Biological Monitoring of Metals

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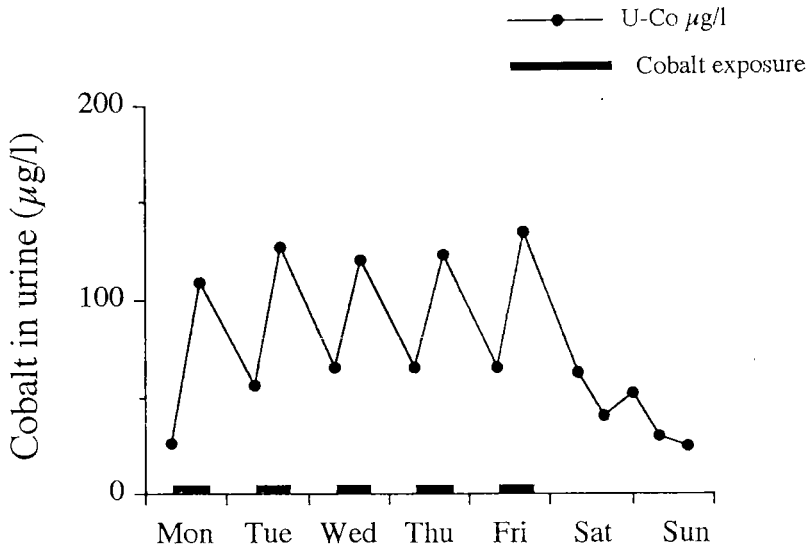
Errata

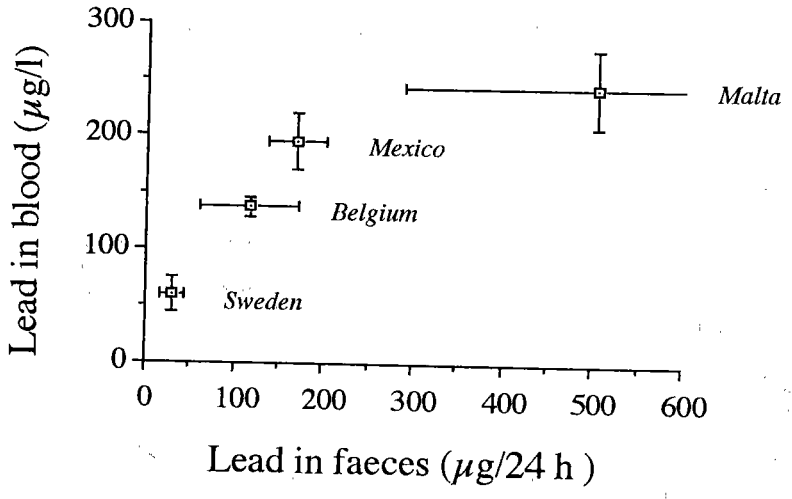
Owing to a printer's error, Figures 9, 17 and 19, on pages 28, 55 and 63, respectively, are incomplete. They are reproduced, in full, below.

Figure 9



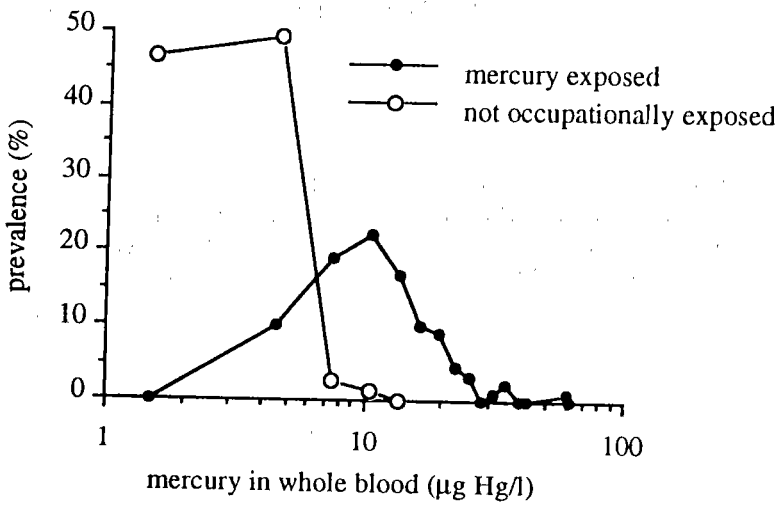
Excretion of cobalt in urine in a group of hard-metal workers before and after their work-shift, during one working week and the following weekend. The air concentration of cobalt averaged 90 μg Co/m³. (Data taken from Alexandersson & Lidums, 1979.)

Figure 17



Daily intake of lead (μg/day) and blood lead concentrations (μg/litre) in four different populations. (Taken from Bruaux & Svartengren, 1985.)

Figure 19



Frequency distribution of mercury concentration in whole blood in Swedish workers in the chlorine industry and non-exposed controls (Langworth et al., 1991).

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Preface

For many years now, biological monitoring has been used to evaluate exposure and risks for various metals, including lead, cadmium and mercury. There are several other metals, for which biological monitoring is of practical value.

Toxicological risk estimations are based on knowledge of the relationships between exposure, dose, effect and response. For substances accumulating in the human body, analysis of tissue, or of biological indicator media such as blood and urine, is an important supplement to analysis of environmental media, such as air and food. Indeed, if there are many simultaneous exposure routes, this is often the only means of estimating total exposure, since the critical organs—those organs where the first adverse effects are observed—are not usually accessible in living individuals.

In order to make a toxicological interpretation of the concentration of a metal in an organ or indicator media, it is necessary to understand the absorption, distribution, biotransformation and excretion kinetics of that particular metal. Likewise, knowledge of the relation between concentrations in indicator media, the internal and organ dose, and anticipated effects is essential for risk estimations.

Chemical analysis of trace elements relies on qualified personnel and adequate equipment. Nevertheless, the accuracy of trace element analysis is often low, due to analytical problems, or to contamination or loss during sampling, storage or analysis. Efficient quality control procedures were not implemented until recently. Consequently, it has often not been possible to use published results for scientific or even practical purposes.

In 1986 a conference was held in Rochester, New York, USA, to define and evaluate the scientific basis for the biological monitoring of metals. It was organized jointly by the Environmental Health Sciences Center at the University of Rochester, and the Scientific Committee on the Toxicology of Metals within the International Commission on Occupational Health at the Karolinska Institute, Stockholm and the University of Umeå, Sweden. The conference was co-sponsored by the World Health Organization through its International Programme on Chemical Safety, and received substantial encouragement and support from the Swedish Work Environment Fund and the United States Environmental Protection Agency. An extensive document based on this conference has been published (Clarkson et al., 1988).

This monograph reviews current knowledge concerning the biological monitoring of metals. We have drawn largely on the material that was presented at the Rochester conference. (We acted as organizers of the scientific part of the meeting and edited the final report.)

The introductory sections present data on exposure to metals in general terms. Initially we discuss what happens when the metals are taken up by the body and how they are absorbed, accumulated and eventually excreted. Later on we consider the concepts relating to biological half-time, metabolic models, and critical organs, as well as the relationships between exposure, dose, effect and response.

Blood and urine are the primary indicator media used for biological monitoring. However, hair and faeces are also used. We believe questions concerning sampling, storage and interpretation of results to be important items of discussion.

It is self-evident that high standards of sampling and analysis are of crucial importance. We review common analytical methods. Special attention is given to analytical quality assurance and quality control. We have also reviewed the measures that can be taken to avoid contamination or loss during sampling and storage.

The emphasis is on biological monitoring, but we also discuss monitoring of environmental media, in both the occupational and the general environment. The aim has been to illustrate the advantages and disadvantages of the different types of monitoring. Sometimes only one of the alternatives is appropriate, but often biological monitoring and environmental monitoring complement each other.

The biological monitoring of a variety of metals and metalloids is covered. In certain cases, such as mercury and arsenic, different chemical species (compounds) are discussed separately due to differences in metabolism, biotransformation and toxicity.

Biological monitoring is used mainly to evaluate the magnitude of the exposure. But sometimes it is also possible to make risk estimations, particularly if the mechanisms of action are known. Under such circumstances, as in the case of arsenic, cadmium, lead and mercury, biological monitoring is of particular value.

For those metals for which the necessary information is available, we discuss how different types of exposure (acute, chronic and intermittent) influence the concentrations of metals in indicator media.

The book is intended as a useful guide for personnel with a background in medicine, science or a technical discipline, who work in an area of occupational or environmental health and prevention. This includes company physicians, industrial hygienists, regulators, lawyers, and health

workers who are interested in the environmental and occupational toxicology of metals.

We hope that the reader will find the text easy to read and understand, but at the same time scientifically correct and pertinent. We have tried to avoid technical terms as far as possible. Some information which might be more difficult to appreciate without special training is summarized in a number of Boxes.

The term "monitoring" is used to refer to repeated measurements of trace elements in biological materials or in environmental media. Expressions such as biological monitoring, environmental monitoring, emission monitoring and health monitoring are also used. The term media refers to the environments in which the metals occur.

Reference is given to original papers, review articles or monographs, at the end of some sections, but a separate reference list for all cited papers can be found at the end of the book.

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1. General Aspects

Where are metals found?

Metals and metalloids are elements and do not break down. They form a natural part of our environment. Metalloids—for example arsenic and selenium—resemble metals and their properties are intermediate between those of the typical metals and non-metals. The term "metal" will generally be used here to cover both metals and metalloids.

Pollution of the environment, and human exposure to metals occur as a result of the natural erosion of metal-containing minerals, and as a result of human activities such as mining, smelting, fossil-fuel combustion and industrial application of metals. Metals can be dissolved in water and in this way become available for uptake by vegetation and consumption by animals. Air pollution is another common exposure route; the highest exposure often occurs within workplaces.

As metals do not break down, they remain in the body until they are excreted. This can take years or decades. Similarly, it is difficult to rid the environment of a metal with which it has been contaminated. Rice and wheat readily take up cadmium from the soil, for instance. In some areas of Japan, the soil became so heavily contaminated with cadmium that it was necessary to replace it with uncontaminated soil. Some metals, such as arsenic and mercury, are biotransformed in nature. Inorganic mercury in lakes is converted to methylmercury, for instance. This very toxic mercury compound accumulates in fish and has caused many serious poisonings.

How are we exposed to metals?

Exposure to metals occurs mainly through polluted air, food or drinking-water. Metal particles deposited in the airways may be transported by mucociliary activity to the larynx. A portion of them will then be swallowed.

During occupational exposure the principal exposure route is usually via inhalation. Similarly, in urban areas and in the vicinity of industries, inhaled air is often a major, direct exposure route.

Significant exposure to metals may also occur through food and beverages. These can become contaminated at various stages of production or during preparation. Grains and vegetables can be polluted by metal particles that have settled from the air, or through contamination of the soil following water pollution. Cooking utensils may contain toxic metals. The use of

soldering containing lead, in the production of canned food, may contribute as much to overall lead exposure as the total weekly intake from other sources.

Alcoholic beverages such as wine sometimes contain high concentrations of lead. Those who drink large quantities of wine have much higher concentrations of lead in their blood than the average individual.

There are many metals in tobacco. For the smoker, smoking is the major source of cadmium exposure. Tobacco contains a significant amount of cadmium, which is vaporized by the high temperature of the glow. Moreover, cigarettes and pipe tobacco are easily contaminated with cadmium in industrial workplaces subject to cadmium exposure.

For most metals it is impossible to define one single exposure route. Different sources expose us to the same metal by different routes.

What happens when metals are taken up by the body?

About 20 metals or metalloids are known to be toxic and there is good reason to assume that several of the more uncommon metals are also toxic. However, as exposure to the latter is rare, poisonings have not been observed or reported. Some metals cause very characteristic changes and symptoms. Neurotoxic signs, similar to Parkinson's disease, are seen in manganese poisoning for instance, while a certain type of kidney disease is common in cadmium poisoning.

The majority of toxic metals perform no useful function in the body and dysfunction is seen even if the normal exposure is exceeded only slightly or moderately.

Essential metals

Some metals are necessary in low concentrations for the normal functioning of the body, and indeed for life. These are called essential metals and have essential biological functions in many enzymes. Thus iron is an integral part of haemoglobin in the red cells and has an important role in the transport of oxygen. Copper is needed for energy metabolism; zinc is found in about 20 enzymes and is crucial to normal development. Zinc deficiency can retard physical, sexual and mental development. It can also lead to anaemia and skin disorders.

However, while insufficient intake of essential metals will result in deficiency symptoms, toxic effects will be experienced if exposure is high.

Where do poisonings occur?

Most information concerning the human toxic effects of metals is based on industrial exposure and some of it dates from long ago. For example, the major health hazards arising from occupational exposure to inorganic mercury in cinnabar mines were recognized by the Romans. More recently, in the 19th century, lead poisoning was observed in lead smelters in the United Kingdom. During this century the occupational health risks for many other metals, including arsenic, cadmium, chromium, nickel and manganese, have been identified.

Environmental exposure to metal among the general population has resulted in epidemics of severe poisoning on several occasions. Mass poisonings occurred in Minamata and Niigata, Japan, in the 1950s, after consumption of fish contaminated with methylmercury, and in Iraq after consumption of methylmercury-treated seed. In Japan, poisonings have also been caused by cadmium in rice and arsenic in milk. Lately, cadmium and arsenic poisoning have been reported from China. In some countries, severe brain damage among children poisoned as a result of accidental consumption of lead paints, can still be observed. Other known or suspected risks include lead in motor exhaust, aluminium in drinking-water and mercury in dental amalgam.

Mechanisms of action

Metals are toxic because they interfere with the biochemical systems of the cells. A toxic metal may compete with an essential metal for a site on an enzyme. It may cause symptoms comparable to those seen in relation to deficiency of an essential metal, as in the case of fetal damage due to secondary zinc deficiency in cadmium poisoning. Cadmium itself passes the blood–fetal barrier only to a very limited extent.

The first adverse effect is called the critical effect. It is usually seen in a specific organ or tissue, known as the critical organ. It is first observed when a certain concentration of the metal (i.e. the critical concentration) has been reached in the organ.

The critical organ may not be the organ or tissue where the highest concentration of a metal is found. For example, inorganic lead accumulates primarily in the skeleton, whereas it is the central nervous system, and occasionally, the bone marrow, which are the critical organs for this particular metal. It is in these that the first adverse effects are seen. Even so, there is sometimes no relation between these first adverse signs and the particular concentration of the metal in that particular organ. This has been observed for the kidneys after exposure to inorganic

mercury. In such cases, the adverse effect is caused by an accumulation in the glomeruli of immune complexes formed in other parts of the body.

