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

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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\(^ {2-13}\) 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 through 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, carboxyhemoglobin, methemoglobin, 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 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.

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. 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 µg/l to 400 µg/l for men and from 300 µg/l to 100 µg/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 (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

<table>
<thead>
<tr>
<th>Categories of DFG recommendations</th>
<th>Substances added</th>
<th>Substances removed</th>
<th>Changes in BAT values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BAT</td>
<td>n-Butyl alcohol, Cumene, Cyclohexane, 1,2-Dichlorobenzene, N,N-Dimethyl acetamide, Ethylene glycol monobutyl ether, Ethylene glycol monobutyl ether acetate, Ethylene glycol monomethyl ether, Isopropyl alcohol, Manganese, 4,4-Methylene diphenyl isocyanate (MDI)</td>
<td>2-Butoxyethanol, 2-Butoxyethylacetate, δ-Aminolevulinic acid, 1,4-Dichlorobenzene, Dichloromethane, 2-Ethoxyethanol, Propanol, Phenol</td>
<td>Lead (B)(a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlorobenzene</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 4-chlorocatechol (U)</td>
</tr>
<tr>
<td>2. EKA</td>
<td>Dichloromethane, Tetrachloroethylene, Trichloroethylene</td>
<td></td>
<td>Dimethyl formamide</td>
</tr>
<tr>
<td>3. Carcinogenic substances without EKA</td>
<td>Antimony and its inorganic compounds, Beryllium, Dichlorobenzene, Ethylbenzene, Mercury, organic compounds, Methyl bromide</td>
<td>Tetrachloroethylene, Trichloroethylene</td>
<td></td>
</tr>
<tr>
<td>4. BLW</td>
<td>Arsenic and inorganic compounds, Cresol, Methyl bromide, Phenol</td>
<td></td>
<td>Carbon tetrachloride (B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tetrahydrofurane (U)</td>
</tr>
</tbody>
</table>

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 3. United Kingdom biological monitoring guidance values

<table>
<thead>
<tr>
<th>Substance</th>
<th>Health guidance value</th>
<th>Sampling time</th>
<th>Benchmark guidance value</th>
<th>Sampling time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butan-2-one*</td>
<td>70 µmol butan-2-one/l in urine</td>
<td>Post-shift</td>
<td>35 µg/g creat. (c)</td>
<td></td>
</tr>
<tr>
<td>2-Butoxyethanol</td>
<td>240 mmol butoxyacetic acid/mol creatinine in urine</td>
<td>Post-shift</td>
<td>5 mg/g creat. (with hydrolysis) (b,c)</td>
<td>0.4 mg/l * (b,c)</td>
</tr>
<tr>
<td>N,N-Dimethylacetamide</td>
<td>100 mmol n-methylacetamide/mol creatinine in urine</td>
<td>Post-shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindane</td>
<td>35 nmol/l (10 µg/l) of lindane in whole blood (equivalent to 70 nmol/l of lindane in plasma)</td>
<td>Random</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MbOCA</td>
<td>35 nmol total MbOCA/mol creatinine in urine</td>
<td>Post-shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>20 µmol mercury/mol creatinine in urine</td>
<td>Random</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4,4'-Methylenedianiline (MDA)</td>
<td>50 µmol total MDA/mol creatinine in urine</td>
<td>Post-shift for inhalation and pre-shift next day for dermal exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Methylpentane-2-one</td>
<td>20 µmol 4-methylpentane-2-one/l in urine</td>
<td>Post-shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>30 ppm carbon monoxide in breath, equivalent to 5% COHb</td>
<td>Post-shift</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Non included in the H&S Guidance on Laboratory Techniques in Occupational Medicine 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 Equivalenti) 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
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 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 $\beta_2$-microglobulin ($\beta_2$M), retinol binding protein
(RBP) and N-acetyl-$\beta$-D-glucosaminidase (NAG), were positively associated with urinary excretion of cadmium.

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(RBP) and N-acetyl-$\beta$-D-glucosaminidase (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 $2 + 4 \mu g/24 h^{33}$. Schütz and Elinder^{34} noted urinary
excretion of $\alpha_1$-microglobulin (HC) above the cut-off level in 10% of the investigated population with cadmium
in urine (Cd-U) concentrations about 1 $\mu g/g$ 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 $\mu g/
g$ creatinine.

