

## Biological monitoring of toxic metals

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FRIBERG L, ELINDER C-G. Biological monitoring of toxic metals. *Scand J Work Environ Health* 1993;19 suppl 1:7—13. The biological monitoring of metals, when used properly, allows total exposure to a particular metal to be measured from various media. It takes into consideration inter- and intraindividual variations in uptake due to differences in metabolism and physical work load and can be used to identify individuals, or groups of individuals, with high exposure or at high risk. As many metals are retained for long periods, biological monitoring may not only provide information on recent exposure, but also on exposure which occurred a long time ago. Under optimal conditions, the concentration of a metal in biological media can be used to assess exposure, the concentration of the metal in the target or critical organ (ie, the organ where the adverse effects are first observed) and the risks for adverse effects. This paper gives an overview of several important aspects of biological monitoring but does not provide detailed information on particular metals.

**Key terms:** blood, dose, exposure, media, metabolism, speciation, urine.

The overall objective of the biological monitoring of toxic metals in humans is to prevent adverse health effects. Toxicologic risk estimations are based on knowledge of the relations between exposure on one hand and the effect or response on the other. The traditional form of exposure monitoring in routine surveillance is environmental monitoring. This procedure includes the sampling and analysis of pollutants in environmental media, such as air, water, and food. It has been used for examining and establishing relationships between the concentrations of various metals in the environment and health effects. For some of the metals, for example, lead, cadmium, and mercury, the analysis of biological indicator media, such as blood and urine, has been important for many years in complementing the analysis of environmental media. Under optimal conditions, the concentration in biological media can be used to assess exposure, the concentration of the metal in the target or critical organ (ie, the organ where the adverse effects are first observed), and risks for adverse effects.

It was not until recently, however, that a more systematic search was conducted for possible means of studying the metabolism and accumulation of metals in environmentally exposed humans and that such data were used as an indicator of both exposure and health risks (1—5). In 1986 an international confer-

ence called “Biological Monitoring of Metals” was held in Rochester, New York, and organized jointly by the Environmental Health Science Center of the University of Rochester and the Scientific Committee on the Toxicology of Metals of the International Commission on Occupational Health (6).

In recent years, efforts have also been made to study substances not only in indicator media, but also directly in the internal organs of living people. For example, cadmium has been monitored in vivo in kidneys and liver by neutron activation techniques. Lead is measured in the skeleton in vivo by X-ray fluorescence. These methods have so far been used mainly for research purposes but may become available for routine monitoring in the future.

Biological monitoring must not be confused with health monitoring, which is also carried out on body fluids, such as blood and urine. The aim of health monitoring is to detect early effects, whether reversible or irreversible. One example is the determination of  $\beta_2$ -microglobulin in urine after exposure to cadmium. Health monitoring does not prevent adverse effects and is not a substitute for biological monitoring. Periodic health monitoring may nevertheless be invaluable in documenting the absence or presence of adverse effects and thus in determining whether the exposure is low enough or too high.

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### Biological monitoring as a measure of total exposure

An important property of biological monitoring is that it measures the total environmental exposure from all sources. Thus the inhalation of air, the consumption of water, food and wine, tobacco smoking, and the effects of leisure-time activities such as painting and gardening can all lead to exposure to

lead. Exposure can be high in certain occupations. Uptake by mouth from toys or soil contaminated by lead (pica) may be considerable in children. It is obvious, therefore, that, if only one or two of the environmental media are analyzed, the resulting estimate of the total daily intake of lead may be in error. A further consequence is that, if the background dose (ie, the blood levels caused by exposure via food, water, and other environmental media) is not known, it is impossible to define an acceptable level of lead in, for example, workroom air. In many countries the background concentrations in blood are already at, or even above, toxic levels, and there is little or no room for additional occupational exposure. In other countries the margin of safety is much greater (7).