Several metals, including chromium, nickel and cobalt, cause allergic skin reactions. Immunotoxic or allergic effects are seen only in predisposed individuals. This increased susceptibility may have a genetic background.

Skin allergy and asthma are often diagnosed by specific skin tests. Relationships between exposure and general immunotoxic effects, which may have a genetic background, are difficult to demonstrate and evaluate.

Solubility and biological availability

The biological availability (bioavailability) of a metal depends on solubilization *in vivo*, after it has been taken in. We should distinguish clearly between *in vitro* and *in vivo* solubility of a given metal; only the latter is important in terms of biological activity. *In vitro* solubility in water may bear some relevance to *in vivo* solubility, although it is by no means predictive for it. For example, both cadmium oxide (CdO) and cadmium sulfide (CdS) are highly insoluble in water, yet after inhalation and deposition in the lung, CdO particles are rapidly solubilized—probably in the acidic milieu within alveolar macrophages after phagocytosis—whereas CdS particles remain highly but not completely insoluble in the lung. Similar differences may also apply to the gastrointestinal tract, i.e. only those metals or metal compounds that are soluble in the respective environment *in vivo* will be available for further absorption.

Metals have different *in vivo* solubilities. They are therefore absorbed to a different degree by the body from the gastrointestinal and respiratory tracts, and from the skin. The absorption may be predicted in part from the chemical and physical characteristics of the metals. It has been shown, however, that absorption often differs from predicted values. Furthermore, a metal may exist in different species during different phases of a process. It is therefore difficult to estimate the bioavailability.

Biological monitoring may give a measure of the total bioavailability since it shows how much of the metal has been taken up by the body. For some effects, such as lung cancer, it will not be the systemically absorbed dose that is the decisive factor for the health risk, but the dose absorbed locally by epithelial cells. This complicates risk estimations. In a smelter, the main exposure is to soluble arsenic trioxide, but there is also a minor exposure to very insoluble arsenic compounds. Animal experiments have shown that these compounds have a very long retention time in the lungs. It would therefore be unwise to rely solely on biological monitoring for the total risk assessment.

Speciation—the need to distinguish between different compounds

Some metals have species with quite different metabolism and toxicity. Mercury forms both inorganic and organic compounds. The inorganic form comprises metallic mercury and monovalent (mercurous) and divalent (mercuric) mercury. In organic compounds the mercury is bound covalently to at least one carbon atom. Arsenic also forms both inorganic and organic compounds.

For mercury it is particularly important to consider the differences between metallic mercury, divalent inorganic mercury and organic methylmercury. For arsenic it is important to distinguish between inorganic arsenic and its metabolites, and the "fish arsenic", particularly arsenobetaine. The latter species is found in high concentrations in shellfish and certain fish, such as flounder.

In the case of other metals, some chemical species have an extremely low *in vivo* solubility and therefore low bioavailability of the respective metal ion. For example, CdS inhalation can result in a very limited accumulation of Cd in the kidney, in contrast to inhalation of CdO.

Critical effect

The following are examples of critical effects:

- early developmental changes after exposure to lead or mercury
- increased concentrations of δ-aminolevulinic acid (ALA) in blood and urine after lead exposure
- increased excretion of low molecular weight proteins in urine after cadmium exposure.

Prevention of the first adverse effect, which is not necessarily important for the development of clinical disease, will also prevent more serious disease.

Individual variations

The critical concentration varies for individuals due to differences in susceptibility. So threshold values above which an adverse effect is seen will also differ for individuals.

The concept of critical concentration is also used for populations. The population critical concentration (PCC) defines in statistical terms how

many individuals, at a defined exposure level, will exceed their individual threshold values, i.e. their individual critical concentrations. The critical concentration for a population follows certain statistical distributions, which are different for different metals. The variation of the critical concentration for cadmium has been shown to follow a "normal" or Gaussian distribution. For some metals it is possible that "log-normal" distributions apply, in which case the distributions will be shelved. If details of the distribution are known, different PCC levels can be established. PCC-1 is the average concentration in the critical organ at which 1% of individuals are affected. At PCC-10 and PCC-20, 10% and 20% of individuals respectively, are adversely affected.

2. Relations Between Exposure, Dose, Effect and Response

The dose of a metal to the organism or to a specific organ depends on the exposure and the specific uptake and pharmacokinetics (metabolism) of the metal. Exposure is not equal to the dose. Exposure to a given concentration of a metal in air or food results in a certain intake which—in the case of exposure via food—is often referred to as the dose to which the person was exposed. The intake then results in a local or deposited dose, part of which will be absorbed to become an internal (or systemic) dose. This then gives rise to an organ dose in specific organs. Once the complex toxicokinetic pathways of a specific metal or metal compound are known, it is possible to derive detailed exposure–dose, dose–effect and exposure–effect relationships (Figure 1). In the absence of such knowledge, description of these relationships is generally restricted to and expressed as exposure–effect relationships (inhalation) or dose–effect relationships (ingestion, for which dose is expressed as intake, e.g. in terms of μg/kg body weight).

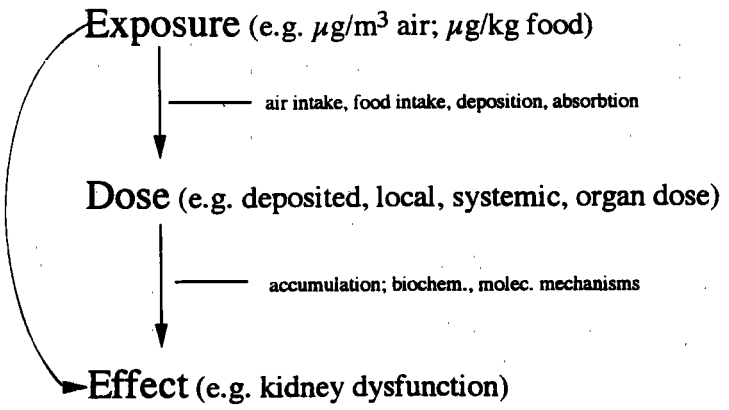
When the dose of a metal increases, as with increasing exposure, it is reasonable to anticipate that the adverse effects will become more pronounced and that a larger number of individuals will be adversely affected. The relationship between dose and effect is expressed as a *dose–effect* relationship; the relationship between the dose and the *percentage* of the exposed population which is affected is known as a *dose–response* relationship. These can also be described as *exposure–effect* or *exposure–response* relationships (particularly if particular exposures occurred through inhalation). Usually an increased dose will give rise both to more severe effects and an increased number of affected individuals. The two concepts are crucial when differentiating between variations in type and degree of effect, and numbers of individuals with defined effects.

Three different dose-response curves are presented in Figure 2. As the dose (X-axis) increases, so too does the prevalence of individuals experiencing minor dysfunction, minor effects and major effects, from a few to almost 100 percent. Examples of dose-response relationships for different types of effects are given in Figures 3 and 4.

Knowledge of the relationships between dose–effect or exposure–effect, and dose–response, or exposure–response is fundamental when estimating risk.

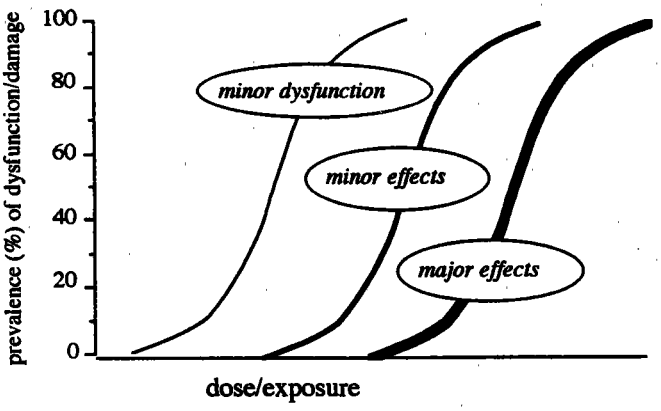
The relationships between dose and response vary according to the particular metal. They may be distributed normally, or follow normally distributed logarithmic function, or other more, or less, complex models.

Figure 1



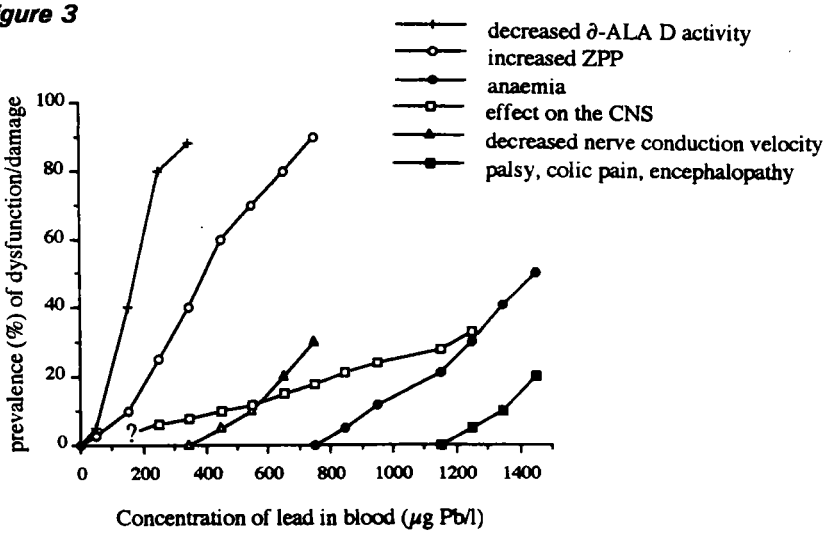
Exposure–dose, dose–effect, and exposure–effect relationships.

Figure 2



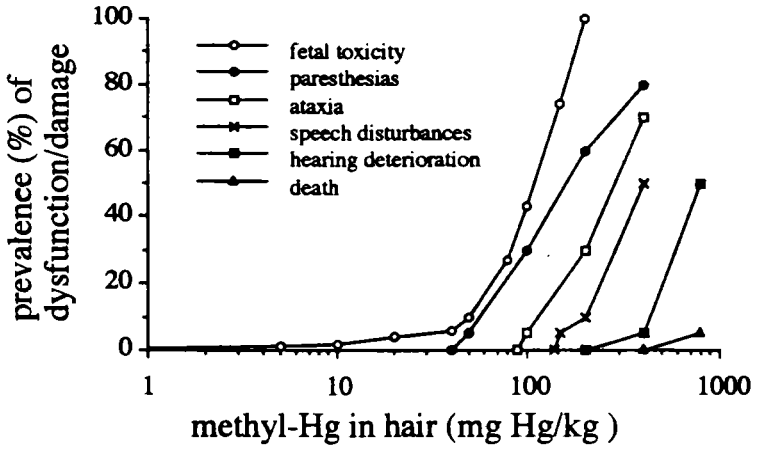
Relationships between dose or exposure and prevalence in percent (response) of individuals experiencing minor dysfunction, minor effects and major effects, respectively.

Figure 3



Prevalence (%) of adverse health effects at different blood lead concentrations. Most of the data are based on data from Friberg et al. (1986) and Skerfving (1988).

Figure 4



Prevalence (%) of symptoms at different concentrations of methylmercury in hair. Note the logarithmic scale for the X-axis. Some data are from WHO (1990).

With few exceptions there are no empirical data concerning relationships between dose and response at low-dose or exposure levels. Using models to predict the response at low-dose levels requires extrapolation from high-dose levels. Sometimes animal data only are available for this.

Different models for dose–response relationships may predict different response rates for low doses, despite good agreement for high doses or high exposures.

How do metals accumulate in the body and how are they distributed?

For risk estimations it is not enough to have information about critical organs, critical concentrations and critical effects. We need to know in addition how the metals accumulate in the body and how they are distributed in different exposure conditions.

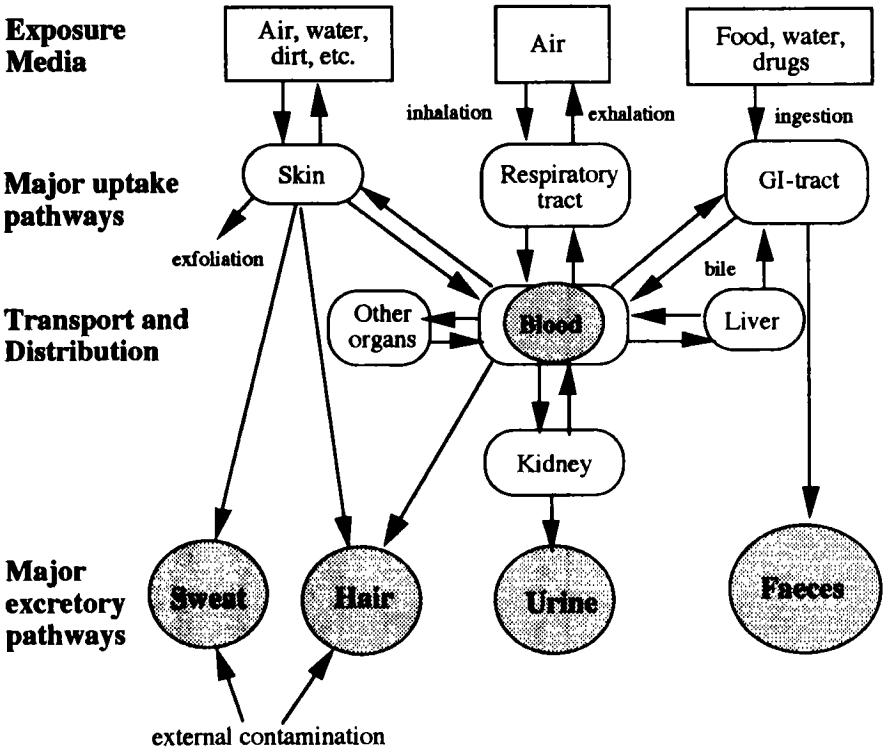
It is important to understand the metabolism of a metal in order to be able to predict its accumulation in the body. How much of the intake is taken up (absorbed) after inhalation? How much is absorbed by the gastrointestinal tract and by the skin? Is the metal changed in the body by biotransformation? How is it distributed between and within different organs? By which routes, e.g. expired air, urine or faeces, is the metal excreted? Consideration should be given to the speed at which the different reactions occur. The biological half-time is a crucial concept and defines the time it takes for the body to excrete half of a certain accumulated amount. It is an integral part of 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 in one concept, the metabolic model for the metal (Figure 5).

Once the metabolic model is known it is possible to estimate the concentration of the metal in the critical organ and in indicator media such as blood and urine.

The biological half-time varies considerably between metals, and between different organs and tissues. It is therefore appropriate to define biological half-times for blood, or body organs such as the brain or the kidneys, or for the body as a whole.

