

Biological monitoring of workers exposed to organic solvents — Past and present

by Jüngen Angerer, PrivDoz Dr¹

ANGERER J. Biological monitoring of workers to organic solvents — Past and present. *Scand J Work Environ Health* 11 (1985): suppl 1, 45–52. The development of biological monitoring for persons exposed to organic solvents is described. The advantages of this supervision strategy, as well as the reservation against it, are discussed. With the target organs of organic solvents, matrices and parameters for biological monitoring taken into consideration, the following recommendations can be given: the determination of solvent level in blood or alveolar air as a substitute is obligatory for the biological monitoring of organic solvents (the toxic stress of the target organ — the brain — is reflected this way); metabolites have to be determined also when they or their predecessors impair other organs. The discussion of chemical analysis, interference and influencing factors, as well as biological limit values, leads to suggestions of how to interpret the results of biological monitoring. Beyond the estimation of the health risk of the individual worker, the results also have to be interpreted on a group basis. Only in this way can all information on biological monitoring be used to the advantage of prevention. In summary, today biological monitoring is possible for most of the organic solvents. Estimation of health risk in the case of simultaneous exposure to several solvents is still not possible. Parameters measuring toxic strain must be established. The various social groups have to be convinced of the advantages of biological monitoring.

Key terms: biological limit values, chemical analysis, interpretation, matrices, parameters, target organs.

After chemistry had been inorganic for 5 000 years, the discovery of organic chemistry began with the last century. It was the hour of birth of organic solvents as well. Two solvents, carbon disulfide and, a little later, benzene, belong to the first representatives of this kind of substances, applications for which, in a mainly inorganic world, had to be searched for. The times of search quickly went by. The demand for those highly volatile, lipophilic substances increased with the further development of organic chemistry according to the principle that only like dissolves like.

Today vast amounts of different solvents cause serious problems for occupational hygiene and medicine. Out of about 275 solvent mixtures used in the Federal Republic of Germany, 14 solvents have turned out to be of utmost importance. They belong to various groups of chemical compounds, ie, aromatic hydrocarbons, esters, ketones, alcohols, chlorinated and aliphatic hydrocarbons, fluorochlorohydrocarbons, and the so-called cellosolves (figure 1).

To estimate individual exposure and the health risk of workers occupationally exposed, biological monitoring is a suitable tool.

In 1980, at a symposium of the European Communities, biological monitoring was defined (42) as:

... continuous ... activity for collection of biological samples for analysis of concentration of

pollutants, metabolites ..., with the objective to assess exposure and health risk to exposed subjects comparing the data observed with a reference level and — if necessary — leading to corrective action.

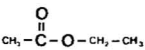
ORGANIC SOLVENTS		
aromatic hydrocarbons		
benzene		
TOLUENE		
XYLENES		
ETHYL BENZENE		
esters		
ETHYL ACETATE		
BUTYL ACETATE		
ketones		
ACETONE		
2-BUTANONE		
alcohols		
METHYL ALCOHOL		$\text{CH}_3 - \text{OH}$
PROPYL ALCOHOL		
BUTYL ALCOHOL		
chlorinated hydrocarbons		
DICHLOROMETHANE		
1,1,1-TRICHLOROETHANE		$\text{Cl}_3\text{C} - \text{CH}_3$
TRICHLOROETHYLENE		
TETRACHLOROETHYLENE		
aliphatic hydrocarbons		
hexane		$\text{CH}_3 - (\text{CH}_2)_4 - \text{CH}_3$
fluorochlorohydrocarbons		
fluorotrichloromethane		CFCI_3
cellosolves		
ethylene glycol monoethyl ether		$\text{CH}_3 - \text{CH}_2 - \text{OCH}_2 - \text{CH}_2 - \text{OH}$

Figure 1. Organic solvents most frequently used in the Federal Republic of Germany (capital letters).

¹ Central Institute of Occupational Health, the Ministry of Health, Hamburg, Federal Republic of Germany.

This is the current understanding of biological monitoring.