One advantage of biological monitoring is that it takes into account inter- and intraindividual variations in uptake due to variations in exposure, metabolism, and physical activity. It thus provides an indication of individual exposure and risk. Time trends can be studied by repeated measurements. For example, repeated monitoring of blood lead levels in samples from the same residents of Stockholm revealed an average decrease of  $25 \mu\text{g} \cdot \text{l}^{-1}$  ( $0.12 \mu\text{mol} \cdot \text{l}^{-1}$ ), or 34%, from 1980 to 1984 (8). As many metals have a long biological half-time, biological monitoring can sometimes give an indication of past exposure, as in the monitoring of cadmium in urine. Before kidney damage develops, cadmium in urine reflects the total accumulation in kidneys. Another example is the measurement of lead in teeth or dentine for the retrospective assessment of lead exposure in early life.

### Need to understand metabolism

Certain criteria must be satisfied if biological monitoring is to be meaningful. If we want to measure internal dose, we must find an indicator medium reflecting total exposure. If, in addition, we want to estimate risk, we need information on the relationship between internal dose and risks for adverse effects. It is therefore essential to understand the metabolism of a metal in order to predict accumulation in the body and assess risk. In other words, we must be able to answer the following questions: How much of the external dose is taken up (absorbed) after inhalation? How much is absorbed by the gastrointestinal tract and by the skin? Is the metal changed in the body by biotransformation? How much is accumulated in the critical organ? By which routes, eg, expired air, urine, feces, is the metal excreted? Consideration should also be given to the rate at which the different reactions take place. The biological half-time is a central concept. It defines the time taken to excrete half of a certain accumulated amount, and it is an integral part of the equations used to predict the accumulation of a metal in the body as a whole

or in individual organs. These components form a pattern which can be summarized by the metabolic model for the metal (figure 1).

The biological half-time for cadmium is 20–30 years in the body as a whole and in the kidneys, but for some metals, such as arsenic, cobalt and chromium, it is only hours or days. For inorganic mercury it is about 2 d in blood but about two months in the body as a whole. A small fraction probably has a much longer half-time. The biological half-time for metals often differs between animal species. For methylmercury it is about 7 d for mice but more than two years for seals. In humans, it averages 70 d, but has large individual variations (10).

### Common indicator media

#### Urine

Urine is the biological indicator medium that is the most readily available. It is collected by means of noninvasive techniques and represents a major route of excretion for absorbed metals. However, the urinary excretion of a metal will occasionally reflect its concentration in the kidneys rather than current exposure, as in the case of cadmium. As urine is not simply an excretory medium, but also a product of kidney function, functional impairment of the kidneys may significantly alter the excretion of metals, independently of changes in exposure or body burden of the metal. For example, the urinary excretion of cadmium and mercury increases when the tubular epithelium is damaged.

It is well established (11) that the release of metallic mercury vapor from dental amalgams constitutes the main source of human uptake of inorganic mercury, except for occupational exposure. Biological monitoring of urine has shown that there is an association between the number of amalgam fillings and urinary mercury (12). In a recent report by Sällsten et al (13) a patient with bruxism and numerous amalgam fillings repeatedly showed urinary mercury concentrations of about  $40 \mu\text{g} \cdot \text{l}^{-1}$  ( $0.12 \mu\text{mol} \cdot \text{l}^{-1}$ ), which is in the range of values that the World Health Organization has associated with the first observed adverse health effects. As bruxism, and even severe manifestations of it, is common in the general population, the finding indicates that the biological monitoring of such individuals may make it possible to identify and study groups at special risk due to a high uptake of mercury.

Ideally, the urinary excretion rate of a metal can be measured through the collection of all the urine produced over a defined and extended period of time, eg, 24 h. In practice, this goal is often difficult to achieve, and spot samples are used. Variability over time and physiological status must then be compensated for by, for example, adjustment for specific gravity or creatinine concentration. To adjust urine samples for different degrees of dilution is of par-

tical and crucial importance when urine is used not only to assess exposure, but also to examine possible effects, for example, by means of urinary protein determination. Without such adjustment, spurious correlations indicating dose-effect relationships can easily be obtained. If, for example, on the one hand zinc is measured as an indicator of exposure, and on the other a tubular enzyme such as N-acetyl- $\beta$ -D-glucosamidase (NAG) is measured as an effect parameter in a urine sample, and this sample is diluted (or concentrated), the concentrations of both the metal and the tubular enzyme will obviously decrease (or increase). Likewise, in a group of individuals with different degrees of urinary dilution, significant correlations are likely to be found between measurements of a metal (dose) and those of a urinary effect parameter if adjustment for dilution has not been made, although they may not be causally related.

