotide molecules per adult cell and over 10^{16} modified nucleotide molecules per adult human body. This would indicate that the effectiveness of repair of the steady state damage is high, so that mutations do not accumulate excessively.

DNA-adducts

The measurement of DNA adducts in human tissues would provide an excellent means to assess the genotoxic damage. A major limitation is the requirement of DNA from biopsy samples; an invasive procedure. An alternative, non-invasive source of tissue would be desirable. Buccal mucosa tissue has been successfully used to measure DNA adducts in smokers[130] and exfoliated urothelial cells for compounds that are associated with urinary bladder cancer[131]. White blood cells are another alternative tissue source, but there are doubts as to what extent the DNA adducts in leukocytes reflect DNA adduct formation in target tissues. For example, DNA adducts in white blood cells of rats and humans exposed to 2-amino-1-methyl-phenylimidazolo[4, 5-b]pyridine (PhIP), a heterocyclic aromatic amine, decline rapidly and do not appear to reflect PhIP-DNA adduct formation in the colon or breast[130]. Also the relationship between smoking history and DNA adducts in the leukocytes has not been adequately demonstrated[132, 133]. According to Bhatnagar *et al*.[131], it is not clear whether blood leukocytes are a valid surrogate for the target tissue level in every exposure.

Individual differences can influence the DNA-adduct levels. As regards the polycyclic aromatic hydrocarbons, exposures that result in the excretion of high concentrations of 1-HP in urine also lead to high DNA adduct levels, but in all the populations studied, there was a substantial individual variation in PAH-DNA adduct levels, after oral or inhalation exposure, that was greater than that described for 1-HP excretion in urine. In one study, about 50-fold individual variations were reported among controls and about 100-fold ones among coke-oven workers[134]. The variations were probably due to differences in the induction of arylhydrocarbon hydroxylase (AHH) activity in lymphocytes and in the subsequent detoxification of carcinogenic PAHs, the ability to repair DNA lesions, and the turnover of damaged cells. These individual variations resulted in a wide overlap in the ranges of values for exposed and unexposed subjects in all studies.

The levels of DNA adducts in controls ranged from

0.2 to about 10 adducts per 10^8 nucleotides in leukocytes. Workers exposed to PAHs had high mean levels of adducts and a higher percentage of positive samples than the controls. In the cases of high exposure, for example in coke-oven workers, 5–70 adducts per 10^8 nucleotides have been detected. DNA adducts are much less sensitive in human exposure assessment than the excretion of 1-HP in urine. This method, however, makes it possible to identify subjects who are highly susceptible to the DNA-damaging properties of PAHs and who are therefore predisposed to lung cancer[135].

Protein adducts

Electrophilic carcinogens can be bound to amino acid residues on such molecules as albumin or hemoglobin. Monitoring carcinogen-protein adducts is possible due to the relative abundance of certain proteins like hemoglobin and albumin in the central compartment. Blood samples are relatively easy to obtain. Because of the long life span of the proteins used for protein adduct determination, as well as the stability of these adducts that allows for their accumulation over the protein life-span, there are some practical advantages of determining protein adducts as a marker of exposure.

Several laboratories have studied the binding of aromatic amines and alkylating agents to hemoglobin or albumin. Recently, this has referred to such compounds as ethylene oxide, propylene oxide, acrylonitrile, acrylamide[135, 136], 1,3-butadiene[137], styrene, styrene-7,8-oxide and benzene[138], heterocyclic amines[140], dimethylformamide, trinitrotoluene and 4,4'-methylenedianiline[141]. Boogaard *et al.*[137] demonstrated that in the case of low-level (0.015–1.1 mg/m^3) occupational exposure to 1,3-butadiene, the correlation between airborne concentrations of 1,3-butadiene and its hemoglobine adducts, 1- and 2-hydroxy-3-butenyl valine, was much closer than for its urinary metabolites. Also in workers exposed to 4,4'-methylenedianiline at concentrations below the detection limit, the adducts were detected in a high percentage of samples[141]. Hagmar *et al.*[136] established a dose-response relationship between hemoglobin adducts of acrylamide and the peripheral nervous system symptoms in tunnel workers, but protein adducts can be seen in supposedly unexposed controls[129, 135, 138].