The biological half-time for cadmium is 20–30 years. For some metals, for example arsenic, cobalt and chromium, it is only hours or days. For inorganic mercury the half-time is a few days for blood, but a few months for the body as whole.

Figure 5



Metabolism after exposure to metals via skin absorption, inhalation and ingestion. The arrows indicate how the metals are transported. Tissues that are potentially useful for biological monitoring are identified by a shaded circle. (Modified from Clarkson et al., 1988.)

The biological half-time often differs for different animal species. The half-time of methylmercury is about 7 days in mice, but over 2 years in seals. In humans it averages 70 days, although there are large individual variations. Figure 6 shows the blood concentration of mercury before, during and after a period of constant exposure to methylmercury. Typically, there is a rapid initial rise in concentration followed by a slow increase, and then a steady state concentration. Once exposure has ceased, decrease occurs, following the same pattern.

The biological half-time in people poisoned by methylmercury in Iraq in the early 1970s ranged from 30 to 120 days. Therefore, although the exposure was similar for all individuals, the concentration of mercury in the brain and blood at steady state should have been about four times higher in individuals with the longest biological half-time than in individuals with the shortest half-time. The mathematical background for biological half-time and different metabolic models is presented in Boxes 1 and 2.

Box 1. Biological half-time

The biological half-time ($T_{1/2}$) expresses the speed at which a substance is excreted from the body or a tissue; it is the time needed to excrete half the amount of the substance. It can often be represented by one or more exponential functions.

$$T_{1/2} = \ln 2/b \qquad (1)$$

ln 2 = 0.693 (the natural logarithm of 2)
b = excretion rate per unit time (t^{-1}) (an excretion constant)

For methylmercury the average biological half-time is 70 days, which gives an excretion constant of about 0.01 per day. This means that 1% of the body burden is excreted daily.

If the excretion is governed only by the concentration of the metal in an organ, the organ concentration can be calculated at different times after the end of exposure using a simple exponential function:

$$c_t = c_0 \times e^{-bt} \qquad (2)$$

where c_t = the concentration in the organ at time t
c_0 = the concentration at time 0
e = 2.72....

In Figure 6 the accumulation and excretion of methylmercury has been calculated for different times during and after exposure to methylmercury.

Box 2. Metabolic models

A metabolic model—either one- or multi-compartment—describes absorption, distribution, biotransformation and excretion in quantitative or qualitative terms, and as a function of time.

One-compartment models use information on biological half-time and calculate the accumulation in the body, an organ or a tissue, following single, repeated or continuous exposure to the substance. When the time interval between the individual doses is relatively short, compared with the biological half-time, the accumulation is:

$$A = a/b[1-e^{-bt})] \quad (3)$$

A = accumulated amount in the organ
a = amount taken up per time unit (e.g. per day) by the organ
b = excretion constant
t = exposure time (the same unit as for a)

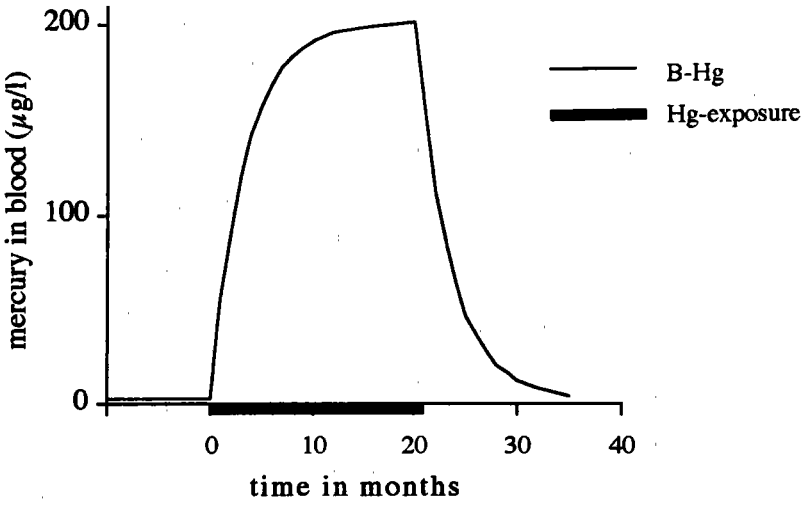
At equilibrium (steady state): $A = a/b$ (4)

Theoretically, equilibrium is not reached until an infinite time period has elapsed. For all practical purposes it is reached within a period equivalent to about 5 biological half-times. The accumulation during exposure to methylmercury (for which the average biological half-time is 70 days) and its excretion after the end of exposure is shown in Figure 6. Both the accumulation and the excretion follow a one-compartment model. The mathematical expressions assume that exposure, absorption and other relevant factors are constant. If such parameters change in a systematic manner during different time periods, as for example when food and calorie intake vary with age, the equations must be modified.

Multi-compartment models have been developed to describe the metabolism of metals such as lead, cadmium and inorganic mercury. (The metabolism of these metals cannot be described in detail using one-compartment models.) For practical purposes, it is often possible to make valid estimations using simpler models, employing one or several exponential functions.

Multi-compartment models have been expanded to create physiologically-based pharmacokinetic (PBPK) models. PBPK models combine detailed physiological parameters, such as blood flow rate and blood distribution, into different organ systems with information on systemic and organ uptake rates, allowing a more precise prediction of dosimetry for acute and chronic exposures (Gerlowski & Jain, 1983; Conolly & Andersen, 1991).

Figure 6



Accumulation and excretion of methylmercury during and after exposure. The average half-time for methylmercury is 70 days. For practical purposes, a steady state may be considered to have been reached after 5 half-times (about 11 1/2 months).

3. Levels in Humans

Biological monitoring

The term biological monitoring is used when the concentration of a metal or its metabolites is monitored in a human indicator media such as blood, urine, faeces, hair, or maternal milk. The same terminology is used for similar monitoring of other substances in the environment to which humans are exposed.

Biological monitoring aims to evaluate exposure and make risk assessments. Since many metals remain in the body for a considerable time after exposure, biological monitoring can provide information on exposures that occurred a considerable time previously. In emergencies, or in long-term epidemiological studies, samples can be stored for future analysis.

Biological monitoring takes into account inter- and intra- individual differences in the uptake of metals. These relate to differences in metabolism and physical workload. This form of monitoring can therefore identify individuals or groups of individuals whose uptake of metals is particularly high. It can also be used to determine the total exposure from different environmental media, which is an advantage when evaluating the risk of systemic effects.

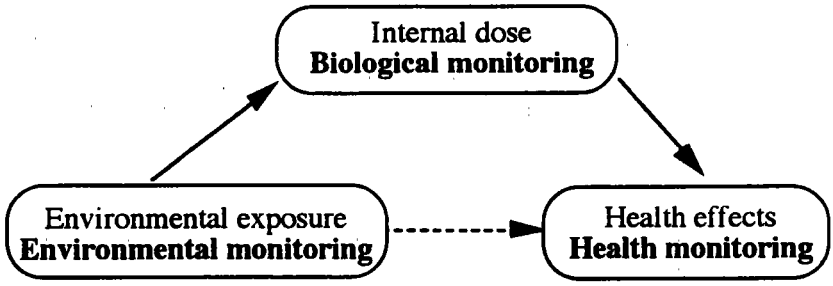
When carrying out epidemiological studies, information about dose–effect or exposure–effect and dose–response or exposure–response relationships can be obtained through biological monitoring.

Biological monitoring considers the total exposure. It gives a measure of exposure and risk both for the individual and for groups of individuals.

As a rule, biological monitoring of a particular metal should not be carried out without knowledge of the relationship between exposure and internal dose, i.e. the concentration in the critical organ or indicator media. Ideally, the relationship to adverse effects of the metal should also be known. The relationships schematically illustrated in Figure 7 are based on knowledge of the metabolic model, the critical organ and the critical concentration. Sometimes a risk estimation can be made directly from relationships between external exposure and adverse effects.

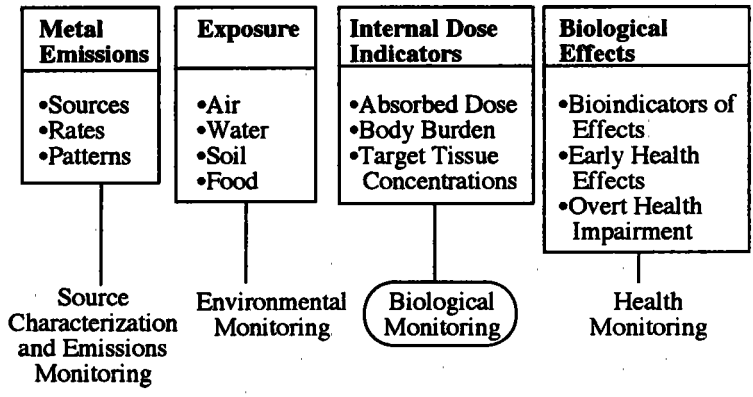
Following a particular exposure—for example, to lead in air in a work room—internal doses may vary since the background concentrations of lead in the blood may also vary. In many countries the background concentration of lead is already generally high, so that even low levels of additional exposure can result in adverse effects. It might be desirable then

Figure 7



Relations between environmental exposure, internal dose and effect. The figure shows that the total internal dose can be determined through use of biological monitoring.

Figure 8



Different types of monitoring and their relation to exposure, dose and effect. Biological monitoring is related to the internal dose.

to have different threshold limit values for lead in air, depending on the general background exposure from food, for instance.

Biological monitoring of cadmium has been of use in identifying increased exposure resulting from poor personal hygiene. For instance, the employees of one particular company who were exposed to considerable levels of cadmium oxide dust, were observed to have much higher blood levels (based on inhalation of cadmium dust) than would normally have been expected. In addition, the cadmium concentrations in faeces were much higher than could be explained by reference to cadmium concentrations in food. It was established that the high blood levels were due to contamination of hands, clothing and cigarettes. A similar situation applied to workers exposed to arsenic in a smelter, some of whom excreted more arsenic (in urine) than they had inhaled. Additional exposure had arisen from contamination of hands and clothing.

Other media used in monitoring

The metals to which we are exposed derive from both natural sources and human activities. If we wish to identify and characterize them, and to quantify the size of the emissions and the speed at which they are contaminating the environment, we must take the measurements at source. This is called **emission monitoring**. By combining the results of such measurements with meteorological data we can predict the concentrations of pollutants around point sources such as industrial stacks.

Emission monitoring is particularly useful if we want to quantify different emissions or to evaluate the efficacy of anti-pollution measures. It is used both within and outside industrial sites.

Environmental monitoring, sometimes known as media monitoring or ambient monitoring, includes sampling and analysis of pollutants in environmental media, such as air or food. It may be carried out at the workplace or in the general environment. This is the most common form of monitoring for routine surveillance of exposure.

Human exposure monitoring can be based on data from environmental monitoring and models of the inhalation of air, or ingestion of food and water. It can serve as a complement to or a replacement for exposure monitoring via biological monitoring, depending on the metal in question and the exposure situation.

Health monitoring is based on fluids such as blood and urine, or on tissue. The aim is to recognize the early biological effects of interactions between the metal and tissue.

Health monitoring aims to identify early effects, be these reversible or irreversible. It does not prevent such effects. Periodic health monitoring can be invaluable for recording the absence of adverse effects thereby verifying that exposure is sufficiently low.

The relations between different types of monitoring are shown in Figure 8.

Environmental monitoring

Environmental monitoring involves determining the level of metals in environmental media, usually air, food or water, but occasionally dust, paint or soil. The measurements are taken in the general or work environment.

Two of the most important uses of environmental monitoring are to measure the magnitude of ongoing exposure and to study changes over time, whether these be in the short or long term. Environmental monitoring is carried out in both the general and occupational environment.

Repeated monitoring of lead in urban air has shown that concentrations have decreased in parallel with the decreased use of lead in gasoline.

One of the useful features of environmental monitoring is that it can help identify specific exposure sources.

If air samples are taken from different places in a dental surgery the relative importance of different mercury exposure sources, such as amalgam formation, insertion of amalgam in teeth, and spillage of mercury on the surgery floor, can be evaluated.

Most occupational threshold limit values are based on relationships between exposure via air and effect/response.

The most common reason for undertaking environmental monitoring is to check that the exposure meets official recommendations and requirements.

Routes of exposure; local and systemic effects

Metals are taken up by the skin, airways or gastrointestinal tract. An exposure occurs when the cells in any of these surfaces comes into contact with the metal.

The deposited dose may remain in the cells of these organs or may be absorbed and transported to different tissues via the blood. An effect at the

place of deposition is known as a **local effect**. An effect of an absorbed dose is a **systemic effect**, and may be observed in any organ. Inhalation of a cadmium aerosol may cause a chemical pneumonitis, which is a local effect, but after absorption may cause kidney disease, which is a systemic effect.

How are metals in air monitored?

It is often necessary to collect and analyse both particles and vapours. Metallic mercury vapour, for instance, may be adsorbed to particles in the air. It can occur together with mercury in particle form when dental amalgam is being polished, and after reaction with chlorine, as mercuric chloride (in the chlorine alkali industry).

Air is usually sampled with stationary samplers, placed at fixed locations in a work room or in an area in the environment. It is important to note that the results of the analyses will be representative only for the defined areas.

If possible, samples should be taken using personal samplers, close to the breathing zone of the individual.

The individual exposure may differ considerably because of differences in breathing pattern, for example as a result of a light or heavy workload, or because the breathing is through the nose rather than the mouth.

The deposition of inhaled particles in the airways depends on their aerodynamic properties. Absorption and effects depend on where the particles are deposited. It is often necessary to separate particles of different size during the sampling.

Some of the particles that are trapped in the airways will be transported by the mucociliary system to the pharynx. When such particles are swallowed they may be absorbed from the gastro-intestinal tract.

How is exposure via food and water monitored?

There are different techniques for measuring metal exposure via food and water. If the concentrations of metals in different foodstuffs are known, the study subjects may be asked to keep a diary of their consumption of different foodstuffs, or to complete a questionnaire.

The dietary intake of metals is often determined using the duplicate diet technique. Duplicate portions of all the foods and beverages (including drinking-water) consumed during a certain time period are collected and

analysed. An advantage of this method is that it takes into consideration special exposures, e.g. high lead exposure from lead soldered cans. Furthermore, analysis of the accumulated total of the low amounts of a metal that occur in some foods becomes possible.

A rough estimate of the exposure can be obtained by using data from studies of consumption patterns.

However, none of the methods takes into consideration the special conditions seen in young children, exposed orally via dust and dirt during play (pica).

If a metal is absorbed only to a very limited extent, or excreted via the gastro-intestinal tract, analysis of faeces may be a useful complement to other forms of sampling and analysis. (Further information is given in the chapter on media for biological monitoring.)