The past

When organic solvents were first used some 180 years ago, there was scarcely anything of what is today called occupational health protection or biological monitoring. In Germany Lehmann was the first to estimate the dose of noxious gases by measuring their concentrations in the atmosphere in the last decades of the 19th century (26). It still took until the 30s of the 20th century to determine organic solvents or their metabolites in blood and urine. The determination of organic and inorganic sulfates in urine as an indicator of the uptake of benzene (41) is one example of this early biological monitoring. For supervision purposes photometric, titrimetric, and infrared spectrometric methods, however, were too laborious and time consuming, and they required too great a volume of body fluid. As a consequence, research on organic solvents had only a small share in occupational health study. Figure 2 shows the relative number of publications on organic solvents within the *Archives of Occupational and Environmental Health*. It never exceeded 15 % before the early 1970s. Then the interest in organic solvents increased tremendously, up to more than 40 % of all papers published. As the dotted lines show, this sudden rise was caused by the onset of biological monitoring. And biological monitoring itself was caused by the new possibilities of analytical chemistry. A very powerful analytical tool with respect to organic solvents — gas chromatography — had conquered the laboratories of occupational toxicology.

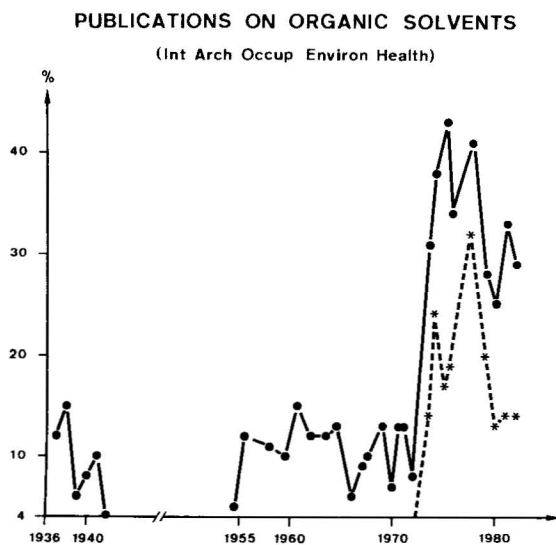


Figure 2. Relative number of publications on organic solvents within the *Archives of Occupational and Environmental Health*.

To summarize, biological monitoring in the sense of a continuous supervision strategy of organic solvents has scarcely any past. That the future belongs to biological monitoring, however, is anything else but sure. At the moment scarcely anybody seems to favor biological monitoring. The workers are suspicious that the results of biological monitoring may be used against their interests, while the employers believe that ambient monitoring provides sufficient protection.

Motives

My own argument in favor of biological monitoring is the following.

The amount of substances taken up is not a function of the concentration at the workplace and the time of exposure only. The dose taken up also depends on *pulmonary ventilation* and *dermal absorption*. But even an estimate of the dose taken up is not enough to assess the health risk of exposed persons.

Equal doses do not cause *equal health risks* but meet with (i) different abilities of the individual organism to cope with them, (ii) genetic differences, and (iii) special sensitivities to certain substances.

Finally the question as to the health effects in the case of simultaneous exposure to several solvents is of outstanding importance because most solvents are used as mixtures. Vesterberg (40) has given an excellent review of the effects influencing the toxic effects of organic substances. A combined exposure to tri- and tetrachloroethylene for instance leads to an inhibition of the metabolism of trichloroethylene and results in higher solvent levels in blood (32). The same is true for the combination of toluene and trichloroethylene (21). Ethanol taken up with beverages also may lead to superadditive effects (35).

All these factors influencing health effects are taken into account by biological monitoring and can therefore be considered in the assessment of health risk. Biological monitoring moreover makes it possible to replace the traditional form of prevention by correlating concentrations in ambient air with clinical symptoms. It measures internal exposure at a time when the impairment of health need not be suspected.

Target organs

Effective prevention of occupational diseases has to be strictly directed towards the most sensitive organs. Since organic solvents are volatile and lipophilic, all of them are inhalation narcotics. These properties are caused by the unchanged molecules. Differences in their narcotic effects are caused by differences in their physicochemical properties, like vapor pressure, solubility, and so on. The central nervous system therefore is the target organ of *all* organic solvents!

Several solvents exert effects on other organs as well. In many cases the metabolites are the noxious substances. The following are some examples:

1. In the case of benzene the predecessors of phenol have been shown to impair the blood-forming system (18). The same might be true for alkylbenzenes.
2. The cardiovascular system is the target organ of carboxyhemoglobin, the metabolite of methylene chloride (20).
3. For the hepatotoxic effects of tri- and tetrachloroethylene, epoxides are made responsible (19).
4. 2,5-Hexanedione, the metabolite of n-hexane, is known to injure the peripheral nervous system (31, 36).