According to Bhatnagar and Talaska[131], the determination of unchanged carcinogenic compounds or their metabolites with relatively short half-lives makes it possible to evaluate only the most recent exposure (1–2 days'). Protein adducts integrate exposure over the half-life of the cells/protein sampled. The estimated lifespan of hemoglobin is 120 d. With such a long lifespan, the day-to-day variation is minimal once exposure has reached a steady state. Sampling for these markers should be performed semi-annually or annually to complement the medical screenings.

The practical application of adduct measurement in order to improve the prevention of diseases caused by hazardous substances in industry is a subject of particular interest in Germany. During the recent DFG round-table discussion on biological monitoring, two sessions were devoted to this problem[141].

Also the use of adduct measurements for evaluating occupational exposure has been proposed only in the German DFG recommendations[4]. The authors postulate the measurement of aniline released from the aniline-haemoglobin conjugation in whole blood after exposure to aniline and nitrobenzene. The recommended concentration is 100 μg aniline released from the conjugate. This conjugate can be measured after a period of at least three working days has elapsed. The proposed value is based on the studies of 1,000 workers exposed regularly to aniline and more than 50 employees with acute aniline intoxication. It was found that at methemoglobin levels of less than 5% also, less than 100 μg aniline was released from the hemoglobin conjugate per litre of whole blood. This approach has not been applied in any other recommendation. The authors of the ACGIH documentation[20] stressed that the kinetics of this indicator was studied only in one volunteer and that the concentration of aniline hemoglobin conjugates varied depending on the population (fast acetylators have a concentration 10 times lower than slow acetylators). Also the measurement of hydroxyethylvaniline after exposure to ethylene oxide and ethylene was recommended by DFG[4].

Although the area of DNA and protein adducts measurement is developing very fast, it appears that as yet little is known about the diagnostic meaningfulness of the results of these measurements. Considerably more studies are required in order to clarify the possible routine application of these methods in occupational practice.

Interlaboratory quality assurance systems and reference materials for a daily quality control program within the laboratory

To meet the demands for reliable biomonitoring determinations is not an easy task. The low analyte levels require complex sample treatment procedures that have to be carried out with a high degree of precision to allow reliable assessment of exposure. An approach widely applied today to achieve, maintain and document the quality of work of a biological monitoring laboratory is the adoption of a quality management program[142–144]. Internal quality control and external quality assurance are important parts of the quality management. The following measures should be undertaken to ensure the highest quality of the determinations[11, 145]:

—to give an exact protocol about the person's working time and exposure conditions (e.g. workload, skin contact, time of specimen collection),

—during the pre-analytical phase, standardize all the procedures that cannot be controlled by a classical quality control, including conditions of specimen collection, handling and storage,
—work out and strictly follow a validated method for the complete analytical procedure. (The appropriate analytical procedures for chemical substances in body fluids can be found in the materials published by ACGIH[20], WHO[15] or DFG[146]),
—establish a well performed system of internal and external quality control.

Quality assessment refers to the quality of the analytical results. It has two components: internal quality control, which is a set of procedures used by the staff of a laboratory to continuously assess the results as they are produced, and external quality assessment, which is a system for objectively checking the laboratory performance by an external agency or institution.

The most popular external quality assurance systems for chemical substances and their metabolites, at concentrations in biological media relevant to occupational exposure, are shown in Table 5. A quality assurance scheme which encompasses the range of concentrations of toxic substances relevant to environmental exposures is available from the Institute of Occupational, Social and Environmental Medicine, University Erlangen—Nürnberg, Germany (Table. 5).

Standard reference materials are the samples whose quantitative composition of certain components has been determined by various methods and by qualified laboratories. They are accompanied by a certificate stating the concentration of these components. Since this material is very expensive, it is usually used during the validation of an analytical procedure rather than for routine accuracy control. In view of the above, the commercially available control samples with an assigned concentration are used for routine internal quality control. The most commonly used certified and routine reference materials are specified in Table 6.