   It has been postulated that for the general population the Cd-U levels should be below 2.5 $\mu g/g$ 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. 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 (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., 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. 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. An increase 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. The obtained benchmark dose (BMDL 5%) of approximately 10 µg/g maternal hair was similar to that calculated for other neurodevelopmental variables in the Faroese children and in the New Zealand population.

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. 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). In the Madeira fishermen and their families, it amounted to 38.9 µg/g in men and 10.4 µg/g in women.

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). The HBM values

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

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

HBM—The concentration of an environmental toxin in human biological material, below which there is no risk of adverse 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. 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, 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, 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.

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 or the trends in the concentration of dioxins in breast milk in the European countries. 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 µg/l; 36 µg/l and 27 µg/l, respectively. In Sweden, the geometric mean of the Pb-B concentration in schoolchildren has decreased from about 60 µg/l in 1978 to about 25 µg/l over a period of 15 yr.

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 on exposure assessment concern the level of metabolites in urine.

Nevertheless, in the occupational settings, VOCs are almost as a rule present in mixtures and for a large number of them, the critical effect consists of a depressive action on the central nervous system. 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 but then the concentrations are...
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. This small amount of solvent dissolved in urine collected in the bladder tends to reach a pressure equilibrium with alveolar air and arterial blood. Therefore, following Ghittori et al., 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. 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. 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, during tank lorry loading, and in road tanker drivers. During the unloading, 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/m³, 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. and Saarinen et al. 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, benzene, and xylenes or tetrachloroethylene 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. 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). 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, methyl ethyl ketone, styrene, toluene and xylene.

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, 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. 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 µg/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 lipophilic 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.
2. Poly cyclic 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-naphthylamine, hydroxy phenanthenes and 1-hydroxypyrene (1-HP)79.

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 factor79–81. Becher and Bjorseth82) 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 plant83) and from coke oven workers84) 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-HP86). 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% pyrene89.

Several authors tried to establish admissible levels of 1-HP in urine for specific exposures. According to Jongenellen80), 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/m³ and 2 µg/m³, respectively. A similar value, of 4 µg/g creat., was proposed by Levin et al.80) A higher value of 6.1 µg/g creat. was suggested by Van Roij et al.81). In the study on workers at an aluminum reduction plant, Tjoe Ny et al.82) assumed that exposure to 0.2 mg/m³ of coal tar pitch or 5 µg/m³ 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.83) concluded that the concentrations of PAHs in the air and 1-HP in urine should be kept below 6.4 µg/m³ and 2.7 µg/g creat., respectively.

Recently Jongenellen84) 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. Only a heavy exposure to coal-tar formulations in patients with psoriasis and in coke oven workers 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 in their notice of intended changes mentioned the measurement of 1-hydroxypropane 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).

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, 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 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. Biological limit values for diethylrdrin, endrin, coumarins, 4-chloro-2-methylphenoxycetic acid (MCPA), and 2,4-dichlorophenoxycetic acid (2,4-D) were also proposed by the Study Group of the Scientific Committee on Pesticides of the International Commission on Occupational Health.

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.

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 µg/l, higher values apply to the monitoring of occupationally exposed persons. Aprea et al. 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 µg/l of urine. Recently, CDC has developed a scientifically sound GC-MS-MS method to quantify non-specific AP. 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 µg/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 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.

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 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 µg/l)99). 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 µg/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 USA117 yielded a 50 percentile of 3 µg/l, and an Italian study101 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 urine118. 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 ifosfamide, 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 week118.

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 µg/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.113 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 µg/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 collision120. 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 aetiological 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 granulomas120. 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 µg/l urinary cobalt for 0.05 mg/m 3 cobalt in air4. ACGIH3 set up two BEIs of 0.31 µg/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 µg/l125. The EKA value for nickel is 15 µg/l for urine and 0.10 mg/m 3 nickel in air18. The reference value for urinary nickel is 2.2 µg/l125.

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 µg/l. The mean tungsten concentrations in the urine of non-exposed people (n=33) were 0.31 µg/l and 0.30 µg/g creatinine. The reference values (95 percentile) were 0.86 µg/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

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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, tungstenenate, 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 µg/l, 0.28 µg/l. In the studies by Apostoli and Schaller or Wegner et al, where beryllium analysis was carried out by the ICP-MS method, the detection limit was 0.03 µg/l, or 0.06 µg/l, and beryllium concentrations in the urine samples of persons not occupationally exposed were below these detection limits.