Parameters

The presented considerations show that the different health effects of organic solvents are caused by different substances, either by the solvents themselves or by their metabolites. Therefore the choice of the parameter is decisive for the success of biological monitoring in the prevention of occupational diseases.

The parameters should fulfill at least two requirements: (i) they should, as closely as possible, reflect the toxic principle of the solvent and (ii) their concentration in biological material should be representative of their concentration in the critical organ.

It is obvious that the substance which is responsible for health impairment must be the best parameter for biological monitoring. An inhibition or induction of metabolism for instance alters the level of solvents or metabolites in biological material and in consequence the effect on workers' health.

These considerations lead to the following conclusions:

1. The determination of the solvent level in biological material should be obligatory because impairment of the central nervous system is common to all organic solvents.
2. In addition metabolites have to be determined in all those cases in which an impairment of other organs occurs.

Matrices

The next decision of importance is the kind of biological material in which the parameters are to be determined. The choice is not very great because there are the following limitations: (i) the specimen collection should not lead to an unacceptable stress for the exposed workers, (ii) the specimen concentration of

the parameter should reflect the condition in the target organ, and (iii) the specimen collection should be practicable under field conditions. These restrictions limit the choice to three materials: blood, alveolar air, and urine.

Blood, ie, the solvent level in blood, should be the best possibility for biological monitoring because the brain belongs to the organs best supplied with blood. The blood level therefore must reflect the solvent concentration in the critical organ. During the last 15 years solvent levels in blood have been measured in a great number of workplace studies (6, 9, 12, 25), as well as in experimental designs (1, 3, 14, 15, 23). In special cases urine may also be a suitable matrix for the determination of solvents when polar solvents like methanol and acetone are directly excreted in urine (10, 17, 34, 39).

The solvent level in alveolar air seems to be an attractive alternative. Some authors (11, 12, 25, 29) have used alveolar air for the biological monitoring of workers exposed to several solvents with great success. In other cases alveolar air levels were determined in experimental exposure studies (37, 38). Since alveolar air is only in indirect relation to the central nervous system, this matrix can only be considered second best. Finally the alveolar air level is diagnostically less sensitive than the blood level. Whereas the solvent concentration in blood is in most cases greater than in ambient air, the reverse is true with alveolar air.

In occupational health practice urine is much more popular than alveolar air or blood, mainly because of the availability of this matrix and the ease of collecting, transporting, and storing it. Urine, therefore, is the classic material for the determination of metabolites excreted via the kidneys. The concentration of metabolites in urine is not merely a function of solvent concentration at the workplace but also a function of exposure time. The fact that urinary levels of metabolites reflect, to a greater extent, the dose taken up is diagnostically advantageous. It is also of analytical interest because urine levels are some orders higher than solvent levels in biological material. The analysis of metabolites of organic solvents like aromatic, chlorinated, and aliphatic hydrocarbons, etc, in urine has been the subject of a great number of papers (4, 6, 16, 22, 28, 33). As in the case of blood and alveolar air, the literature mentioned is by no means comprehensive.

Chemical analysis

Biological monitoring cannot be done in a suitable manner without the properties, possibilities, and necessities of chemical analysis being kept in mind. Biological monitoring must determine — very *small amounts* of substances — in very *small volumes* — of very *complex matrices*.

Table 1. Comparison of the detection limits of headspace analysis of organic solvents in blood with biological limit values.

Solvent group	Detection limit (mg/l)	Limit values (mg/l)
Aromatic hydrocarbons	<0.001	< 3
Ketones	<1	<200
Alcohols	<1	< 30
Chlorinated hydrocarbons	<0.05	< 5
Aliphatic hydrocarbons	<0.01	> 0.1
Fluorochlorohydrocarbons	<0.02	< 2
Cellosolves	—	?

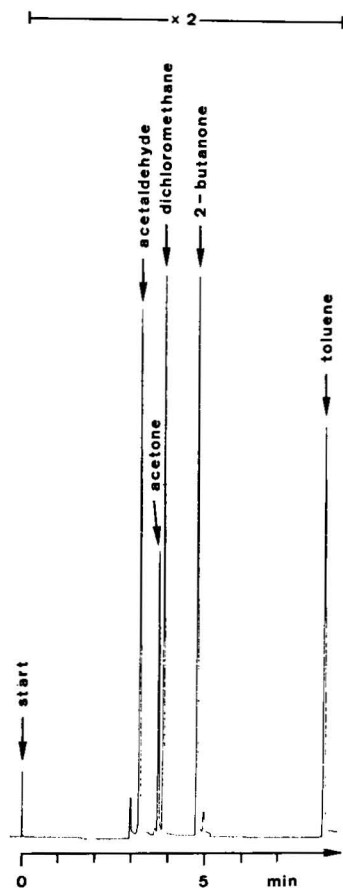


Figure 3. Capillary gas chromatogram of a blood sample of a varnishing sprayman.