Potential users of BM and an attitude towards the practical application of BM in different countries.

It is not clear whether BM actually belongs to occupational hygiene or occupational medicine. Traditionally, biological monitoring has been conducted by occupational physicians and health professionals, and this is still the case in many European countries. But, the focus on noninvasive sampling (urine, and exhaled air sampling) and the growing awareness of the usefulness of biological monitoring has shifted BM closer to the activity area of occupational hygienists and work safety professionals. In fact, a vast majority of BEIs are directly related to the corresponding TLV values. The comparative ease of biological sample collection makes it a simple procedure that small firms may find useful, for example, urine samples collected at the end of the workday. But the use of biological monitoring as a tool for occupational hygienists needs more simplified data for the interpretation of results and implementation of the methods reflecting exposure to several compounds in a mixture that have similar endpoints (e.g. determination of unchanged VOCs in urine).

Despite the numerous long-term studies and considerable efforts of the researchers, the so-called 'health-based' reference values have been proposed and validated only for several chemical substances or groups of substances. These recommendations are of great value to health professionals because the health effect of exposure can be predicted directly from the determination of a biomarker of exposure. It is possible to predict early direct health effects of lead based substances on blood lead levels[1]. The results shown in Fig.1 indicate the advantage of using an integrated index of cadmium exposure CdB × t (cadmium in blood ($\mu g/l$) × years of exposure) as a predictor of kidney dysfunction in workers chronically exposed to cadmium (Jakubowski *et al.*[157]). This is also possible in the case of other biomarkers of exposure (mercury, fluorides and to some extent arsenic) or biomarkers of early reversible effects (the carboxyhemoglobin or methemoglobin concentration in blood, decreased cholinesterase activity in red blood cells). Such measurements can constitute an integral part of periodical medical examination and can be interpreted without knowing the results of environmental monitoring.

Recent policy developments in the United Kingdom have been aimed at clarifying the role of biological monitoring which can be used both for exposure assessment and health surveillance[28]. With regard to health surveillance, biological monitoring is applied when it is possible to link the results of biological tests to (an) adverse health effect(s). What is implicit in this requirement is that a no-adverse-effect level can be established. Where biological monitoring is being carried out as a part of health surveillance, it should be performed under the supervision of an occupational health professional; in some cases this must be a registered medical practitioner.

In Germany, biomonitoring is required by law and explicitly addressed in the German Ordinance on Dangerous Substances[32]. Section 18 deals with the "duty of surveillance". If the existence of dangerous substances in the workplace cannot be excluded, it must be assured that maximum concentration at the work place (MAK) values, technical exposure limits (TRK) values or Biological Exposure Values (BAT) are not exceeded.

The application of biological monitoring is regulated in completely different ways in the European countries. While BM is required by law in Germany, some countries carry out BM only where there are corresponding instructions from the European Union. This applies e.g.

Table 5. The most popular External Quality Assessment Schemes

Organizer	Determined chemical substances						References
	Blood		Serum		Urine		
	Metals	Solvents	Organo-chlorine compounds	Metals	Inorganic compounds	Organic compounds	
	Occupational medicine						
German Society for Occupational and Environmental Medicine e.V., Institute and Outpatient Clinic for Occup., Social and Environ. Medicine, University Erlangen - Nuremberg, Erlangen (Germany).	Cd Co Cr Hg Mn Ni Pb	*Aromatic hydrocarbons:* Benzene Toluene Xylenes Ethylobenzene *Chlorinated Hydrocarbons:* Dichloromethane Trichloroethane Tetrachloroethane	DDT, p,p'DDE HCB α, *β*, γ HCH PCBs (6 congeners) PCP	Al Co Cr Cu Fe Mn Ni Pt Se Zn	Al As As -species Be Cd Co Cr Cu F Hg Mn Ni Pb Sb Tl V Zn	o-Aminolevulinic acid Butoxyacetie acid o-Cresol Ethoxyacetic acid 2,5 Hexandione Hippurie acid l-Hydroxypyrene Mandelic acid N-methylformamide Methylhippuric acids t,t-Muconic acid Pentachlorophenol Phenol Phenyl glyoxylic acid S-phenylmercapturic acid 2- Thio-thiazolidine-4-carboxylic acid Triehloroacetic acid *Alcohols/ketones* Methanol, acetone, Methylethylketone	Schaller *et. al*[145, 147–149] Lehnert[150] Heinrich-Ramm[151]
	Environmental medicine						
	Cd Pb Hg		p,p'DDE HCB α, β, γ HCH PCBs (6 congeners) PCP	See -occupational medicine	As Cr Hg Ni Pt	Hydroxypyrene, Penta chlorophenol, four metabolites of pyrethroides (Br2-CA, cis-CI2-CA, *trans-CI2-CA*, 3-PBA) 2,5-dichlorophenol, 2,4,6-trichlorophenol, cotinine, nicotine	