4. Media for Biological Monitoring

Blood and urine samples are readily obtainable and the materials most commonly used for biological monitoring. Occasionally it may be useful to measure concentrations in additional materials that are relatively easy to obtain, such as hair or faeces. The time relationship between the measurement and the sampling period must be taken into account when interpreting data: a blood sample may represent 10 seconds of blood flow; a urine sample represent 10 hours of collection in the bladder; and a hair sample 10 cm in length may represent 10 months of hair growth.

Theoretically, the concentration of a metal in an internal organ such as the brain, liver or kidneys, or in the skeleton, should be measured, since this permits concentration of the metal in the critical organ or skeleton to be determined. The concentration can then be compared with the critical concentration, i.e. that which causes adverse effects. However, it is rarely possible to determine directly the concentration of a substance in internal organs, unless an autopsy or surgery is being performed.

New techniques, using *in vivo* neutron activation and X-ray fluorescence, now make it possible to measure lead in the skeleton, and cadmium in the liver and kidneys. With both methods, analysis is carried out in the manner of a routine X-ray examination; there is no need to take samples for chemical analysis. However, the equipment for neutron activation and X-ray fluorescence is only available in a few research laboratories.

Urine

Urine samples are often used for biological monitoring. They are easy to collect in large volumes, and the procedure is non-invasive. For many metals, urine is an important route of excretion and frequently the predominant one.

The concentration of a metal in urine is influenced by a number of factors: the degree of dilution, the kidney function, the body burden of the metal, the metabolic and kinetic pathways, and current exposure.

Urine is produced continuously by the kidneys as part of the complex process of the body's control of water and electrolyte equilibrium. The kidney's glomeruli produce an ultra-filtrate (the primary urine) at a rate of 125 ml/min, consisting of water, salts and small molecules. Large molecules such as immune globulins and albumin, as well as blood cells, do not pass through the glomerular filter but remain in the blood. A total blood volume of about 300 litres is filtered every day.

If the glomerular filtration capacity (GFR) is decreased, the capacity for eliminating metals also decreases. The concentration of the metal in the urine will become lower while the body burden increases. This is the case for aluminium, a metal that is normally excreted in the urine, but which accumulates in the bodies of those suffering from kidney disease.

Fluids and substances, which the body needs to keep, for example, some salts, amino acids, sugar and small proteins, are reabsorbed from the primary urine (more than 99%) in the kidney tubules. Substances that are not reabsorbed remain in the concentrated urine and are eliminated from the body. Some substances are actively excreted from the blood into the urine, making the total elimination of waste products still more effective.

Many metals are bound to small proteins, and are reabsorbed in the tubules. But if there is tubular kidney damage, and reabsorption fails, the urinary excretion of metals increases. This has been shown for both cadmium and copper.

If possible, all urine produced during a defined time period, e.g. 24 hours, should be collected. The excretion (μg/hour) of a metal can then be calculated and related to the exposure or body burden. If stable results are to be obtained, the urine must be collected over a reasonably long time period (12–24 hours). This may of course be difficult. The concentration of a metal, rather than the excretion rate, can be a useful measure, provided it is adjusted to a defined specific gravity, or to the concentration of creatinine in the sample (see below).

Adjustment of urine samples

The composition of urine is usually compatible with maintenance of body water and solute content within physiological limits. A short time after consumption of a large volume of fluid, the urine will become diluted, with a low solute content and a low specific gravity. When water is evaporated, for example due to perspiration as a result of high environmental temperatures or hard physical work, the urine concentration increases.

To evaluate a metal concentration it is necessary to consider the degree of concentration of the urine. This can be done easily by specifying the concentration in relation to creatinine or to an adjusted specific gravity.

Creatinine is a metabolic product of the muscles and is excreted in the urine in fairly constant quantities. This excretion is higher in males, muscular individuals and those who eat a lot of meat. Young and middle-aged males excrete between 1.4 to 1.9 g creatinine/day, while the excretion in women is usually 40% less.

If the metal excretion is reported as microgram (or μmole) per gram (or mmole) creatinine, it is possible to calculate an approximate 24-hour excretion of the metal, by multiplying it by the normal 24-hour excretion of creatinine.

The other alternative to compensate for different degrees of dilution is to adjust to a defined specific gravity. If we have a urine sample with a specific gravity of 1.012, i.e. a fairly diluted urine, and want to adjust it to a urine with a more normal specific gravity (1.022), the following calculation should be made:

concentration of urine sample x (1.022-1.0000)/(1.012-1.000).

The factor of 1.000, which is the specific density for water, must be subtracted from both numerator and denominator. The other decimals represent approximately the solute concentration, i.e. the degree of concentration of the urine. (See Box 3 for a description of units and conversion factors.)

Sampling and storage of urine

To avoid contamination of urine samples, the urine should be voided in a completely metal-free and cleaned vessel. Collection of urine in metal jars or bottles that have not been specially cleaned invariably leads to contamination; the results of the analyses will be worthless even if the analytical method is excellent. If subjects come directly from their workplace, they must clean their hands carefully before the urine is voided and collected. Sometimes it is necessary for the subject to take a shower in order to prevent the sample from becoming contaminated with dust from clothing.

Urine samples must be stored suitably prior to the chemical analyses. Since the human urethra generally 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 if stored at room temperature. If the bacterial growth is excessive, the sample will contain precipitates, smell foul and become difficult to analyse. To prevent this, urine samples should be stored at 1–4°C or, if possible, frozen. Sometimes it is useful to add small amounts of bactericidal chemicals, such as a few mg of sodium azide, to prevent bacterial growth.

Box 3. Units and conversion factors

The concentrations of a metal can be expressed in different ways:

μg/g, μg/litre or as μmole/g, μmole/litre.

In urine, the metal concentration is often expressed per g creatinine or mole creatinine.

Different laboratories often report concentrations in different ways, making interpretation of results difficult. Similarly, different scientific publications use different units.

In this review we have consistently used μg and g, or kg, as we consider these units to be less abstract than units such as μmole of a metal per μmole creatinine.

Concentrations in μmole/litre are obtained by dividing metal concentrations expressed as μg/litre by the atomic weight of the metal, e.g.:

10 μg Cd/litre = (10/112.4)μmole Cd/litre = 0.089 μmole Cd/litre = 89 nmole Cd/litre.

Similarly, μmole/litre, or nmole/litre, is converted to μg/litre by multiplying with the atomic weight:

5 nmole Cd/litre = (5x112.4) ng Cd/litre = 0.56 μg Cd/litre

If the concentration is reported in relation to creatinine, the molecular weight of creatinine (113) must be taken into consideration. A mercury concentration of 5 μg Hg/g creatinine corresponds to:

(5/200.6)/(1/113) = 2.8 μmole Hg/mole creatinine

Conversion from μmole/mole creatinine to μg/g creatinine is carried out by multiplying with the atomic weight and molecular weight, respectively:

1 μmole Cr/mole creatinine = (1x52)/(1x113) = 0.46 μg Cr/g creatinine

Other conversion factors are presented in Table 1.

Table 1. Conversion factors for metal concentrations

metal	symbol	atomic weight	μg/litre to μmole/litre	μmole/litre to μg/litre	μg/g creatinine to μmole/mole creatinine	μmole/mole to μg/g creatinine
aluminium	Al	27.0	0.037	27.0	4.19	0.24
antimony	Sb	121.8	0.008	121.8	0.93	1.08
arsenic	As	74.9	0.013	74.9	1.51	0.66
cadmium	Cd	112.4	0.009	112.4	1.01	0.99
chromium	Cr	52.0	0.019	52.0	2.17	0.46
cobalt	Co	58.9	0.017	58.9	1.92	0.52
lead	Pb	207.2	0.005	207.2	0.55	1.83
manganese	Mn	54.9	0.018	54.9	2.06	0.49
mercury	Hg	200.6	0.005	200.6	0.56	1.78
nickel	Ni	58.7	0.017	58.7	1.93	0.52
selenium	Se	79.0	0.013	79.0	1.43	0.70
tin	Sn	118.7	0.008	118.7	0.95	1.05
vanadium	V	50.9	0.020	50.9	2.22	0.45

The molecular weight of creatinine is 113
m = mill (thousandth, 10^{-3})
μ = micro (millionth, 10^{-6})
n = nano (thousand-millionth, 10^{-9})

Blood

Blood is a transport media. After uptake from the gastrointestinal tract or the lungs, metals are transported via the blood to different tissues and organs where they accumulate. Metals that have been taken up by tissues will be released by normal tissue metabolism and once again transported in the blood, and eventually eliminated from the body via the kidneys or liver (see Figure 5).

The blood level of a metal is influenced by the exposure and the concentrations in the internal organs (the body burden). The relative importance of these two factors varies according to the metal in question and the exposure conditions.

When in the blood, metals are bound to the red cells or to plasma proteins. For most essential metals, such as iron, copper and zinc, the body has special transport proteins, such as transferrin, ceruloplasmin and alpha-2-macroglobulin. Many non-essential and toxic metals bind preferentially to the red cells. Cadmium and lead are almost completely bound to the red cells. When lead or cadmium levels in whole blood are being compared between different groups and individuals, the concentration of red cells in the blood (i.e. the hematocrit) must be taken into account. If the hematocrit is low, the concentration of lead and cadmium will be lower, even if the exposure is the same.

The concentration of metals in plasma is of particular interest, since it constitutes the fraction of the metals in blood that is readily available for transport in and out of the tissues. However, for many toxic metals, including lead and cadmium, concentrations are so low that they are very difficult to measure. The presence of other metals, for example aluminium, chromium and mercury, is easier to determine in plasma.

Sampling and storage of blood

There are two common means of collecting blood samples: from the finger tip or the ear lobe to take a capillary sample, or from a vein, usually in the elbow. Capillary sampling yields only small volumes, and there is a risk of contamination, even if the fingers have been thoroughly cleaned. There is also a substantial risk that the blood cells will lyse (haemolysis) due to the sampling, and if they do so, this will influence the plasma:serum ratio. Nevertheless, when analysing the metal concentrations in the blood of small children, capillary samples must be taken.

For venous sampling, blood (5–10 ml) is as a rule collected in a vacutainer tube. Needles, tubes and stoppers must be checked carefully before sampling to avoid contamination. There have been many instances when

blood has been collected with a faulty technique, or in contaminated tubes, making it impossible to evaluate the results. Cobalt, chromium, manganese and nickel may contaminate the sample via the needle. Special precautions must therefore be taken to avoid contamination.

Blood collected in a tube will soon coagulate. The clear and slightly yellow fluid above the clot is called serum and is suitable for metal analysis. It is often desirable to analyse the metal in plasma or whole blood. A substance that prevents coagulation, usually heparin, must then be added to the sample. This substance is often already in the tube. It is necessary to check the metal content of these chemicals. Plasma is obtained by centrifuging whole non-coagulated blood.

Blood specimens must be kept cool. However, in a frozen sample, the red cells will lyse, making it impossible to separate the cells from the plasma.

When should blood and urine samples be collected?

The concentration of a metal in biological media such as blood and urine may vary during a day or a week. If blood and urine samples are collected for evaluation of exposure and risk, it is important to standardize the sampling, particularly for occupational exposure.

Figure 9 represents the excretion of cobalt in urine for a group of hard-metal workers. It can be seen that the urinary levels increase considerably during the working day. But due to rapid excretion and short half-time, the urinary concentration of cobalt decreases and is considerably lower by the next morning. There is a certain accumulation of cobalt over the week, however, as can be seen from the increase in morning concentrations. The exposure can be evaluated by comparing the cobalt excretion before and after the work shifts. The accumulation of cobalt in the body can be evaluated by analysing cobalt in urine before and after a period without exposure, such as a weekend or vacation.

These observations are similar to those concerning several other metals, such as arsenic, chromium and nickel, all of which are eliminated rapidly via urine. Conversely, for metals with a very long biological half-time, such as lead and cadmium, the timing of the sample is not so important.

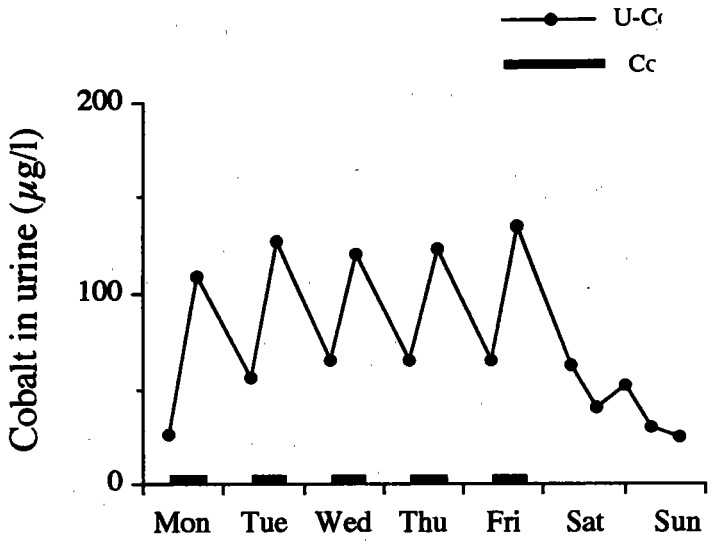
The timing of blood sampling should also be considered carefully before a monitoring programme is started. If the metal (e.g. cadmium or lead) is firmly bound to and mainly recovered in the red blood cells, which have an average life span of 120 days, the timing is less crucial than when monitoring a metal such as aluminium which is transported mainly in and eliminated from plasma.

How should blood and urine samples be collected?

Urine (at least 50 ml) should be collected in specially cleaned plastic containers, free from metals. Frequently, 250–500 ml polyethylene containers are used. Laboratories which undertake analyses of metals usually provide suitable containers, washed with acid and rinsed with deionized water, or cleaned in some other suitable way.

Whole blood or plasma should be collected in 5 or 10 ml vacutainers to which heparin or EDTA has been added to prevent coagulation. Suitable tubes include Venoject VT-100, Venoject T-100 H or Vacutainer A 32045 SVO 73.

Figure 9 SEE ERRATA



Excretion of cobalt in urine in a group of hard-metal workers before and after their work-shift, during one working week and the following weekend. The air concentration of cobalt averaged 90 µg Co/m^3. (Data taken from Alexandersson & Lidums, 1979.)

Hair

As the hair grows, i.e. during the anagene phase, metals from the blood and glands become incorporated in it. Nevertheless, it is seldom meaningful to measure body burden by determining the metal concentration in hair.