After many years in which such analyses were impossible gas chromatography brought the breakthrough. It is the method of choice for the determination of volatile substances like organic solvents. Without any preparation of the sample, solvents can be determined in air and alveolar air. Headspace analysis then was the ingenious invention which eliminated the complex biological matrix by a simple application of the elevated temperatures, which thus reduced the analytical problem to that of air analysis. A comparison of the detection limits of solvents in biological material with biological limit values shows

that the latter are one to three orders greater (table 1). Gas chromatographic headspace analysis can therefore cope with the whole range of occupationally relevant concentrations without the application of enrichment techniques.

In addition an evolution in the field of headspace analysis is taking place today. Gas chromatography with fused silica capillary columns with chemically bonded phases improves separation capacity tremendously (7). A series of solvents, even very different ones, can be caught this way in one operation. A gas chromatogram of a blood sample from a varnishing sprayman is shown as an example in figure 3.

High-pressure liquid chromatography, on the other hand, seems to be the method of choice for the determination of metabolites in urine. Derivation steps are not necessary. The determination of a series of metabolites of several solvents like benzene, toluene, and chlorobenzenes gives an impression of these analytical techniques. This method has been developed by the working group "Analytical Chemistry" of the German "MAK-Commission" (27) (figure 4).

The results of biological monitoring may be altered by the following three groups of factors; (i) analytical errors which can be minimized by quality assurance, (ii) interference factors, and (iii) influence factors.

Interference factors

The interference factors include all factors altering the results *in vitro*, ie, after specimen collection and before analysis. They cannot be controlled by quality assurance programs. Biological monitoring therefore must act according to the interference factors. If the blood samples are put into vials closed by rubber stoppers immediately after their collection, the solvent level in blood is rather unaffected by interference factors. Tetrachloroethane or acrylonitrile are examples of substances reacting at the elevated temperatures of headspace analysis. The vessels used up till now for alveolar air collection, on the other hand, present problems of adsorption and leakage, altering results on a large scale. Urinary excretions may be affected by sedimentation processes, especially in the case of purely soluble substances like hippuric acid, for instance (8). *In vitro* hydrolysis of esters in blood hinders the determination of solvent levels for biological monitoring purposes. This example leads to a discussion of the influence factors.

Influence factors

Influence factors alter specimen composition *in vivo*. The rapid processes of uptake and excretion make solvent and metabolite concentrations rise and fall in biological materials within short periods. The time of specimen collection therefore has a decisive influence on the results.

This is a problem for health supervision practice. It shall be demonstrated for some solvents which dif-