Wegner et al 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 µg/l (<0.06 to 0.56 µg/l) and for the post-shift urine samples <0.06 µg/l (<0.06–0.29 µg/l). No analysis of the correlation between external and internal exposure was carried out.

Apostoli and Schaller 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 µg/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 µg/l whereas the concentrations of Be in inhalable dust were below the recommended threshold limit value–time weighted average (TLV-TWA) of 0.2 µg/m³.

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, the sensitivity of the currently available methods (³²P 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 10⁶ nucleotides, which stands for at least 600 modified nucleotide molecules per adult cell and over 10⁵ 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 and exfoliated urothelial cells for compounds that are associated with urinary bladder cancer. 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-methylphenylimidazolo[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. Also the relationship between smoking history and DNA adducts in the leukocytes has not been adequately demonstrated. According to Bhatnagar et al., 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. 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.

**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, 1,3-butadiene, styrene, styrene-7,8-oxide and benzene, heterocyclic amines, dimethylformamide, trinitrotoluene and 4,4′-methyleneedianiline. Boogaard et al. 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 hemoglobin adducts, 1- and 2-hydroxy-3-butenyl valine, was much closer than for its urinary metabolites. Also in workers exposed to 4,4′-methyleneedianiline at concentrations below the detection limit, the adducts were detected in a high percentage of samples.

Hagmar et al. 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. According to Bhatnagar and Talaska, 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.

Also the use of adduct measurements for evaluating occupational exposure has been proposed only in the German DFG recommendations. The authors postulate the measurement of aniline released from the aniline-hemoglobin 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 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.

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. 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:

—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\textsuperscript{20}, WHO\textsuperscript{15} or DFG\textsuperscript{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\textsuperscript{15}. The results shown in Fig.1 indicate the advantage of using an integrated index of cadmium exposure $\text{CdB} \times t$ (cadmium in blood (μg/l) × years of exposure) as a predictor of kidney dysfunction in workers chronically exposed to cadmium (Jakubowski et al.\textsuperscript{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\textsuperscript{20}. 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\textsuperscript{30}. 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

<table>
<thead>
<tr>
<th>Organizer</th>
<th>Blood</th>
<th>Determined chemical substances</th>
<th>Serum</th>
<th>Urine</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metals</td>
<td>Solvents</td>
<td>Organo-chlorine compounds</td>
<td>Metals</td>
<td>Inorganic compounds</td>
</tr>
<tr>
<td>Occupational medicine</td>
<td>Cd</td>
<td>Aromatic hydrocarbons:</td>
<td>DDT, p,p’DDE</td>
<td>Al</td>
<td>Al</td>
</tr>
<tr>
<td></td>
<td>Co</td>
<td>Benzene</td>
<td>HCB</td>
<td>Co</td>
<td>As</td>
</tr>
<tr>
<td></td>
<td>Cr</td>
<td>Toluene</td>
<td>α, β, γ HCH</td>
<td>Cr</td>
<td>As -species</td>
</tr>
<tr>
<td></td>
<td>Hg</td>
<td>Xylenes</td>
<td>PCBs</td>
<td>Cu</td>
<td>Be</td>
</tr>
<tr>
<td></td>
<td>Mn</td>
<td>Ethylbenzene</td>
<td>(6 congeners)</td>
<td>Fe</td>
<td>Cd</td>
</tr>
<tr>
<td></td>
<td>Ni</td>
<td>PCP</td>
<td>Mn</td>
<td>Ni</td>
<td>Cr</td>
</tr>
<tr>
<td></td>
<td>Pb</td>
<td>Chlorinated</td>
<td>Pt</td>
<td>Cu</td>
<td>Mandelic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrocarbons:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dichloromethane</td>
<td>Se</td>
<td>F</td>
<td>N-methylformamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichloroethane</td>
<td>Mn</td>
<td>Hg</td>
<td>Methylhippuric acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetrachloroethane</td>
<td>Ni</td>
<td>Mn</td>
<td>t,t-Muconic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ni</td>
<td>Pentachlorophenol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phenol</td>
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<td></td>
<td></td>
<td></td>
<td>Sb</td>
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<td></td>
<td>Tl</td>
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<td></td>
<td>V</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Environmental medicine

| Cd | p,p’DDE | See -occupational medicine | As | Hydroxyproline, Penta chlorophenol, four |
| Pb | HCB | Cr | metabolites of pyrethroids |
| Hg | α, β, γ HCH | Hg | (Br2-CA, cis-CI2-CA, |
| | PCBs | Ni | trans-CI2-CA, 3-PBA) 2,5- |
| | (6 congeners) | Pt | dichlorophenol, 2,4,6- |
| | | | trichlorophenol, cotinine, |
| | | | nicotine | |