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Organizer	Determined chemical substances			References
	Blood	Serum	Urine	
Finnish Institute of Occupational Health, Biomonitoring Laboratory, Helsinki (Finland) FIOH.			mandelic acid, methylenedianiline, *trans*, *trans*-muconic acid, methylhippuric acid; phenol, trichloroacetic acid 2,5-heksanedione, creatinine and relative density	Valkonen *et-al*.[152, 153]
Wolfson EQA Laboratory, PO Box 3909, Birmingham, B15 2UE (Great Britain) UK NEQAS.	Cd, Pb			Bullock[154] Taylor *et al*.[155]
School of Biomedical and Life Sciences University of Surrey, Guildford, Surrey, GU2 7XH (Great Britain). UK NEQAS.	As, Cd, Pb, Hg, Mn	Al, Cu, Se, Zn		Report and Directory, 4th Edition, 2000, UK NEQAS
Danish National Institute of Occupational Health - AMI, Denmark (DEQAS).	Pb			Chrisitansen *et al* .[156]
Centre de Toxicologie du Québec, Toxicology Laboratory, Québec, Canada (CTQ).	Cd, Pb, Hg	Al, Cu, Mn, Se, Zn	As, Cd, Cr, Cu, F, Hg, Pb, Se, Zn	http://www.ctq.qc.ca/
Center for Disease Control and Prevention, Blood Lead Laboratory Reference System, USA (BLLRC).	Pb			http://www.cdc.gov/nceh/dls/lead.htm

Table 6. Selected commercially available reference materials for biological monitoring

Source/label Order	Matrix	Analyte(s) with certified concentrations	Analyte(s) with non-certified concentrations	Number of concentration levels
NIST				
2671a, 2672b,	Human urine	F, Hg		2
	Human serum	Ca, K, Li, Mg, Na		1
1589, 956A,		PCB's, Pesticides and Dioxin/Furans		1
955, 966	Bovine blood	Cd, Pb,		2 or 4
BCR				
194, 195, 196,	Bovine blood	Cd, Pb		3
397,	Human hair	Cd, Hg, Pb, Se, Zn		1
304,	Human serum	Ca, Mg, Li		1
573, 574, 575	Human serum	creatinine		1
IAEA				
A13	Animal blood	Br, Ca, Cu, Fe, K, Na, RB, S, Se, Zn	Mg, Ni, P, Pb	1
085	Human hair	Hg, methylmercury	Ca, Cu, Mg,	2
Recipe (ClinCheck®)				
RP8883, RP8881, RP8882	Human serum		Al, As, Cd, Co, Cr, Cu, F, Fe, Mn, Ni, Se, Zn	3 2
RP8883, RP8884, RP8885	Human plasma		Al, As, Cd, Co, Cr, Cu, Fe, Li, Mg, Ni, Pt, Se, Zn	2
RP8847, RP8848, RP8849	Human urine		Al, As, Cd, Co, Cr, Cu, F, Hg, Mn, Ni, Pt, Pb, Sb, Th, Zn	2
RP8867, RP8868, RP8869	Human urine Toxic organic compounds		Cotinine, nicotine, 2,5-dichlorophenol, HA, 1-HP, o-cresol, MA, MHA, *t,t-MCA*, PCP, phenol, PGA, TCA, pyrethroid metabolites, (Br_2-CA, cis-CI_2-CA, *trans-CI_2-CA*, 3-PBA)	3
RP8860 RP8861	Human serum Organochloric compounds		PCB 28, 52, 101, 138, 153, 180	