As in all forms of biological monitoring it is essential to obtain an uncontaminated sample. Special cleaning procedures and metal-free polyethylene containers are recommended to eliminate contamination. For the same reason careful personal hygiene is necessary before the urinary samples are voided. Because the human urethra contains bacteria, it is virtually impossible to obtain a sterile urine sample. Even urine samples from healthy people become overgrown with bacteria after only a few hours at room temperature. Urine should therefore be stored at low temperatures, and frozen if possible. A bactericidal substance, such as sodium azide, can be added to the urine. This procedure may, however, reduce certain metal compounds; in particular, bivalent mercury can be reduced to give volatile metallic mercury, which might evaporate from the container.

### Blood

Blood is the major vehicle for the transport of absorbed metals. After uptake from the gastrointestinal tract or the lungs, metals are transported via blood to different tissues and organs, where they are accumulated. Metals which have been taken up by tissues will, by the normal metabolism of these tissues, be released, and once again transported with the blood until they are eventually eliminated from the body via the kidneys or liver. (See figure 1.) The blood level is thus influenced both by current exposure and by the concentrations in the internal organs (ie, the body burden), the relationship between them differing for different metals and exposure conditions.

Metals in blood are bound to the red cells or to plasma proteins. Cadmium and lead are bound almost completely to the red cells. It is sometimes necessary to take into consideration the volume percentage of red cells in blood (ie, the hematocrit) when cadmium or lead levels in whole blood in different groups and individuals are compared. If the hematocrit is low, the concentration of cadmium and lead will be lower even if the exposure is the same. The

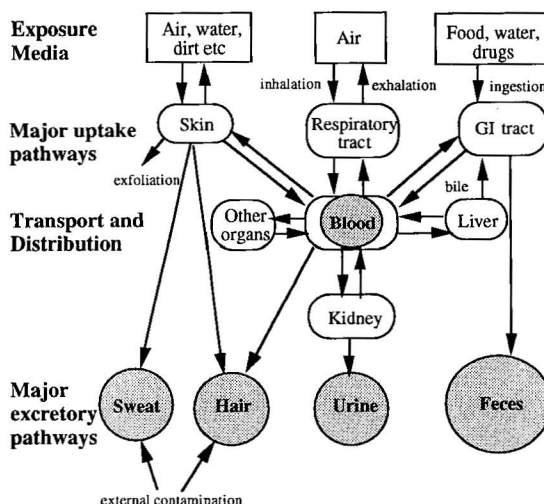


**Figure 1.** Metabolism after exposure to metals via skin absorption, inhalation, and ingestion. The arrows indicate how the metals are transported. Tissues potentially useful for biological monitoring are identified by shaded circles (modified from reference 9). In addition some other tissues, notably kidney for cadmium and bone for lead, may be monitored by *in vivo* techniques. (GI = gastrointestinal)

concentration of metals in plasma is of particular interest, as it represents the fraction of the metals in blood that is easily available for transport into and out of the tissues. The concentrations are, however, for many toxic metals (eg, lead and cadmium) so low that they are very difficult to measure. Other metals (eg, aluminum, chromium and inorganic mercury) are easier to determine in plasma.

Blood samples are usually collected either as a capillary sample from the fingertip or the ear lobe or from a vein, usually in the elbow. Capillary sampling gives small volumes, and there is a risk of contamination even if the fingers have been thoroughly cleaned. There is also a substantial risk of hemolysis. For practical reasons it has, however, become necessary to take capillary samples when metal concentrations in the blood of small children are studied.