The major problem with biological monitoring of hair is the risk that metals from the environment have become trapped in it. For most metals, it has proven impossible to eliminate external contamination of the hair, and several studies have shown that the correlation between metal concentrations in hair and blood is poor.

However, analysis of metal levels in hair has been used to study different degrees of external contamination. It has been observed, for example, that hair samples from children living in the vicinity of large point sources, such as smelters, may have levels of the emitted metals which are more than 10 times higher those of non-exposed children. In such cases, the hair acts as a dust collector.

Moreover, if the metal exposure is exclusively from food, there will be no problem of external contamination. Methylmercury, for instance, is found in high concentrations in certain foodstuffs, particularly fish. In populations which consume fish with a high methylmercury content, methylmercury is absorbed from food into the blood and subsequently incorporated in the hair during the growth phase. A close relationship has been found between mercury in whole blood and in hair.

Analysis of mercury in hair has also been of great value in studies which have correlated methylmercury exposure during pregnancy with fetal damage. By analysing methylmercury in hair, it has been possible to reconstruct the methylmercury exposure experienced by the mother during her pregnancy. Hair normally grows at a rate of 10 mm/month. Therefore analysis of different sections of a hair strand 100 mm in length will give a good indication of the blood mercury levels of the mother during the different months of her pregnancy.

Bone and teeth

Some metals, such as aluminium and lead, accumulate in the skeleton. By analysing bone tissue, therefore, it is possible to estimate what the body burden and exposure were when the bone tissue was formed. Concentrations in bone may be reported per g wet weight, dry weight, ash weight, or sometimes in relation to the calcium content of the bone sample.

Teeth consist of bone tissue, dentine and enamel. Enamel is of special interest as it is formed during childhood. There is only a very small exchange of mineral after that period. Analysis of the mineral concentrations of enamel from deciduous teeth (milk teeth) can be used to estimate exposure retrospectively (cf. methylmercury for hair). For example, analysis of lead in deciduous teeth has provided estimates of exposure for early childhood which have been correlated with neurobehavioural deficits in children.

It is obviously more difficult to obtain bone samples than blood and urine samples. A bone biopsy can be performed with a special instrument, under local anaesthetic. This method has been shown to be of value for estimating the body burden of lead resulting from lead exposure earlier in life. It has also been used to study aluminium accumulation in the skeleton of dialysis patients. A technique for measuring exposure, but which does not require a bone sample, has also been developed. It uses X-ray fluorescence.

Faeces

Several metals are only incompletely absorbed from the gastrointestinal tract. This means that the quantity of a metal that is eliminated with the faeces may correspond roughly with the intake of that metal via food. So for some metals, such as aluminium, lead and cadmium, daily intake can be estimated by analysing the concentration of the metal in faeces and then multiplying it by the amount of faeces produced per 24 hours. But defecation habits vary considerably among individuals and it is relatively difficult to obtain representative samples; it may be necessary to collect all faeces during several days.

Analysis of faeces has been used to compare the daily intake of heavy metals of different populations, and to identify individuals and groups of people at high risk, due to their high intake of toxic metals.

Analyses of the faeces of workers exposed to metal dust have shown that industrial exposure often takes place through both inhalation and ingestion. If the workplace is contaminated with metal dust it can be expected that workers' hands, food and cigarettes will also be contaminated.

If the concentration of lead in faeces is higher than would be expected solely as a result of lead concentrations in food, exposure via dust may be indicated. For example, dust which contains lead is frequently emitted by industries and motor vehicles, contaminating soil and playgrounds. The hands and toys of small children may likewise become contaminated and the children exposed via the gastrointestinal tract.

Other media

Some studies have monitored metals in saliva and sweat. Since the composition of both saliva and sweat varies, the time and method of collection must be taken into account. The risk of contamination is substantial when sweat is collected. These media are at present not suitable for use in routine monitoring.

Breast milk is a useful medium as the newborn child obtains all its nutrition from this milk. Monitoring of breast milk has generally been carried out to estimate the exposure of the child, rather than that of the mother, and is thus a form of environmental monitoring.

Analysis of the placenta can also be used in biological monitoring. For example, analysis of the methylmercury and metallic mercury, and possibly also cadmium, in the placenta, can indicate what the mother's exposure was during her pregnancy.

Specimen collection

Specimen collection is a critical step in all trace metal analyses of body fluids and organs.

Contamination must be avoided as well as losses due to evaporation and wall effects.

Instruments and vessels must be cleaned carefully, and the procedures checked by analysing blanks. Only acid-washed tubes or certified tubes should be used. Any other materials, such as stoppers and covers, must also be checked. The same holds true for anti-coagulants or other chemicals added to the sample.

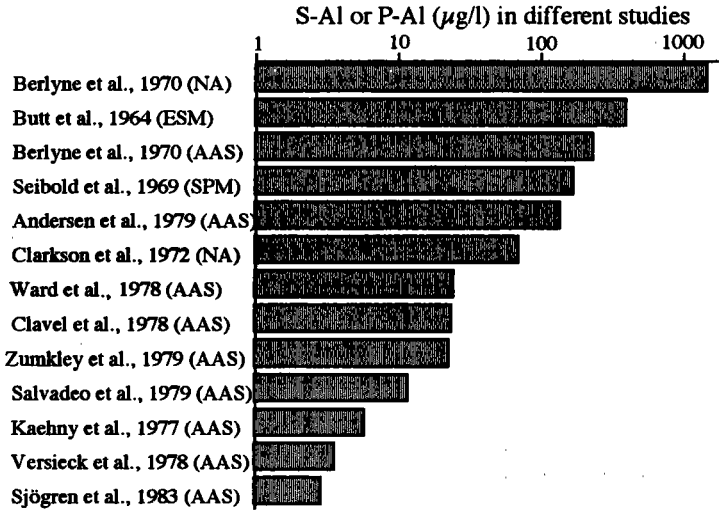
Long-term storage

The storage of biological samples for long periods—perhaps years—creates special problems. There is a tendency for blood, urine and tissues to dry out even if the samples are stored at -20°C. So if the concentration of the metal is determined based on wet weight, the results will be too high. There will also be a risk that small amounts of the metal in the sample will react with the wall of the container and adhere. Wall effects may be significant, particularly if the concentration of a metal in the sample is low, and lead to false conclusions when the sample is analysed. When creating tissue banks, particularly for reference materials, due attention must be given to this problem and, if necessary, to improved storage methods.

Analytical accuracy

During recent years the capacity to analyse even low concentrations of trace metals has improved dramatically due to the development of new and advanced analytical instruments and methods. It is now possible to determine concentrations in the μg/kg range or sometimes in the ng/kg range in biological materials. Consequently, the levels for "normal" concentrations have gradually been adjusted downwards, apparently without any real decrease in the concentrations. The "normal" values for aluminium established by studies during different time periods are shown in Figure 10.

Figure 10



The "normal" concentration of aluminium in serum/plasma, as reported by different authors. Only more recent reports (Versieck and Cornelis, 1980 and 1989, and Sjögren et al., 1983) are reasonable. This figure has been modified from Versieck et al., 1980.

The accuracy of analytical data has not always improved in parallel with the development of analytical methods. Yet with the lower detection limits there is a need for increased accuracy of data, otherwise the risk of error caused by contamination or losses before and during analysis increases.

Box 4. Analytical accuracy

To obtain reliable analytical results it is necessary to consider the accuracy, precision and detection limit of the method.

Accuracy shows to what extent the results differ systematically from the "true" value.

Precision of a method is a measure of the spread round the mean, when analysing the same sample repeatedly. One measure of the precision is the standard deviation (SD). It is often given as the coefficient of variation (CV), which is SD divided by the mean and expressed as a percentage.

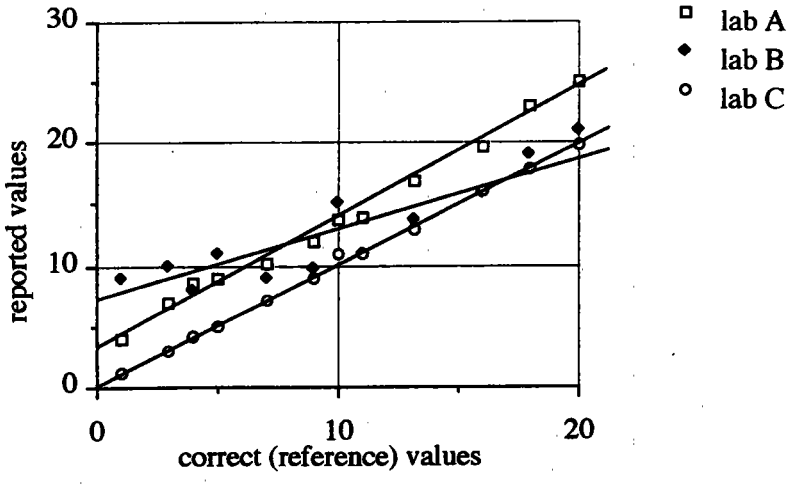
Detection limit is the lowest level at which the substance can be detected and measured. Consideration should be given to two different statistical errors: alpha and beta errors. The alpha error refers to a conclusion that the substance was in the sample, when in reality it was absent. The beta error refers to a conclusion that the component was not in the sample, when in reality it was present. Both errors can be expressed in quantitative forms.

Many examples show, that even during recent years, grossly erroneous results have been reported in scientific papers and in routine reports from commercial laboratories. In one study, blood was taken from one person on a single occasion and divided into 35 subsamples, and together with a number of routine samples sent over a nine-month period to a well-known analytical laboratory in the USA for analysis of lead. The reported mean was 191.3 μg per litre of blood, with a standard deviation of 57.2 μg/litre. In other words, approximately one-third of the results differed from the mean by more than 30%.

Figure 11 presents the results of quality control samples for cadmium from three well-established Nordic laboratories. Gross systematic errors can be observed in the results from two of the laboratories.

The aim of biological monitoring is to provide reliable information on metal concentrations in examined tissues or body fluids. Yet it is only during recent years that it has become common practice to implement adequate quality control for routine analysis of metals in biological material. Not surprisingly, many analytical results of the past have been shown to be erroneous. However, it is often not possible to evaluate published results since there is simply no information which would allow the accuracy of the results to be checked. Ten years ago, an international study undertaken by the World Health Organization and the United Nations Environment Programme evaluated a large number of reports of cadmium and lead levels in blood. An acceptable quality control was reported for

Figure 11



Results from quality control analyses showing gross analytical errors. Laboratory C consistently reported values almost identical to the correct values. The values that Laboratory A reported were too high for the whole concentration range, due to a systematic analytical error. The values reported by Laboratory B were far too high within the low concentration range (of correct values). If quality control samples containing high concentrations of cadmium only had been analysed, the poor performance of Laboratory B would not have been detected.

only 10 or so of the published reports which were examined (Vahter, 1982). More recently, unsatisfactory quality control has been reported for mercury in blood, based on an evaluation of around 100 published reports (Nordberg, et al., 1992).

Evaluation of a large number of published papers has shown that the accuracy of analytical results is often low. It has sometimes been possible to estimate the magnitude of the errors. It is not uncommon to find metal concentrations which are 10–50 times too high. The evaluations mainly involved examination of published results which suggests that errors are probably larger still for routine analyses.

Blood samples are usually taken from a vein in the elbow. The best procedure entails use of stainless steel needles and vacutainers. Particular caution must be exercised when analysing chromium or nickel.

Particular problems arise when taking taking blood samples from small children since in their case it is difficult to obtain blood from the elbow. If capillary blood is taken from a finger tip instead, the finger should be cleaned carefully beforehand.

Urine may be collected in acid-washed plastic containers. To avoid contamination the urine sample must be voided in a place that is separate from the working area, and the worker should first wash himself/herself carefully. It is therefore often worthwhile to collect the sample in the worker's home. For metals with a short biological half-time, such as arsenic and cobalt, possible changes over time must also be taken into account (see Figure 9).

Analytical methods

When choosing analytical methods, accuracy, precision and detection limits (see Box 4) must be considered. Additionally, there are practical aspects relating to cost and availability.

Isotope dilution/mass spectrometry (IDMS) is considered an absolute method and involves adding a known concentration of a stable isotope to the sample. (Many elements have two or more stable isotopes occurring in nature in a constant relation.) However, IDMS is an absolute method only if the analysis is carried out under optimal conditions, with ultra-pure chemicals, and in an ultra-clean laboratory.

Neutron activation (NAA), if properly executed, is a suitable reference method for many metals. Accuracy is high and the cost of the analyses reasonable. Radioactive isotopes are formed when a sample is irradiated with neutrons. The element to be measured is identified by the type and energy of the emitted radiation, as well as by its decay characteristics. Neutron activation can be carried out after radiochemical separation (RNAA) or directly, as instrumental neutron activation (INAA) of the sample. Several metals can be measured simultaneously. This method has a low detection limit for most metals, although there are exceptions. For example, NAA cannot be used to analyse either lead, cadmium, nickel or tin at low concentrations.

Most routine methods for analysing metals use some form of atomic absorption spectrometry (AAS). Very sophisticated instruments are now available for this. When analysing low concentrations (of less than 1 μg/litre in the sample), an electrothermal pretreatment (ETA) is used. High concentrations can be analysed directly using a flame method.

Some metals are analysed with cold vapour technique (CVAS). If the technique is modified, separate analysis of total mercury and inorganic

mercury can also be carried out. Methylmercury can be analysed using gaschromatography.

AAS may cause an unspecific absorption due to the presence of atoms and molecules. Sodium chloride and phosphates are known to cause interference. This can be avoided by background correction with deuterium lamps, or systems that incorporate the Zeeman effect, which splits absorption lines through use of magnetic fields. If it is not possible to avoid interference (e.g. when analysing cadmium in urine), a chemical extraction should be carried out prior to the analysis.

Inductively coupled plasma atomic emission together with mass spectrometry (ICP-MS), was introduced fairly recently. Several elements can be determined simultaneously and this method may become of great importance in the future.

Quality control

There are many potential sources of error when conducting analyses of trace elements in biological material. But a number of control measures can be carried out before, during and after analysis to ensure accurate results (Friberg, 1988). Further detail is given in the report of the WHO/United Nations Environment Programme Monitoring project (Vahter, 1982) and also in reports from the WHO/United Nations Environment Programme Human Exposure Assessment project (HEALs).

There is a conceptual difference between quality assurance (QA) and quality control (QC).

***Quality assurance** is the wider concept and refers to the steps which may be taken to ensure that data are reliable. It covers: the utilization of scientifically and technically sound practices for collecting, transporting and storing samples; laboratory analysis, and the recording, reporting and interpretation of results.*

***Quality control** refers more specifically to the quality of the laboratory results and has two components: external quality control (EQC), which refers to the control of laboratory performance by an external organization, and internal quality control (IQC), which is a set of procedures used by the laboratory itself for assessing results as they are produced, in order to decide whether they are reliable enough to be released.*

The use of reference samples with known concentrations of the metal is an important component of both external and internal quality control. The reference samples should be certified for a certain concentration and, if possible, the margins of uncertainty should be given.