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(continued)

Source/label Order	Matrix	Analyte(s) with certified concentrations	Analyte(s) with non-certified concentrations	Number of concentration levels
RP8862, RP8889			P,p1-DDE, DDT, α-HCH, β-HCH, γ-HCH, HCB (Heksachlorobenzen), PCP (pentachlorofenol)	3
RP8863 RP8864	Bovine blood Organochloric compounds		PCB 28, 52, 101, 138, 153, 180	
RP8865, RP8886			p,p'-DDE, γ-HCH, HCB (Heksachlorobenzen)	
AMI B1701, B1702, B1703	Human blood		Pb, Cd, Cr, Mn	3
Seronorm™ -Trace Elements				3
SERO 201505, 201605, 201705	Human blood		Al, As, Be, Bi, Cd, Co, Cr, F, Hg, Mn, Mo Ni, Pb, Sb, Se, Tl, V	
SERO 201405, 203105	Human serum	Al., Au, Ca, Co, Cr, Cu, F, Fe, K, Li, Mg, Mn, Na, Ni, P, S, Se, Zn		2
SERO 201305, 201205	Human urine	Al, As, Ca, Cd, Cl, Co, Cr, Cu, F, Hg, K, Mg, Mn, Na, Ni, P, Pb, Sb, Se, Tl, creatinine, formic acid, hippuric acid, 1-hydroxypyrene, phenol, TCA, urea		2
BioRad Lab, *Lyphocheck®*	Human blood	Al, As, Cd, Co, Cu, Cr, Sb, Pb, F, Hg, Mn, Ni, Se, Tl, Zn,		2
	Metals and Toxic organic compounds	ALA, HA, MA, PGA, PCP, Phenol, TCA		2
	Human blood	Pb		3

Addresses of the some of the main producers

1) AMI, LGC Nordic AB, P.O. Box 1737 SE-50117 Boras, Sweden 2) BCR = European Community Measurements and Testing, Institute for Reference Materials and Measurements (IRMM), Retieseweg, B-2440 Geel, Belgium 3) International Atomic Energy Agency, P.O.Box 100, A-1400 Vienna, Austria; 4) Recipe Chemicals+Instruments. GmbH, Labortechnik-Sandstrasse 37-39, D-80335 Munich, Germany. 5) Seronorm -SERO AS, P.O. Box 24, NO-1375 Billingstad, Norway; 6) NIST-National Institute of Standards & Technology, Standard Reference Materials Program 100 Bureau Drive Gaithersburg MD 20899-2322, USA. 7) Bio-Rad Laboratories, 1000 Alfred Nobel Drive Hercules, California 94547, US