For venous sampling, blood (5–10 ml) is collected, as a rule, in a Vacutainer® tube. Needles, tubes, and stoppers must be checked carefully before the sampling to avoid contamination; for example, cobalt, chromium, manganese, and nickel may be released from the needle.

Blood collected in a tube will coagulate rapidly. If, as is often the case, it is desirable to determine the metal in plasma or whole blood, an anticoagulant must be added. This substance is often already present in the tube. The metal content of the anticoagulant used should be determined.

Blood specimens must be kept cool and preferably frozen. Freezing leads to the break up of the red cells, however, and makes it impossible to separate them from the plasma.

There are special problems when biological samples have to be stored for long periods or even years. There is a tendency for blood, urine, and tissues to dry out even if the samples are stored at  $-20^{\circ}\text{C}$ . If the concentration of the metal is determined on the basis of the wet weight, the results will be too high. There is also a risk that small amounts of metal in the sample will react with the wall of the container and adhere to it. Such wall effects may become very important, particularly when the concentration of the metal in the sample is low. Due attention must be paid to this effect when tissue banks are established, particularly if they contain reference materials (14).

### Timing

The concentration of a metal in blood and urine can vary with time. If blood and urine samples are collected for the evaluation of exposure and risk, in particular during occupational exposure, it is important to standardize the sampling procedure. Figure 2 shows the excretion of cobalt in urine in a group of hard-metal workers; from this figure it can be seen that the urinary levels increased considerably during the workday. As a result of rapid excretion and a short half-time, the urinary concentration of cobalt decreases and is considerably lower the following morning. There is nevertheless a certain accumulation of cobalt over the week, as can be seen from the increase in the morning concentrations. Current exposure can be evaluated from comparisons of cobalt excretion before and after each shift. The accumulation of cobalt in the body can be studied by determining cobalt in urine before and after a period without exposure (eg, a weekend or a vacation).

For metals with a very long biological half-time, such as lead and cadmium, the timing of sampling is not so important. It is however very important when metals are monitored which are rapidly eliminated, such as arsenic, cobalt, chromium, and nickel.

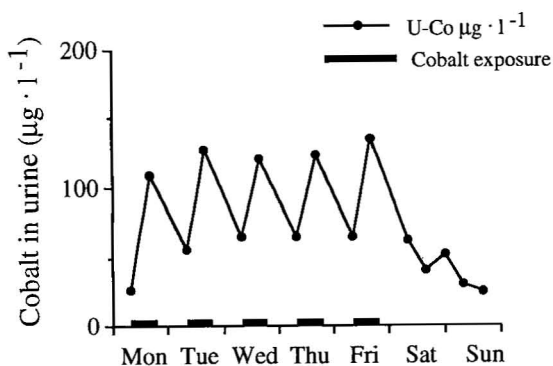


**Figure 2.** Excretion of cobalt in urine (U-Co) in a group of hard-metal workers before and after a shift, during one work week and the following weekend. The concentration of cobalt averaged  $90 \mu\text{g} \cdot \text{m}^{-3}$  (modified from reference 15).

### Other media

Hair is sometimes used for the biological monitoring of metals. When hair grows (ie, in the anagen phase) metals from blood and glands (eg, sweat) are incorporated into it. Nevertheless it is seldom appropriate to regard the metal concentration in hair as a measure of body burden. The major problem with the biological monitoring of hair is that there is a risk that metals from the environment are trapped in it. It has proved impossible to avoid such external contamination of hair, and several studies have shown that the correlation between metal concentrations in hair and blood is poor.

Monitoring methylmercury in hair constitutes an important exception to the rule that hair samples are difficult to use to estimate internal dose. Methylmercury occurs in certain foodstuffs, particularly fish, and problems due to external contamination are rare. It is incorporated in the hair during the growth phase, and a close association has been found between mercury in whole blood and in hair. Determining methylmercury in different parts of the hair strands, at different distances from the scalp, has made it possible to reconstruct exposure to methylmercury during different time periods. Hair normally grows with a speed of about  $0.33 \text{ mm}$  in  $24 \text{ h}$ . Analyses of pieces of hair taken, for example,  $10 \text{ cm}$  from the scalp will give a good indication of the mercury content in blood about  $300 \text{ d}$  earlier. Figure 3 summarizes the results from several studies in which the prevalence of symptoms or signs are related to the concentration of methylmercury in hair.