(continued on next page)
(continued)

<table>
<thead>
<tr>
<th>Organizer</th>
<th>Determined chemical substances</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finnish Institute of Occupational Health, Biomonitoring Laboratory, Helsinki (Finland) FIOH.</strong></td>
<td>mandelic acid, methylenedianiline, trans, trans-muconic acid, methylhippuric acid; phenol, trichloroacetic acid 2,5-heksanedione, creatinine and relative density</td>
<td>Valkonen et al.(^{152,153})</td>
</tr>
<tr>
<td>Wolfson EQA Laboratory, PO Box 3909, Birmingham, B15 2UE (Great Britain) UK NEQAS.</td>
<td>Cd, Pb</td>
<td>Bullock(^{154}) Taylor et al.(^{155})</td>
</tr>
<tr>
<td>School of Biomedical and Life Sciences University of Surrey, Guildford, Surrey, GU2 7XH (Great Britain). UK NEQAS.</td>
<td>As, Cd, Pb, Hg, Mn</td>
<td>Report and Directory, 4(^{th}) Edition, 2000, UK NEQAS</td>
</tr>
<tr>
<td>Danish National Institute of Occupational Health - AMI, Denmark (DEQAS).</td>
<td>Pb</td>
<td>Christiansen et al.(^{156})</td>
</tr>
<tr>
<td>Centre de Toxicologie du Québec, Toxicology Laboratory, Québec, Canada (CTQ).</td>
<td>Cd, Pb, Hg</td>
<td><a href="http://www.ctq.qc.ca/">http://www.ctq.qc.ca/</a></td>
</tr>
<tr>
<td>Center for Disease Control and Prevention, Blood Lead Laboratory Reference System, USA (BLLRC).</td>
<td>Pb</td>
<td><a href="http://www.cdc.gov/nceh/dls/lead.htm">http://www.cdc.gov/nceh/dls/lead.htm</a></td>
</tr>
<tr>
<td>Source/Label Order</td>
<td>Matrix</td>
<td>Analyte(s) with certified concentrations</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>NIST 2671a, 2672b, 1589, 956A, 955, 966</td>
<td>Human urine</td>
<td>F, Hg</td>
</tr>
<tr>
<td></td>
<td>Human serum</td>
<td>Ca, K, Li, Mg, Na</td>
</tr>
<tr>
<td></td>
<td>Bovine blood</td>
<td>Cd, Pb</td>
</tr>
<tr>
<td>BCR 194, 195, 196, 397, 304, 573, 574, 575</td>
<td>Bovine blood</td>
<td>Cd, Pb</td>
</tr>
<tr>
<td></td>
<td>Human hair</td>
<td>Cd, Hg, Pb, Se, Zn</td>
</tr>
<tr>
<td></td>
<td>Human serum</td>
<td>Ca, Mg, Li</td>
</tr>
<tr>
<td>IAEA A13 085</td>
<td>Animal blood</td>
<td>Br, Ca, Cu, Fe, K, Na, RB, S, Sc, Zn</td>
</tr>
<tr>
<td></td>
<td>Human hair</td>
<td>Hg, methylmercury</td>
</tr>
<tr>
<td>Recipe (ClinCheck®)</td>
<td>Human serum</td>
<td>Al, As, Cd, Co, Cr, Cu, F, Fe, Mn, Ni, Se, Zn</td>
</tr>
<tr>
<td>RP8883, RP8881, RP8882</td>
<td>Human plasma</td>
<td>Al, As, Cd, Co, Cr, Cu, Fe, Li, Mg, Ni, Pt, Se, Zn</td>
</tr>
<tr>
<td>RP8883, RP8884, RP8885</td>
<td>Human urine</td>
<td>Al, As, Cd, Co, Cr, Cu, F, Hg, Mn, Ni, Pt, Pb, Sb, Th, Zn</td>
</tr>
<tr>
<td>RP8847, RP8848, RP8849</td>
<td>Human urine</td>
<td>Cotinine, nicotine, 2,5-dichlorophenol, HA, l-HP, o-cresol, MA, MHA, t,t-MCA, PCP, phenol, PGA, TCA, pyrethroid metabolites, (Br₂-CA, cis-Cl₂-CA, trans-Cl₂-CA, 3-PBA)</td>
</tr>
<tr>
<td>RP8867, RP8868, RP8869</td>
<td>Human urine</td>
<td>Toxic organic compounds</td>
</tr>
<tr>
<td></td>
<td>Human serum</td>
<td>Organochloric compounds</td>
</tr>
</tbody>
</table>