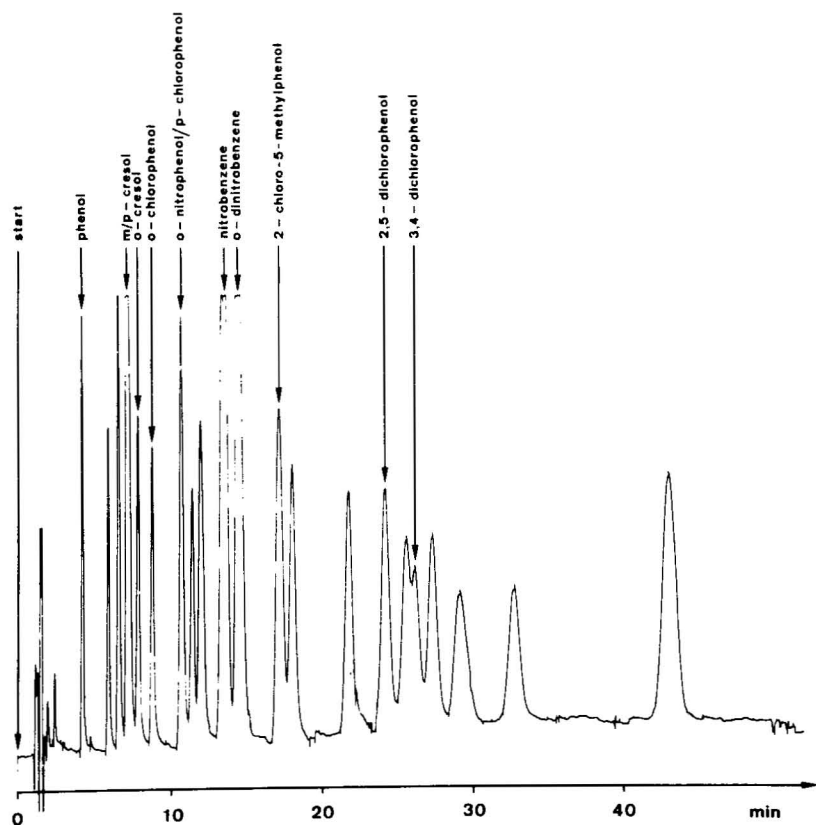


Figure 4. High-pressure liquid chromatogram of benzene derivatives.

fer in their speeds of reaching steady state in blood and their speeds of excretion. The level of 2-butanone, being very soluble in blood, increases during an 8-h shift and decreases slowly after the exposure (30). In contrast the concentration of n-hexane, which is only slightly soluble in blood, quickly reaches steady state and quickly drops after the termination of the exposure (Angerer, unpublished results). The behavior of aromatic hydrocarbons lies between these extremes (2) (figure 5).

Obviously the influence of time on the findings of biological monitoring decreases with the increasing solubility of organic solvents in blood and with an increasing time lapse after the termination of exposure. Diagnostic sensitivity decreases as well, however. To take blood or alveolar air samples 30 min after the end of exposure seems to be a satisfying compromise, decreasing, but not eliminating, errors.

The influence of time on the excretion of metabolites in urine is much less marked. This advantage is offset by the different dilutions of urine which greatly influence metabolite concentration. Several procedures have been discussed to compensate for this influence, eg, the sampling of urine within defined times, etc (24). Scientific and practical reasons, however, induced the working group "BAT-Werte" of the German "MAK-Commission" to propose end-of-shift urine samples and to use specific weight as an exclusion factor only.

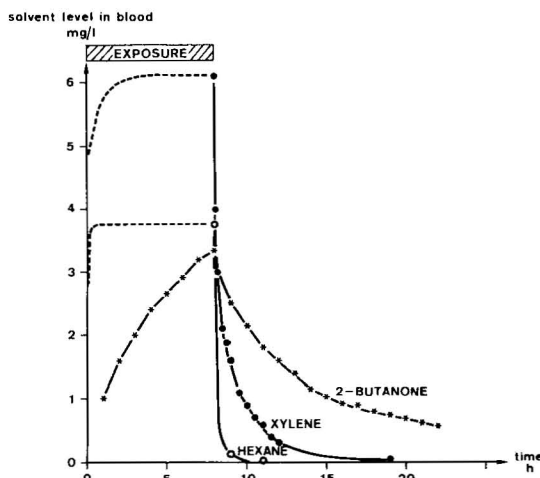


Figure 5. Time course of solvent levels in blood.

Physiological levels, as in the case of phenol, hippuric acid, acetone, formic acid, etc, as well as substance levels caused by beverages, drugs or cigarette smoking, are influence factors which, in special cases, may give rise to erroneous interpretations.

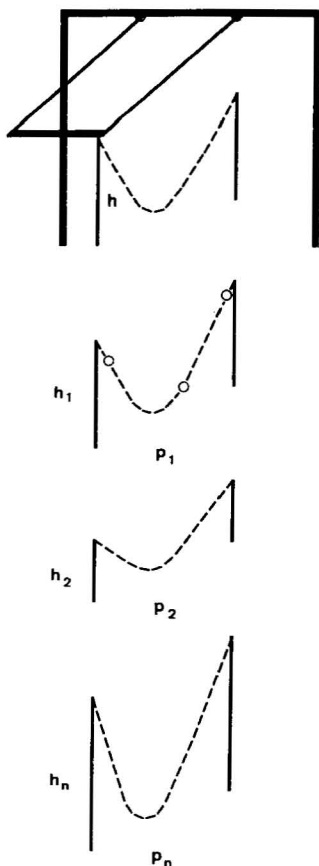


Figure 6. The swing as a model for the biological monitoring of organic solvents.