Some metals (eg, aluminum and lead) accumulate in the skeleton. Analyses of bone tissue can be used to estimate body burden and exposure when the tissue was formed.

Teeth consist of bone tissue (dentine) and enamel. Enamel is of special interest as it is formed during childhood, and there is only a very small exchange of mineral thereafter. Determinations of mineral concentrations in enamel from deciduous teeth

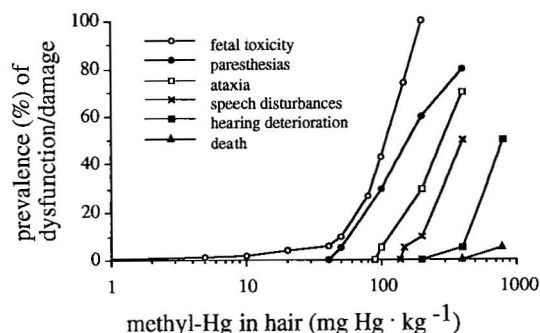


**Figure 3.** Prevalence of affected subjects at different concentrations of methylmercury (methyl-Hg) in hair. Note the logarithmic scale for the x-axis (data taken from references 10 and 16). ( $1 \text{ mg} \cdot \text{kg}^{-1} = 5 \mu\text{mol} \cdot \text{kg}^{-1}$ )

make it possible to estimate exposure retrospectively.

It is obviously more complicated to perform bone biopsies than to take blood or urine samples. In recent years a noninvasive technique, using X-ray fluorescence, has been developed. It has proved to be of great value in studies of the metabolic model of lead.

Several metals are absorbed only incompletely from the gastrointestinal tract, and the amount that is eliminated in the feces may roughly correspond to the intake via food. If the concentration of metal in feces is determined and multiplied by the quantity of feces produced in 24 h, a good estimate of the daily intake is possible for some metals (eg, aluminum, lead, and cadmium). Since the frequency of defecation varies considerably among people, it is fairly difficult to obtain representative samples, and it may be necessary to collect all the feces produced during several days.

Analysis of metals in feces has been used to compare the daily intake of heavy metals in different countries and among different populations. It has also been used to identify individuals and groups of people at high risk due to a particularly high intake of toxic metals.

Analyses of feces samples from workers exposed to metal dust have shown that industrial exposure often takes place both by inhalation and ingestion. If the workplace is contaminated with metal dust, it is not surprising that workers' hands, and then also their food and cigarettes, become contaminated (17).

Dust containing lead, emitted from industrial plants and motor vehicles, will contaminate soil and playgrounds. Small children are thus exposed to lead via the gastrointestinal tract from contaminated hands and toys. A higher concentration of lead in feces than expected from the lead concentrations in food indicates such exposure. Figure 4 presents data on the relationship between the daily intake of lead, measured as lead in feces, and lead levels in blood from four different countries. It should be noted that the relationship is not linear. If the background exposure is high, a further increase in lead exposure does not increase the blood lead level to the same extent as with a lower background exposure.

## Speciation

Some metals have species of widely differing metabolism and toxicity. Mercury forms both inorganic and organic compounds, of which the first includes metallic mercury, and monovalent (mercurous) and bivalent (mercuric) mercury. In organic compounds, mercury is bound covalently to at least one carbon atom. Arsenic also forms several inorganic and organic compounds.

For mercury it is particularly important to consider the differences between metallic mercury, bivalent

inorganic mercury compounds, and methylmercury. There are important differences in absorption, distribution, biotransformation, and excretion both between the species and between different exposure routes. Blood, particularly red cells, and hair are the media of choice for methylmercury, which is excreted only to a very limited extent via urine; this medium is therefore usually not suitable for the biological monitoring of methylmercury. Inorganic mercury is excreted via urine after exposure both to metallic mercury vapor and to inorganic mercury compounds. It can also be monitored in blood, particularly in plasma (10, 11).