As far as possible, reference samples should have the same matrix as the monitoring samples; i.e. they should all be made from the same material. The reference samples should contain the metal in approximately the same concentrations as the monitoring samples.

Unfortunately the availability of suitable reference materials for different metals, concentrations and tissues is limited.

Reference materials can be obtained from the following:

***Behring Institute**, P.O. Box 1140, D-3550 Marburg 1, Germany.*
***Community Bureau of Reference** (CBR), Commission of the European Communities, 200 Rue de la Loi, B-1049 Brussels, Belgium.*
***International Atomic Energy Agency** (IAEA), Analytical Quality Control Services, Laboratory Seibersdorf, A-1400 Vienna, Austria.*
***Kaulson Laboratories Inc.**, 691 Bloomfield Avenue, Caldwell, New Jersey 07006, USA.*
***National Institute for Environmental Studies** (NIES), Japan Environment Agency, P.O. Yatabe, Tsukuba Ibaraki 300-21, Japan.*
***National Institute of Standards and Technology** (NIST), Rm B311, Chemistry Bldg., Gaithersburg, MD 20899, USA.*
***National Research Council Canada** (NRCC), Division of Chemistry, Ottawa KIA 0R6, Canada.*
***Nycomed AS Diagnostics**, P.O. Box 4220, Torshov, 0401 Oslo 4, Norway.*

If it is not possible to carry out the external quality control with reference material, analysis of quality control samples at different laboratories, and using different analytical methods, has to be relied upon. In fact, it is usually through such collaboration that certified reference materials are produced.

Laboratories which carry out trace element analyses commercially, or on request, should be able to present results from the quality control programmes in which they participate. This information should include information about control measures, criteria for acceptance of analytical results, and their own results.

It is not considered sufficient or acceptable as quality control to refer to a specific analytical method, even if that method produced satisfactory results on another occasion, perhaps at another laboratory. Similarly, it is not meaningful to refer to participation in a quality control programme if the results of the tests are not reported.

As the quality of a laboratory's analytical work may differ between different time periods and for different metals and media, results from participation in quality control programmes should be presented separately for different metals, tissues and time periods.

Further information can be found in the extensive report from the *Symposium on the Biological Monitoring of Toxic Metals* held in Rochester, New York, USA in 1986 (Clarkson et al., 1988). A description of a recommended regression method, which uses reference materials containing a range of concentrations, can also be found in this report. Roels et al. (1987) have successfully used another regression method for quality control of mercury in urine.

How are metal analyses carried out?

Most analyses are carried out with atomic absorption, usually with graphite furnace (GFAAS), although for mercury analyses a cold vapour technique (CVAAS) is more appropriate. Neutron activation is available only to a very limited extent, as is X-ray fluorescence analysis (EDXRF) and particle-induced X-ray emission (PIXE).

Quality control varies between laboratories. Many of them analyse reference materials and/or participate in intercalibration programmes. Some laboratories have documented results of their QC programmes in scientific papers.

Several laboratories have prepared detailed recommendations on how to take samples. And often, if requested, laboratories will indicate to customers the methodology they use and the results of their QC programmes.

It is recommended that potential customers make a practice of agreeing with the laboratory—before it undertakes any work—not only the costs for the analyses, but also the sampling methods to be used, and the extent and reports of results of the quality control. (See the previous sections on analytical accuracy, specimen collection and quality control for guidance on the issues that should be covered in an agreement.)

As an additional check, the customer can include one or more samples with a known concentration of the metal among the samples to be analysed.

Statistical and epidemiological sampling

In order to fully interpret biological monitoring data from studies of exposed groups, it is essential that the number of people studied and the selection of them are considered carefully. Appropriate statistical and epidemiological approaches should be used. These have been described in other WHO publications, including *Basic Epidemiology*.

Ethical aspects

Biological monitoring should be carried out on a voluntary basis only and in such a way that the volunteers are not exposed to any risks. Any possibility of transmission of infectious diseases via needles or the actual specimens must be excluded.

Any individual who provides a biological sample must be informed of the purpose of the monitoring, and the analyses that will be carried out.

If any individual refuses to participate in a biological monitoring exercise, he or she must not be punished in any way.

Volunteers must be informed of the results of the analyses and given assistance, as required, to enable them to interpret these.

Certain problems may arise when monitoring takes place in an area in which occupational exposure to metals occurs. In some countries, once certain concentrations of cadmium or lead in blood have been reached, the exposure must be curtailed. This usually means that the employee must change employment, but is entitled to retain his/her salary. It is important that such decisions are taken in full cooperation with a company doctor, in whom the employee has complete confidence.

Information on metal concentrations in biological samples should be treated with the same confidentiality as any other type of medical information. Information pertaining to an individual should not be given to the employer or a trade union without the permission of the individual concerned.

Non-individual data, such as group averages, ranges, etc., should, however, be made available to the employer. It should be possible to follow time trends and to identify any subgroup which is subject to high exposure. This should be undertaken with the aim of decreasing the exposure and thereby securing a healthier work environment.

5. Biological Monitoring of Different Metals

The following sections describe how biological monitoring can be used to evaluate exposure and risks for the following metals: aluminium, antimony, arsenic, cadmium, chromium, cobalt, lead, manganese, mercury, nickel, selenium, tin and vanadium.

A summary review concerning occurrence, exposure, metabolism and health effects of the metals is presented here. For more detailed information, the reader should consult more extensive reviews, for example, Friberg et al., (1986).

ALUMINIUM

Occurrence

Aluminium (Al) is the most abundant metal, constituting as much as 8% of the earth's crust. But in spite of this, the concentration of aluminium in water and most biological material is very low. Aluminium concentrations are usually less than 0.1 mg/litre in drinking water and less than 1 μg/litre in seawater. Common foodstuffs usually contain 2–20 mg Al/kg.

Exposure

The daily intake of aluminium from food is estimated to be about 7 mg. Workroom concentrations of 1 mg/m^3 (and also substantially above this level) have been reported for aluminium welding and the production of aluminium powder. Antacids contain high concentrations of aluminium; for patients taking such drugs, daily intake of aluminium may exceed 1 g.

Metabolism

There is very little information concerning the uptake, excretion and accumulation of aluminium. It has been shown, however, that the small amounts (0.01–1%) of aluminium to which we are exposed via food or drugs are absorbed from the gastrointestinal tract. Simultaneous intake of citric acid increases the absorption considerably. During occupational exposure the metal is absorbed as a result of inhalation. The degree of absorption has been estimated to be at least 0.2%.

The major part of absorbed aluminium is excreted relatively quickly via the kidneys. The biological half-time following a heavy exposure is about 8 hours. After long-term heavy exposure via inhalation—for example, in aluminium welders—the aluminium accumulates in the skeleton and is eliminated very slowly, with a half-time of several years. Patients with chronic kidney disease constitute a risk group. The kidneys of such patients do not function normally and their excretion of aluminium is therefore decreased, leading to an accumulation of aluminium in the body.

Health effects

Occupational exposure to aluminium powder may produce a characteristic pneumoconiosis, aluminosis. Exposure to aluminium compounds, such as aluminium fluoride, has been associated with irritation of the lung. Long-term accumulation of aluminium can damage both the central nervous system and the skeleton. Dialysis encephalopathy, a serious disease of the central nervous system, has been observed in patients with chronic kidney disease. Such severe damage has not been observed for aluminium-exposed workers. It is suspected that long-term exposure may result in increased incidence of neuropsychiatric symptoms.

Biological monitoring of aluminium

Aluminium is abundant in the environment, so there is a high risk of contamination when analysing aluminium in biological materials. Indeed, much of the published information on normal levels of aluminium in plasma and serum is erroneous (Figure 10). For people who do not suffer from kidney disease, and who are not occupationally exposed, the aluminium concentration in blood and urine is less than 3 μg/litre.

Biological monitoring is useful for evaluating occupational exposure to aluminium. After a heavy exposure via inhalation, and within a few hours, there will be substantial excretion of aluminium via the urine. There is also a correlation between the number of exposure years (the cumulative exposure) and the aluminium excretion in urine. It is still uncertain to what extent health risks in occupationally exposed workers can be predicted by measurements of concentrations in blood and urine.

For patients with chronic kidney disease, there is a relationship between the concentration of aluminium in serum, and symptoms affecting the central nervous system. Signs of severe brain damage may occur at serum concentrations exceeding 200 μg Al/litre, and minor symptoms at lower levels (50–100μg Al/litre).

References: de Broe & Coburn (1990); Sjögren et al. (1988)

ANTIMONY

Occurrence

Antimony is often found together with arsenic. The two metals have some chemical and physical similarities. Antimony exists in tri- and pentavalent forms.

Exposure

The daily intake with food is approximately 10 μg. During industrial exposure, air concentrations may exceed 1 mg/m^3.

Metabolism

The extent of absorption from the gastrointestinal tract is not known. The metal is excreted via urine (primarily in the pentavalent form) and faeces (primarily as trivalent antimony). The elimination rate seems to be higher for the pentavalent than for the trivalent form. About 90% of a single injection of pentavalent antimony is eliminated via urine within 24 hours.

Health effects

Inhalation of high amounts of antimony causes irritation of the upper respiratory tract. After many years of industrial exposure, pneumoconioses may develop. The lung function is affected only slightly. In animal studies, antimony has been found to be carcinogenic, but nothing is known about its possible carcinogenicity in humans. There are reports of adverse effects on the heart after antimony exposure but to date the causality is unproven.

Biological monitoring of antimony

As occupational exposure to antimony is rare, experience of biological monitoring of this metal is very limited. The normal concentration of antimony in serum, whole blood and urine is reported to be about 1 μg/litre. During occupational exposure to antimony, levels in urine increase markedly. Biological monitoring may indicate an approximate measure of exposure. It is still not possible to present a mathematical relationship between air and urine concentrations of antimony.

It is not known to what extent increased concentrations of antimony in urine are related to health risks, such as risks for lung cancer or heart disease.

Reference: Lüdersdorf et al. (1987)

ARSENIC

Occurrence

Inorganic arsenic occurs in the environment as trivalent and pentavalent compounds. Arsenic trioxide is obtained as a by-product during the production of copper and lead from sulfide ores. Inorganic arsenic compounds are used for wood impregnation and in the production of gallium arsenide for electronic components. Lead arsenate and methylated arsenic compounds are used as herbicides.

Fish arsenic comprises a special group of methylated arsenic compounds—but principally arsenobetain—and is found in marine fish and shellfish.

Exposure

The most significant human exposure to arsenic compounds originates from fish. There may be more than 1 mg of fish arsenic in one meal of fish. The maximum daily intake of other arsenic compounds is normally around 10 μg, but will be much higher if contaminated water or food is consumed. Arsenic (As) in food (both fish arsenic and other compounds) is absorbed effectively from the gastrointestinal tract.

Occupational exposure to arsenic may be very high, for instance in smelters.

Metabolism

Arsenic is methylated in the body. The major part of absorbed inorganic arsenic is excreted in urine as monomethylarsonic acid (MMA) and dimethylarsenic acid (DMA). A small part (1–20%) of absorbed arsenic is excreted in the urine without methylation. The relative fraction of non-methylated arsenic compounds increases with the intensity of the exposure.

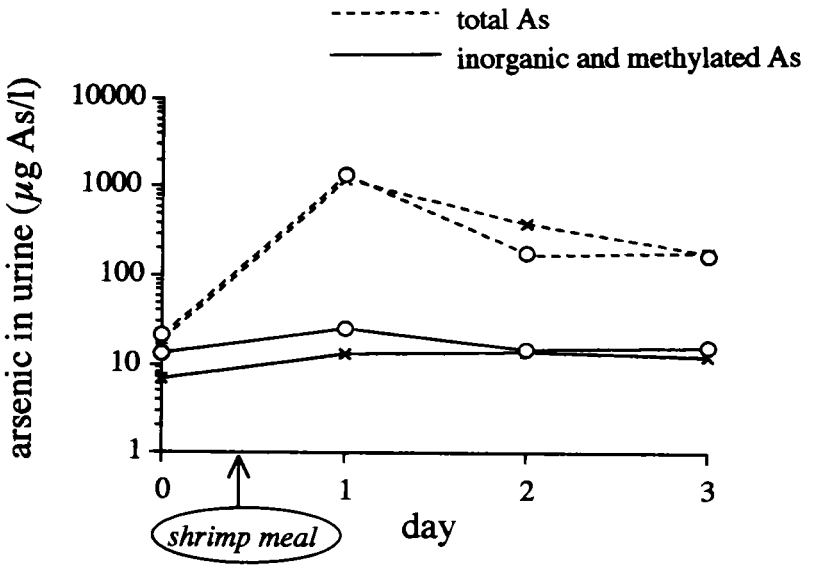
At least 50% of ingested arsenic is excreted in the urine within a week. Thus arsenic has a relatively short half-time.

Health effects

Inorganic arsenic compounds can cause acute poisonings and chronic disease. Epidemics of poisoning have occurred in Japan and South America due to exposure via drugs, contaminated food and water. Lesions of the skin, such as hyperpigmentation and warts, as well as skin cancer, were observed. Effects in the blood vessels may lead to impaired blood circulation in the feet and amputation may be necessary (blackfoot disease). Inhalation of inorganic arsenic compounds has caused lung cancer in smelter workers.

People who consume large amounts of certain marine organisms, such as sole, shrimp and lobster, are exposed to tens of thousands μg of fish arsenic, but there have been no reports of poisoning from this source. It therefore seems that this form of arsenic is much less toxic than the inorganic forms of arsenic.

Figure 12



Urinary excretion of inorganic and methylated arsenic compounds, and total arsenic (including fish arsenic) in two subjects, after a shrimp meal. Note that the scale of the Y-axis is logarithmic.

Biological monitoring of arsenic

The normal concentration of arsenic in blood is about 1–4 μg/litre. Soon after exposure to organic or inorganic arsenic, the concentration in the

blood increases, but decreases soon after exposure has ceased, due to effective elimination via the kidneys. In urine, the concentration is usually less than 10 μg/litre. Much higher levels (50–100 μg/litre) are seen among people who have eaten large amounts of fish or shellfish, or who have been exposed to arsenic via food or inhalation. Figure 12 shows how the urinary excretion of total arsenic increased after a shrimp meal, while the excretion of inorganic arsenic remained unchanged.