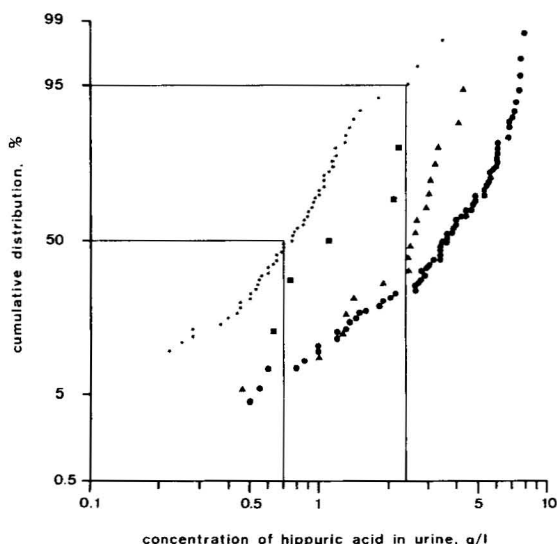


Figure 7. Cumulative frequencies of hippuric acid concentration in urine samples of three groups of toluene-exposed persons (median concentration of toluene in ambient air: ■ 11 ml/m³; ▲ 24 ml/m³; ● 132 ml/m³) and one group of unexposed persons (*).

Limit values

Limit values are necessary for the interpretation of biological monitoring results. The German "MAK-Commission" evaluates biological tolerance (BAT) values. BAT values are the maximum permissible quantity of a chemical compound, its metabolites, etc, which do not impair the health of employees. In 1984 BAT values for eight organic solvents were published (13).

After the considerations concerning influence and interference factors, individual factors, and other influences, it seems obvious that a simple comparison of a single result with BAT values is definitely not sufficient for the interpretation of individual health risk.

Interpretation

To make things clearer let me try to compare occupational stress by organic solvents with physical stress while moving a swing. Physical stress will surely depend on the dimensions of the swing and the physical efforts of the swinging person (figure 6). Measuring chemical stress at the workplace is at least as difficult as measuring the physical stress of the swinging person. The maximum distance from the ground may be used as a parameter for physical stress. It is difficult to measure accurately, however, because of the fast movement of the swing. In fact in the case of the swing the data more or less deviate from the maximum distance. On the basis of several measurements of the position of the person swinging, extrapolation will give a good estimate of the physical stress characteristic for each person. The same is true for the estimate of internal exposure to organic solvents with the use of biological monitoring. For every worker data more or less deviate from definite exposure. After a certain time of supervision, in spite of all interfering influences, a valid picture will be provided of the exposure.

The image of the swing, however, calls up further associations:

- Comparing the results of all persons swinging, one can see outstandingly high stresses, which, in the case of occupational exposure, can be used to search for special sources of risk.
- And one can draw conclusions as to the dimensions of the swing, even if one cannot measure the swing itself. In other words workplace conditions are to some extent measurable and controllable by biological monitoring.

This possibility suggests an extension of the understanding of biological monitoring. Results of biological monitoring are mainly considered with regard to the individual worker only. Much information is lost this way. Evaluating biological monitoring re-

sults on a group basis can reveal further valuable hints.

The example of hippuric acid excretion may demonstrate what interpretation on a group basis can do. Figure 7 shows cumulative frequencies of the hippuric acid excretion of three groups of workers exposed to toluene and one group of persons not exposed to chemical substances. It can be seen that normal excretion overlaps great areas of hippuric acid concentration in the urine of workers exposed to toluene. Even an exposure to about 100 ppm cannot be established by means of hippuric acid concentration. Regarding median values, however, one can see that an exposure of only 10 ppm already causes a doubling of the median hippuric concentration in urine (5, 6).

The future

To summarize, exposure to most organic solvents can be estimated by biological monitoring today. Some problems, however, are still to be solved, for example:

- Health risk caused by simultaneous exposure to several solvents cannot yet be assessed.
- Parameters measuring toxic strain have to be established.
- For some solvents like cellosolves analytical methods have to be found.

A still more important task must be done. The different social groups have to be convinced of the advantages of biological monitoring for the prevention of occupational diseases. It must be shown that biological monitoring results are not used against workers. This point is especially important for results not connected with the workplace, for instance, in the case of the consumption of drugs or alcoholic beverages, etc. All data have to be handled with absolute discretion. Biological monitoring should never be used to select suitable workers for unsuitable workplaces. These conditions have to be fulfilled before biological monitoring can have the sort of future that leads to the prevention of occupational diseases.

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