For arsenic it is first necessary to differentiate between inorganic arsenic and its metabolites and the "fish arsenic," particularly arsenobetaine, which is found in high concentrations in shellfish and certain fish (eg, flounder). Figure 5 shows how the urinary

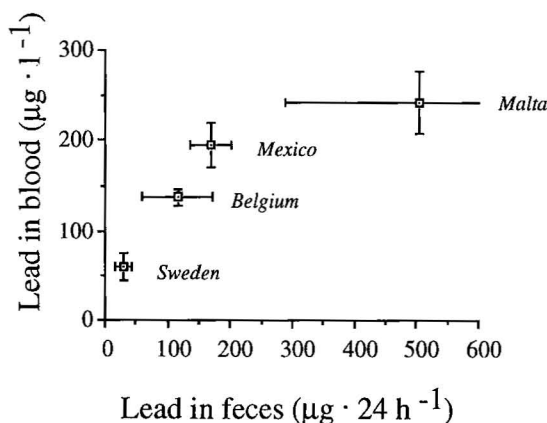


Figure 4. Daily intake of lead ( $\mu\text{g} \cdot 24 \text{ h}^{-1}$ ) and the blood lead concentrations ( $\mu\text{g} \cdot \text{l}^{-1}$ ) in four different populations (modified from reference 7). ( $1 \mu\text{g} \cdot 24 \text{ h}^{-1} = 5 \text{ nmol} \cdot 24 \text{ h}^{-1}$ ;  $1 \mu\text{g} \cdot \text{l}^{-1} = 5 \text{ nmol} \cdot \text{l}^{-1}$ )

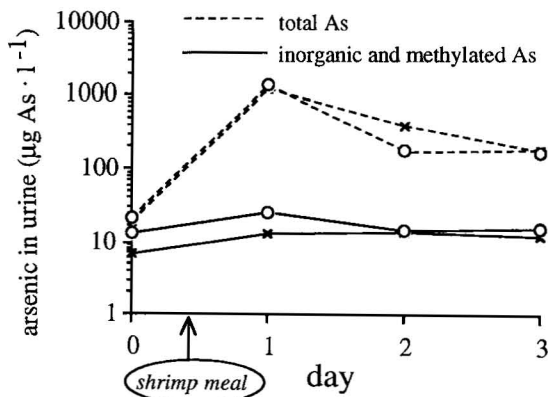


Figure 5. Urinary excretion of inorganic and methylated arsenic (As) compounds and total arsenic (including fish arsenic) in two subjects after a shrimp meal. Note that the scale of the y-axis is logarithmic (data from reference 18). ( $1 \mu\text{g} \cdot \text{l}^{-1} = 13 \text{ nmol} \cdot \text{l}^{-1}$ )

excretion of total arsenic increased dramatically after a shrimp meal, while the excretion of inorganic arsenic remained low and unchanged. When exposure to inorganic arsenic is monitored, it is therefore important to distinguish between fish arsenic and inorganic arsenic with its metabolites monomethylarsonic acid and dimethylarsinic acid.

### Analytical accuracy

The aim of biological monitoring is to obtain reliable information on metal concentrations in tissues or body fluids. In recent years the ability to determine even low concentrations of trace metals has improved dramatically, thanks to the development of new and advanced analytical instruments and methods. Today it is possible to determine concentrations in the microgram per kilogram range or sometimes in the nanogram per kilogram range in biological materials on a routine basis. As a consequence the "normal" concentrations have gradually been adjusted downwards without any accompanying real decrease in the levels. "Normal" values for aluminum in blood and serum in the early 1970s were reported to be of the order of  $100 \mu\text{g} \cdot \text{l}^{-1}$  ( $3.1 \mu\text{mol} \cdot \text{l}^{-1}$ ) or even higher, whereas the true normal concentration of aluminum in blood is around, or perhaps below, a few micrograms per liter (19).