Studies of smelter workers have shown a linear relationship between the arsenic concentrations in workplace air and the excretion of arsenic and its metabolites in urine. In a study for which urine samples had been collected about 16 hours after exposure had ceased, the following relationship was found to apply:

Urine arsenic-As (μg As/g creatinine) = 29 μg As/g creatinine + 2 x air arsenic concentration (μg As/m^3 air).

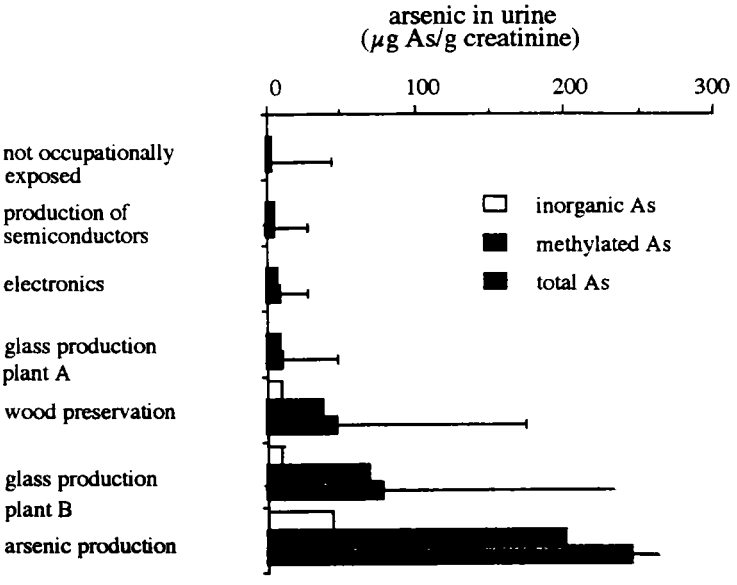
Figure 13 presents the urinary excretion of methylated and inorganic arsenic compounds among different groups of arsenic-exposed people.

Urine samples may thus be used to identify and quantify the exposure to both fish arsenic and inorganic arsenic. A close relationship can be observed between air concentrations and urinary levels of arsenic. Arsenic taken orally is absorbed effectively. Contaminated food will therefore greatly influence the urinary concentration of arsenic. This also holds true for fish arsenic.

When analysing arsenic in urine it is possible to differentiate between "dangerous" exposure to inorganic arsenic and "innocent" exposure to fish arsenic. This is done by using analytical methods that separate fish arsenic from inorganic arsenic with the metabolites MMA and DMA (Vahter, 1988).

In cases of acute arsenic poisoning the excretion of arsenic increases considerably. Increased arsenic concentrations in urine over long periods of time indicate continuous exposure. Such exposure has been associated with the development of skin and lung cancer among people occupationally exposed or exposed to contaminated water. Urinary concentrations of inorganic arsenic and its metabolites may be used for risk assessment. In the absence of confounding effects from fish arsenic, a urinary excretion exceeding 100 μg As/g creatinine would indicate a fairly high exposure to inorganic arsenic.

Figure 13



Urinary excretion of inorganic and methylated arsenic compounds and total arsenic among different groups of arsenic-exposed people. T indicates standard deviation.

It is less advisable to use urinary concentrations of different arsenic species for risk estimation of different types of occupational exposure. Inorganic arsenic compounds with a high solubility are eliminated from the body at a faster rate than more soluble species, resulting in higher concentrations of arsenic in urine. It is possible that insoluble inorganic arsenic compounds remain in the lung for longer time periods than do more soluble aresenic compounds, and therefore contribute to the development of lung cancer to a higher extent.

References: Farmer & Johnson (1990); Foa et al. (1987); Vahter (1982; 1988)

CADMIUM

Occurrence

The occurrence of cadmium (Cd) varies considerably between environments. Air from uncontaminated areas contains less than 0.001 μg Cd/m^3. Fresh water and seawater usually contain about 0.1 μg Cd/litre. The cadmium concentrations in most foodstuffs vary between 1 and 50 μg/kg, although they may exceed 1 mg/kg in some foods, such as liver, kidney, oysters, mussels and certain mushrooms.

Exposure

In most countries, daily cadmium intake via food is between 10 and 25 μg. There are indications that the occurrence of cadmium in foodstuffs has increased this century as a result of contamination of the environment. A study of human kidneys, kept in a museum since the middle of the 19th century, showed that they contained considerably less cadmium than kidneys of individuals who had died in recent years. Smokers are exposed to concentrations of cadmium that lead to significant cadmium accumulation in the lungs, liver and kidneys. In some industries, workers inhale air containing about 10–30 μg Cd/m^3.

Metabolism

The absorption of cadmium from the gastrointestinal system is relatively low (on average only 5%). Retention of inhaled respirable particles, i.e. particles that penetrate as far as the alveoli, can reach 50%.

Absorbed cadmium is transported via the blood to the liver. In the liver, cadmium is bound to a sulfur-containing protein (metallothionein) which binds cadmium to a great extent. Small amounts of cadmium metallothionein pass continuously from the liver to the blood. The cadmium is transported to the kidneys and filtered through the glomeruli, then reabsorbed and stored in the tubular cells of the kidneys. This mechanism leads to a very pronounced accumulation of cadmium in the kidneys. Concentration in this organ is about 10 000 times higher than in blood.

Health effects

Since cadmium is eliminated only very slowly from the kidneys, cadmium will accumulate in them, and once the critical concentration has been

reached, kidney damage will develop. The first sign of damage is tubular proteinuria, with an increased excretion of low molecular weight proteins, such as β2-microglobuline. If this damage worsens, glomerular filtration (GFR) becomes impaired. In severe cases, uremia may develop. Tubular kidney dysfunction also results in increased urinary excretion of calcium, which can lead to osteoporosis and formation of kidney stones.

Inhaled cadmium may damage the lungs. Chronic obstructive lung disease has been observed in workers exposed to high concentrations of cadmium. During recent years, there have been indications of an association between occupational exposure to cadmium and lung cancer. Animal experiments have shown that cadmium exposure causes lung cancer.

Biological monitoring of cadmium

Cadmium in blood is bound mainly to the red cells. The concentration in plasma/serum is low and difficult to determine. In non-smoking, non-occupationally-exposed individuals, the blood levels are usually between 0.2 and 0.8 μg Cd/litre; while in smokers the concentrations are considerably higher (1.4–4.5 μg/litre). There is a close relationship between the number of cigarettes smoked per day and the concentration of cadmium in blood.

During occupational exposure to cadmium, the cadmium levels in blood increase relatively quickly. After one or two months the blood levels will have reached a concentration which corresponds to the intensity of the exposure. Once exposure has ceased, the blood cadmium level will decrease fairly rapidly. The initial half-time for cadmium has been calculated to be between 2 and 3 months.

Cadmium will accumulate in the body as a result of cadmium exposure. The blood concentration will therefore not decrease to the pre-exposure level once exposure has ceased (Figure 14). Blood cadmium generally reflects the current exposure. By analysing blood, individuals with a particularly high exposure can be identified, and preventive measures taken to decrease exposure before kidney damage occurs. From one study it was calculated that workers with blood cadmium concentrations of 10 μg/litre over a period of 20 years run a 14% risk of developing tubular kidney damage. If exposure occurs over still longer periods, the risk of kidney disease at lower blood cadmium levels of 5–10 μg/litre is probably increased.

The cadmium concentration in urine is influenced more by the body burden than by the current exposure. Non-smokers have urine levels of between 0.1 and 0.7 μg Cd/g creatinine, or per litre, slowly increasing with age. This increase is caused by the accumulation of cadmium in the body.

Smokers and people living in contaminated areas have higher urine cadmium levels. During long-term occupational exposure, the concentration of cadmium in urine increases slowly and in proportion to the accumulated amount in the body (Figure 14).

The excretion of cadmium is proportional to the concentration of cadmium in the kidneys. There is a close relationship between the cadmium concentration in urine and the prevalence of tubular kidney damage.

A cadmium concentration in urine of 5 μg/g creatinine corresponds to a cadmium concentration in the kidneys of about 150 mg/kg. At urine cadmium levels of between 5 and 10 μg Cd/g creatinine, the prevalence of tubular kidney damage is between 5 and 20%. If the cadmium concentration is higher than 10 μg/g creatinine, the risk of tubular damage is still higher. A study from Belgium reported that a small fraction of the general population had an increased prevalence of tubular dysfunction at urine cadmium levels exceeding 2 μg/24 hours (Buchet et al., 1990).

When there is severe tubular kidney damage, the normal reabsorption of cadmium bound to metallothionein decreases. As a result there is an increased excretion of cadmium in urine. Thus, paradoxically, when cadmium causes a kidney disease, the excretion of cadmium may increase, and the cadmium concentration in the kidneys gradually decrease. Unfortunately, the damage is not reversible, even if the cadmium concentration later decreases. Shortly after a very heavy exposure to cadmium, for example after unintentional exposure to cadmium fumes, the urinary excretion of cadmium may be very much increased temporarily, but without reflecting an increased body burden. The ability of the kidneys to bind cadmium will be exceeded for some time.

Thus results of biological monitoring of cadmium can be interpreted and evaluated only if the duration and approximate intensity of the exposure are known.

References: Buchet et al. (1990); Elinder (1991); Friberg et al. (1986); Nordberg & Nordberg (1988)

CHROMIUM

Occurrence

Chromium (Cr) occurs in several different oxidation states, the most common being di-, tri- and hexavalent. Hexavalent chromium is found in chromates. The concentration of chromium in the earth's crust is on average 125 mg/kg. Small amounts are found in fresh water and foodstuffs.

Exposure

Daily intake with food is about 60 μg. Chromium is used in chrome plating of metals and is one of the components of stainless steel. Welders of stainless steel may be exposed to 10–500 μg hexavalent chromium per m^3/air. Air concentrations of between 1 and 20 μg have been reported.

Metabolism

Trivalent chromium is essential to humans. Despite this, the uptake from the gastrointestinal tract is very low, i.e. 0.2–0.4% of a given dose. The uptake of hexavalent chromium is higher (about 2–6%).

In plasma and tissue cells, a reduction of hexavalent chromium to trivalent chromium takes place, the latter being less toxic.

Health effects

Hexavalent chromium is corrosive and sensitizing. Skin ulcers, perforation of the nasal septum and lung cancer may occur in workers exposed to hexavalent chromium compounds. Chronic bronchitis is common among welders of stainless steel, and hexavalent chromium has been suggested as a causative agent.

Exposure to trivalent chromium is probably less dangerous than exposure to hexavalent compounds. It is possible, however, that small amounts of trivalent chromium may be oxidized to hexavalent forms and become a health hazard.

Biological monitoring of chromium

Chromium is difficult to analyse, and there is substantial risk of contamination of samples. Small amounts of chromium may derive from needles used for collecting blood. The concentration of chromium in the plasma/serum of non-occupationally exposed people is about 0.1 μg/litre. Urinary concentrations vary between 0.1 and 0.5 μg/litre.

Occupational exposure to chromium increases the concentration of chromium in both blood and urine. There is a linear relationship between air concentrations and the excretion of chromium in urine among chromate workers and stainless steel welders. The mathematical relationship between chromium in air and in urine in these two groups differs, however. The urinary excretion is considerably higher in chromate workers than in

welders (Figure 15). The reason for this difference is not known, but may be caused by differences in particle size and bioavailability of the aerosols.

An excretion of more than 5 μg Cr/litre in urine has been associated with chromium ulcers in the noses of chromate workers. It has not been possible to relate increased chromium excretion in urine to any health effects among welders. As there is a relationship between chromium in air and chromium in urine, urine samples can be used to estimate exposure. As inhalation of hexavalent chromium is primarily a risk for the lung (in the form of irritation or cancer), the usefulness of biological monitoring of chromium in urine when making risk estimations is debatable.

References: IARC (1990); Lindberg & Vesterberg (1983); Sjögren et al. (1983); Welinder et al. (1989)

COBALT

Occurrence

Cobalt (Co) is a relatively rare metal. The concentration in soil is between 1 and 40 μg/kg.

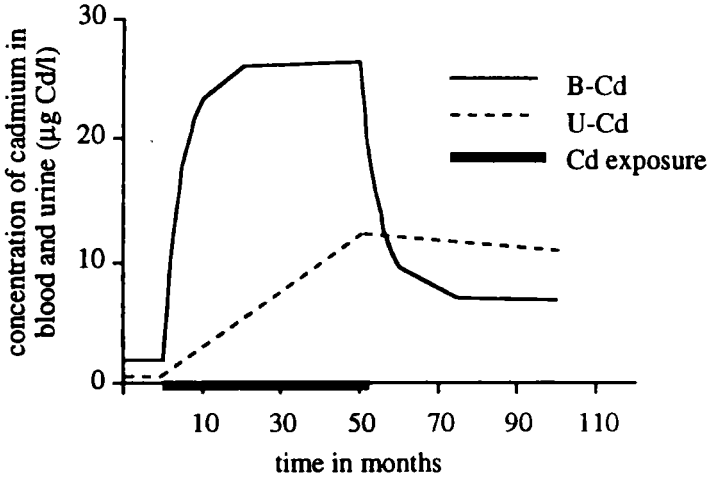
Exposure

The daily intake via food is about 5–45 μg Co/day. Occupational exposure to cobalt occurs during the production of hard metals from cobalt, tungsten and carbide, and sometimes in combination with other rare metals such as titanium and tantalum. Air concentrations of cobalt in the manufacturing of hard metal may vary between <0.01 mg/m^3 and >1 mg/m^3.

Metabolism

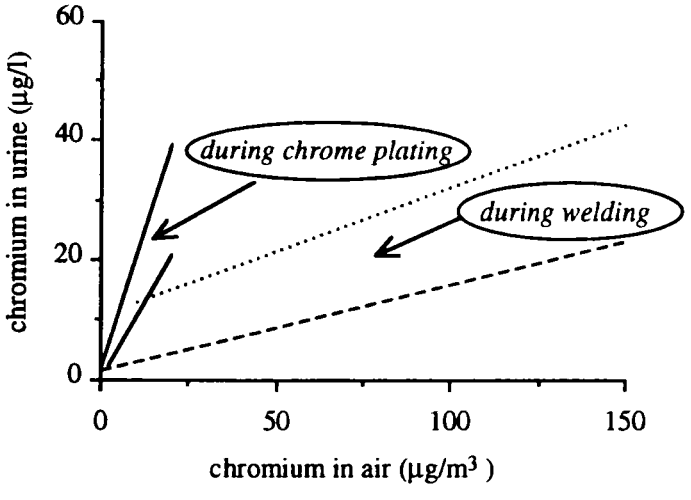
The absorption of cobalt from food is 30–40%. Cobalt is also taken up through inhalation, but it is not known to what extent. The major part of absorbed cobalt is eliminated rapidly in urine (Figure 16). Some data indicate that a small fraction of absorbed cobalt remains in the body for months. Cobalt is contained in the vitamin B_{12} molecule and is essential to the human body in this form.