(continued on next page)
### Organochloric compounds (continued)

<table>
<thead>
<tr>
<th>Source/label Order</th>
<th>Matrix</th>
<th>Analyte(s) with certified concentrations</th>
<th>Analyte(s) with non-certified concentrations</th>
<th>Number of concentration levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP8862, RP8889</td>
<td>Bovine blood</td>
<td>P, p, DDE, DDT, α-HCH, β-HCH, γ-HCH, HCB (Heksachlorobenzen), PCP (pentachlorofenol)</td>
<td>PCB 28, 52, 101, 138, 153, 180</td>
<td>3</td>
</tr>
<tr>
<td>AMI, B1701, B1702, B1703</td>
<td>Human blood</td>
<td>Pb, Cd, Cr, Mn</td>
<td>p, p'-DDE, γ-HCH, HCB (Heksachlorobenzen)</td>
<td>3</td>
</tr>
</tbody>
</table>

**Addresses of some of the main producers**

Marek Jakubowski, et al.: Biological Monitoring of Exposure

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 document26). 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 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 µg/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.

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-0207 from the European Chemical Industry Council-CEFIC.

Glossary of abbreviations:

\( \beta_2 \text{M} \) β₂ microglobulin
ACGIH The American Conference of Governmental Industrial Hygienists
AchE acetylcholinesterase
ADI acceptable daily intake
AHH arhdrocarbon hydroxylase
BaP benz[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 chlorpyritos
CHPM chlorpyritos-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 \( \alpha_1 \)-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-amyel ether
MTBE methyl tert-butyl ether
NAG N-acetyl \( \beta \)-D glucosaminidase
NHANES National Health and Nutrition Examination Survey
NOAEL no observed adverse effect level
OEL occupational exposure limit
OP organophosphorous pesticides
PAH polycyclic 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-amyel 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)
References
6) HB Elkins: The Chemistry of Industrial Toxicology. 2nd edn. New York: John Wiley and Sons, Inc., 1959: 452
13) MS Morgan and KH Schaller: An analysis of criteria for biological limit values developed in Germany and in the United States. Int Arch Occup Environ Health 72, 195–102 (1999)
17) Que Hee SS. Biological Monitoring. An Introduction. Van Nostrand Reinhold, N.Y.
34) A Schütz and CG Elinder: Low-level exposure to cadmium and early kidney damage; the OSCAR study.


64) FRX Van Leeuwen and R Malisch: Results of the third round of the WHO-coordinated study on the levels of PCBs, PCDDs and PCDFs in human milk.
Organohalogen Compounds 56, 311–316 (2002)


107) SA Harris, PN Corey, AM Sass-Kortsak and JT Purdham: The development of a new method to estimate total daily dose of pesticides in professional turf applicators following multiple and varied exposures in occupational settings. Int Arch Occup Environ Health 74, 345–358 (2001)


116) HM Koch, J Hardt and J Angerer: Biological monitoring of exposure of the general population to the organophosphorous pesticides chlorpyrifos and chlorpyrifos-methyl by determination of their specific metabolite 3,5,6-trichloro-2-pyridinol. Int J Hyg Environ Health 204, 175–180 (2001)


121) PJM Sessink, KA Boer, APH Schefhals, RMB Anzion and RP Bos: Occupational exposure to antineoplastic agents at several departments in a hospital. Occup Environ Med 64, 105–112 (1992)


146) J Angerer, K-H Schaller, eds. Analyses of Hazardous Substances in Biological Materials, Vols. 1 to


159) Boogaard PJ. Personal information on establishment of the Shell Biomedical Laboratory. 2004.