The accuracy of analytical data has not always improved in parallel with the analytical methods. With lower detection limits there is a need for increased accuracy, as the risk of errors caused by contamination or losses before and during the analyses increases. There are many examples showing that, even in recent years, grossly erroneous results have been reported both in scientific papers and in routine reports from commercial laboratories.

**Table 1.** Usefulness of biological monitoring of metals for exposure and risk assessment. (B = blood, plasma or serum, U = urine, H = hair)

| Metal or metal compound | Media | Exposure assessment <sup>a</sup> | Risk assessment <sup>a</sup> |
|-------------------------|-------|----------------------------------|------------------------------|
| Aluminum <sup>b</sup>   | B,    | ++                               | ++                           |
| Aluminum <sup>c</sup>   | U     | ++                               | ?                            |
| Antimony                | B     | +                                | ?                            |
| Arsenic (inorganic)     | U     | ++                               | ++                           |
| Cadmium                 | B, U  | +++                              | +++                          |
| Chromium                | U     | ++                               | +                            |
| Cobalt                  | U     | ++                               | ?                            |
| Lead (inorganic)        | B     | +++                              | +++                          |
| Lead (organic)          | U     | +                                | ++                           |
| Manganese (inorganic)   | B, U  | —                                | ?                            |
| Manganese (organic)     | U     | ++                               | ?                            |
| Methylmercury           | B, H  | +++                              | +++                          |
| Metallic mercury        | B, U  | +++                              | +++                          |
| Nickel                  | B, U  | ++                               | ?                            |
| Selenium                | B, U  | ++                               | ++                           |
| Tin                     | B, U  | ?                                | ?                            |
| Vanadium                | B, U  | +                                | ?                            |

<sup>a</sup> — = no relationship, + = some information available or weak relationship; ++ = relationship exists, +++ = well-established relationship — used on a routine basis, ? = relationship unknown.

<sup>b</sup> Patients with kidney disease.

<sup>c</sup> Aluminum welders.

It is only in recent years that it has become common practice to ensure adequate quality control in connection with the routine analysis of metals in biological materials. As a result, many analytical results have been shown to be erroneous.

An evaluation of a large number of published papers has shown that the accuracy of the analytical results is often low. It has sometimes been possible to estimate the magnitude of the errors, and it is not uncommon to find metal concentrations which must have been 10—50 times too high. The question of quality control was dealt with in great detail in a paper presented at the Rochester conference (20), as well as in a report by Friberg & Vahter (4) on a global study, coordinated on behalf of the World Health Organization.

### Ethical issues

Biological monitoring involves analyses of body fluids or tissues of individual human subjects and must therefore be carried out only on a voluntary basis. Appropriate measures must be taken to avoid the spread of infectious diseases and to ensure minimum risks of other adverse reactions. Furthermore, the resulting data may be directly linked to specific individuals and may, in some cases, lead to unfortunate consequences, including loss of jobs. If biological monitoring is to become widely accepted as a preventive tool, ethical issues must be addressed as carefully as the scientific ones. Several important questions to be considered were discussed at the Rochester conference (6).

### Review of specific metals

In this presentation it has not been possible to include information on the usefulness of the biological monitoring of different metals. The overview report of the Rochester conference (8) and the accompanying background documents provide a useful basis for making the necessary decisions on biological monitoring. Several of the presentations in this volume will also provide valuable assistance.

A summary of the results is presented in table 1. Biological monitoring has so far proved to be of value for about 10 metals.

### Concluding remarks

In conclusion, biological monitoring can be a very useful, and sometimes indispensable, way of evaluating exposure to certain metals and the associated risks and can therefore be of great value in preventive programs, providing certain criteria are met. It is important to point out, however, that biological monitoring covers only one aspect of a preventive program and should not be considered in isolation. When a monitoring program is planned, its purpose

must be considered in detail. Often some form of integrated monitoring will be the method of choice, where biological monitoring will complement the conventional monitoring of the different environmental media (eg, air, food, water).

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