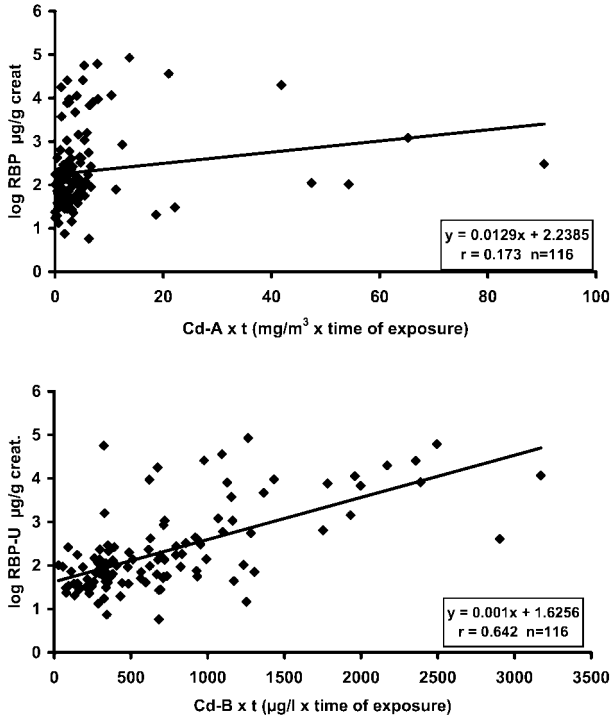

Fig. 1. Relationship between integrated indexes of exposure (Cd-A × t or Cd-B × t) and RBP concentrations in urine of exposed workers[157)]

to lead where the binding biological limit is 700 $\mu g/l$ of blood (Council Directive 98/24/EC of April 1998). Presently, biological limits are being proposed also for other substances (mercury in blood and urine, and 4,6-dinitro-o-cresol in blood). This attitude may change in the near future because a chapter concerning Biological Limit Values (BLVs) has been included in the SCOEL document[26)]. It says that, where appropriate, SCOEL will recommend BLVs on the basis of the currently available scientific data which indicate that the concentrations or levels of activity equivalent to the BLV are unlikely to result in adverse effects on health.

Japan can serve as an example to what extent the administrative decisions can influence the practical application of BM. Periodical biomonitoring of workers exposed to lead and eight popular organic solvents, including solvent mixtures, became mandatory on October 1, 1989, with an ordinance issued by the Ministry of Labour. The total number of cases examined in 1990 was about 110,000 for the biomonitoring of lead, and about 520,000, for the monitoring of urinary metabolites of the eight organic solvents. In 1986, BM for lead in blood was carried out in 6,907 workers. In addition, 3,947 workers were monitored for hippuric acid, 1,523 for methylhippuric acid and 1,609 for total trichloro-compounds in urine. The findings of a large-scale biological monitoring program in Japan were published by Ogata *et al.*[158)] All workers handling lead and eight kinds of major organic solvents had physical examinations and biological monitoring performed at the same time. The total number of cases examined from 1989 to 1994 was about 661,000 for lead and about 4,1732,300 for the urinary metabolites of organic solvents. The results were classified into three categories and category 3 were workers having the urinary levels of metabolites of organic solvents higher than the ACGIH recommendations issued in 1988–1989 and blood lead levels higher than 400 $\mu g/l$. The percentage of workers in category 3 was 1.4% for lead in blood and 0.2–2.4% for the urinary metabolites of the eight organic solvents. Japan represents a centralized solution to BM application which enables exposure evaluation on the national level.

A very good example of the practical use of BM at the level of a large enterprise is the BASF company in Ludwigshafen, Germany[32)], or the Shell Company where the Biomedical Laboratory was established in 1979[159)] and a step-by- step procedures have been implemented. The most important elements of the procedures include deciding (a) whether or not to perform BM; (b) how to interpret the BM results (existing data, development of internal action levels); (c) how to design the implementation of an intelligent monitoring strategy and inform the participants about the reasons for initiating the program, the procedures to be used and the potential consequences; (d) how to communicate individual results to the workers concerned and the group results to supervisory personnel, plant management and the Work Council. The publication of the findings is also an integral part of the process. For substances with no recommendations for BM, these companies have developed their own internal "action levels".

The above examples demonstrate how BM can be successfully applied to occupational health for exposure monitoring and health surveillance on a routine basis. They also show how practical and ethical problems can be solved by a close cooperation between the health service, the plant management and the employees.

Conclusions

—Biological monitoring (BM) of exposure and early health effects has an important role to play both in health surveillance and exposure assessment. There are considerable discrepancies between Europe and the United States regarding the role of biological monitoring of occupational exposure . BM has been an important tool of medical health surveillance in the European countries. In the United States, it belongs to the field of occupational hygiene rather than health surveillance. It seems that both the approaches can be accepted. But the practical application of biological monitoring requires qualified personnel who can choose the right methods to

evaluate health risk (medical health surveillance) or quantify dermal exposure, or the quality of individual protective measures (mask, clothes). Small and medium enterprises can rent services in regional laboratories.

—In spite of the tendency to reduce the occupational exposure limits, the recommended BAT or BEI values can be applied for routine measurements. New areas of BM application to occupational exposure include the determination of DNA and protein adducts, unchanged volatile organic compounds in urine, the monitoring of exposure to pesticides, antineoplastic drugs, hard metals, and polycyclic aromatic hydrocarbons. These areas require sophisticated analytical methods such as GC-MS-MS, HPLC-MS-MS and ICP-MS.

—More attention should be paid to the development of truly health-based biomarkers of exposure based on the dose-effect and dose-response relationships.

—In the general environment, BM is the most valuable tool for acquiring knowledge of current levels of internal exposure to xenobiotics, identifying the hot spots and developments in the trends of exposure. BM can provide policy makers with more accurate information on the control measures undertaken. At present, the main areas include heavy metals, persistent organic pollutants and pesticides.

—The use of BM for the assessment of exposure to chemical substances has recently found its place in the official recommendations of the European Union and is assumed to be helpful for the prevention of adverse health effects. This may position biological monitoring next to environmental monitoring where the data for the interpretation of results are available. Therefore, it would be worthwhile to include BM in the training curricula for occupational hygienists and occupational physicians.

Acknowledgments: This review was supported by Grant NMALRI-D1.1NOFE-0207from the European Chemical Industry Council- CEFIC.

Glossary of abbreviations:

β_2M	β_2 microgobulin
ACGIH	The American Conference of Governmental Industrial Hygienists
AchE	acethylcholinesterase
ADI	acceptable daily intake
AHH	arhydrocarbon hydroxylase
BaP	benzeno [*a*] pyrene
BAT	Biologische Arbeitstofftoleranzwerte
BEI	Biological Exposure Indices
BGV	benchmark guidance values
BLV	biological limit values
BM	biological monitoring
BMDL	bench-mark dose
CBD	chronic beryllium disease
CDC	Center for Disease Control and Prevention
Cd-U	cadmium in urine
CHP	chlorpyrifos
CHPM	chlorpyrifos-methyl
CNS	central nervous system
DFG	Deutsche Forschungsgemeinschaft
EKA	exposure equivalents for carcinogenic materials
EM	environmental monitoring
EPA	Environmental Protection Agency
FL-AAS	—flame atomic absorption spectrometry
GC	gas chromatography
GC-ECD	gas chromatography with electron capture detector
GC-FPD	gas chromatography with photometric detection
GC-MS	gas chromatography with mass detection
GF-ASA	flameless atomic absorption spectrometry
HBM	human biological monitoring values
HC	α_1-microglobulin
HFC	high frequency cells
Hg-H	mercury in hair
HGV	health guidance values
HP	hydroxy-pyrene
HPLC	high-pressure liquid chromatography
HS	head space
HS-SPME	head space solid phase microextraction
IPC-MS	inductively coupled plasma with mass spectrometry
IPCS	International Program of Chemical Safety
LOAEL	lowest observed adverse effect level
LOD	limit of detection
MAK	maximum concentration in the workplace
MCPA	4-chloro-2-methylphenoxyacetic acid
MS	mass detector
MTAE	methyl *tert*-amyl ether
MTBE	methyl *tert*-butyl ether
NAG	N-acetyl β-D glucosaminidase
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
OEL	occupational exposure limit
OP	organophosphorous pesticides
PAH	policyclic aromatic hydrocarbons
Pb-B	lead in blood
PTWI	Provisionally Tolerated Weekly Intake
RBP	retinol binding protein
RfD	reference dose
SCOEL	Scientific Committee on Occupational Exposure Limits
TAME	*tert*-amyl methyl ether
TCPyr	3,5,6-trichloro-2-piridinol
TLV	threshold limit value
TLV-TWA	threshold limit value—time weighted average
TRK	technical exposure limits
US EPA	Environmental Protection Agency (USA)

VOC volatile organic compounds
WHO-FAO World Health Organization—Food and Agricultural Organization

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