Figure 14



Schematic presentation of blood and urine cadmium concentration before, during and after a period of relatively high exposure.

Figure 15



Relationship between air concentration and urinary excretion of chromium during chromate work and welding of stainless steel. The unbroken lines represent data from two studies of chromate workers. The two dotted lines are from studies of welders.

Health effects

Exposure to cobalt may cause both local and systemic effects. Allergic eczema is observed among those who work with the metal. Inhalation of cobalt during the manufacture and grinding of hard metal can cause adverse effects in the respiratory tract, including fibrosis of the lung (hard metal lung). Results from a recent epidemiological study in Sweden indicate that hard metal work increases the risk of lung cancer.

Cobalt may also have adverse effects on the heart muscle, as was observed in people who had consumed large quantities of beer, to which cobalt had been added to improve the quality of the foam. (Currently, cobalt is not used in the production of beer.) However, the evidence so far does not prove that occupational exposure to cobalt causes heart disease.

Biological monitoring of cobalt

The levels of cobalt in blood and urine among people who are not occupationally exposed to this metal are about 0.1–2 μg/litre. Occupational exposure increases the cobalt concentrations in both blood and urine, the increase being most pronounced in urine.

The excretion of cobalt primarily reflects the exposure during the period just before the sampling time. It has been shown, however, that there is a continuous increase in urinary levels of cobalt during the working week (Figures 9 and 16). By comparing cobalt concentrations in urine before and after the daily work-shifts, it is possible to obtain information on the intensity of the exposure. It is not known whether blood or urine concentrations of cobalt can be used for risk estimation.

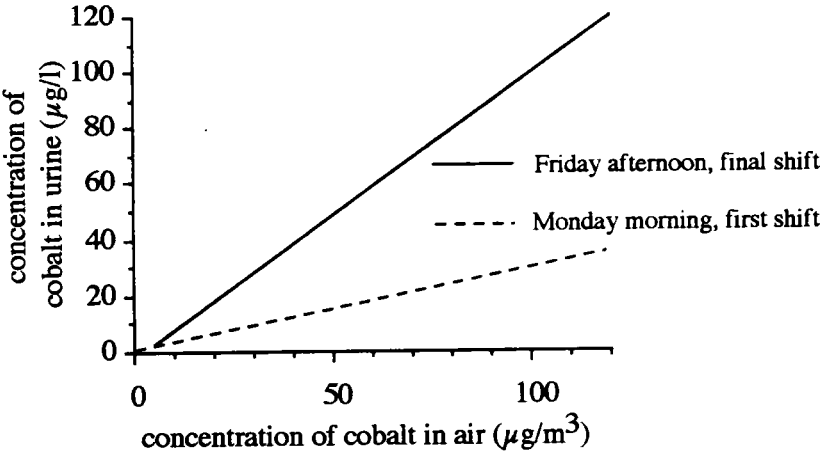
References: Alexandersson & Lidums (1979); Ferioli et al. (1987); Scansetti et al. (1985)

INORGANIC LEAD

Occurrence

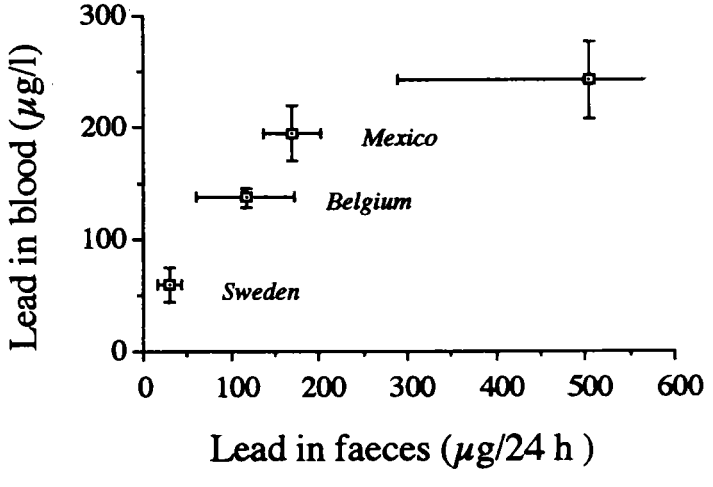
The environment is contaminated with lead, having been used by humans for more than a thousand years. For example, the addition of lead to gasoline, to increase the latter's octane content, has been a major source of contamination during the last decades. However, in terms of the general population, it is exposure through ingestion which is of most concern. This includes exposure through not only food but also as a result of contamination of china, cooking utensils and containers.

Figure 16



Relationships between air and urinary concentrations of cobalt at the beginning and end of a work period.

Figure 17



Daily intake of lead (μg/day) and blood lead concentrations (μg/litre) in four different populations. (Taken from Bruaux & Svartengren, 1985.)

Exposure

In Sweden, daily lead intake is about 35 μg, with large variations from day to day and also between individuals, depending on eating and drinking habits, as well as methods of food preparation. International comparisons have shown that there are large differences between countries in the daily intake of lead (Figure 17). The concentration of lead in wine is often high (10–200 μg/litre). Individuals whose wine consumption is high may have blood lead concentrations which are more than twice those of individuals whose wine consumption is low. Dust from smelters, highways and lead-containing paints comprises a major exposure source for children.

Occupational exposure occurs in lead mines, storage battery factories and glass works, and during the grinding, welding and cutting of materials painted with lead-containing paints.

Metabolism

The normal absorption of lead from the gastrointestinal tract is 5–10%. The degree of absorption probably increases in individuals with an increased calcium or iron demand. After inhalation of lead particles, about 20–50% of the lead is absorbed, depending on particle size. Absorbed lead is excreted slowly, mainly via urine. An accumulation takes place in the body, principally in the skeleton, which contains about 90% of the total amount of lead in the body.

The biological half-time for inorganic lead varies between different organs. Shortly after a heavy exposure the blood level will decrease, with a half-time of one or two months. The elimination of lead from bone tissue is a much slower process, with a half-time of 5–50 years. In the case of long-term exposure, with considerable accumulation of lead in the body, the blood lead concentration will remain high for many years after exposure has ceased, and the lead half-time will be several years.

Health effects

The highest concentrations of lead are found in the skeleton, but the first adverse effects of lead exposure are not observed here. Rather, it is bone marrow, and the central and peripheral nerve system, which are the critical areas. Decreased activity of the enzyme delta aminolevulinic acid dehydratase (ALA-D) is the earliest biochemical effect on the synthesis of haemoglobin. Additionally, the prevalence of an abnormal protoporphyrin (ZPP) in the red cells will increase. With increasing lead exposure, the production of haemoglobin and red blood cells becomes impaired. This can lead to anaemia.

Heavy exposure to lead may cause severe acute poisoning, a fact that has been known for several hundred years. Unconsciousness and cramps may occur. Other signs of acute lead poisoning include abdominal pains and paralysis. Polyneuropathy and anaemia were observed among heavily-exposed industrial workers in Britain during the 19th century and at the beginning of this century. Heavy exposure can also be observed today, particularly in developing countries and Eastern Europe.

Research during recent decades has shown that damage to the nerve system can result even from low-level exposure. Children are at particular risk. Several studies have shown a statistical relationship between lead exposure and decreased intellectual capacity. The signs and symptoms of brain effects are non-specific, but include mood change, and decreased concentration and learning capacity.

Biological monitoring of lead

Biological monitoring of lead continues to be of great value. The lead concentration in blood reflects the intensity of the exposure. However, the relationship between lead exposure through food and/or air and blood lead is not linear. If background exposure is high, an additional increase will not increase the blood lead levels to the same extent as would occur if background exposure was low. This is illustrated in Figure 17, which shows the relationships between daily intake of lead through food and blood lead levels in people in Belgium, Malta, Mexico, and Sweden.

When people are exposed to lead through many different exposure routes, for example, through food, cooking utensils, wine, and dust, or occupationally, it is important to obtain a measure of the integrated dose. Repeated studies of blood lead levels in adults and children in different countries have shown a decrease of more than one-third since the beginning of the 1980s. This is probably a result of improved control of foodstuffs (particularly canned food), and decreased contamination of the environment by motor exhaust following the successive lowering of lead in gasoline.

There is a close relationship between lead in blood and adverse health effects. Figure 3 shows the relationship between lead concentrations in blood and the prevalence of different health effects. Decreased activity of the enzyme ALA-D is seen once lead levels exceed 50–199 μg/litre, while the ZPP-concentration starts to increase at blood levels exceeding 200–250 μg/litre. Acute severe effects in the central nervous system are observed at blood lead levels above 1000 μg/litre. A decrease of the conductivity of the peripheral nerves may be observed at concentrations of about 450–550 μg/litre. The central nervous system of children is particularly susceptible to negative effects arising from lead exposure. Adverse effects have been clearly documented for blood lead levels of 300 μg/litre. Results from

some studies indicate that children and fetuses might be affected at blood levels of about 100 μg/litre.

It is also possible to carry out biological monitoring of lead in urine, bone and teeth.

The excretion of lead in urine increases linearly with the intensity of exposure. The lead levels in urine are influenced by the urinary volume. It is therefore necessary to collect all urine for a long time period, e.g. 48 hours, or to adjust the concentrations to the creatinine concentrations. Analyses of lead in urine does not yield any information which is additional to that provided by blood lead analyses, and is carried out infrequently.

The monitoring of lead in the skeleton gives information on the total amount of lead accumulated in the body. The normal concentration of lead in bone tissue is only a few μg/g dry weight, although concentrations of several hundred μg/g have been observed in heavily exposed individuals.

Lead in deciduous teeth is of great value when estimating the exposure which occurred during early childhood. The technique involved is complicated, however, and therefore used only for research purposes.

Reference: Skerfving (1988)

ORGANIC LEAD COMPOUNDS

Occurrence and exposure

Tetra ethyl lead is added to gasoline to increase its octane level. Thus occupational exposure may occur through handling leaded gasoline; for example when cleaning gasoline containers.

Metabolism

The organic lead compounds are lipid soluble and taken up by the lungs during inhalation. They may also be absorbed via the skin. Tetra ethyl lead is metabolized in the body—mainly in the liver—to tri alkyl lead. It is a very toxic lead compound and has a relatively long biological half-time of one or two months. After a certain period of time, tri alkyl lead is metabolized to inorganic lead and this is eliminated slowly over months, or years.

Health effects

Acute poisonings can cause convulsions and unconsciousness. Less severe signs of poisoning include general malaise, headache and vomiting.

Biological monitoring of organic lead compounds

Biological monitoring of organic lead compounds can help identify exposure. The most suitable medium is urine. Poisoning may occur if urine levels exceed 150 μg tetraethyl lead/litre.

It is not meaningful to measure the concentration of total lead in blood, as it is only increased after very high exposure to tetra ethyl lead.

Reference: Alessio et al. (1986)

MANGANESE

Occurrence and exposure

Manganese (Mn) is an essential metal. It is used in the production of steel and is a constituent of some alloys and batteries. Heavy exposure may occur in mines and during the production of metals. Manganese is also used in the chemical industry. Organic manganese compounds such as MMT have been used to increase the octane level in gasoline.

Metabolism

The absorption of manganese from food is only a few percent and dependent on the body's requirement of the metal. Most of the metal is excreted via the gastrointestinal tract. Only small amounts are eliminated in urine.

Health effects

Accumulation of manganese in the brain can result from long-term exposure via inhalation; the manganese will be eliminated from the brain very slowly. Inhalation of high concentrations of manganese may lead to chemical pneumonitis. Occupational exposure can give rise to neurological symptoms.

Biological monitoring of manganese

The blood concentration of manganese increases during exposure, but is increased for a very short time only. The urinary excretion is only a few μg Mn/litre and is not substantially influenced by air exposures. So far it has been very difficult to establish a mathematical relationship between air concentrations and urine and blood levels of manganese.

Following exposure to MMT, the excretion of manganese in urine increases linearly. It might be possible to use biological monitoring to quantify exposure.

It has not been possible to demonstrate relationships between levels of manganese in biological media and adverse effects.

References: Oberdörster & Cherian (1988); Valentin & Schiele (1983)

MERCURY

When evaluating exposure and the health hazards of mercury (Hg), as well as data from biological monitoring of mercury, it is necessary to differentiate between different groups of mercury compounds, i.e. metallic mercury, inorganic mercury compounds and organic compounds.

Occurrence and exposure

Metallic mercury is used in thermometers and electrolytic cells, for instance, and is a component of dental amalgam. The concentration of inorganic mercury in food is generally very low, and daily intake below 1 μg/day. The release of mercury vapour from amalgam fillings in the teeth contributes significantly to background exposure to mercury. The absorption of metallic mercury from the gastrointestinal tract is insignificant. Vapour is released from metallic mercury even at room temperature and is effectively absorbed through inhalation. High exposure to metallic mercury vapour currently occurs mainly within the chlorine alkali industry, where air concentrations range between 10 and 50 μg Hg/m^3. Some exposure may occur in dental surgeries.

Inorganic mercury compounds were formerly used in some drugs. Exposure may occur industrially, but this is rare.

Organic mercury compounds, mainly methylmercury, are prevalent in the environment. Inorganic mercury is partly transformed by microorganisms to organic alkyl mercury compounds, principally methylmercury. This

compound is found in lakes, particularly those with a low Ph, and accumulates in food chains. High concentrations of methylmercury (> 1 mg/kg) have been found in fish, particularly predatory fish and lake fish. The main exposure to methylmercury is via food and almost exclusively through fish. In Iraq, large-scale poisoning occurred after consumption of mercury-treated grain.

Metabolism and health effects

Metallic mercury is readily absorbed (about 80%) after inhalation of mercury vapour, but not (< 1%) after ingestion. When metallic mercury is taken up by the body, it exists initially as soluble mercury vapour in the blood. This form of mercury is lipid soluble and is distributed to all organs, including the brain, and the fetus. However, the mercury vapour is oxidized to divalent mercury within only a few minutes. It is then unable to pass either the blood–brain or the blood–placenta barrier. Excretion takes place via urine and faeces.

The biological half-time of mercury is different for different organs. For the body as a whole, the half-time has been estimated to be a few months after inhalation of mercury vapour, while it is only a few days or weeks in blood. A fraction of the absorbed mercury will remain in the body for a longer time. Some of the mercury that reaches the brain will thus be eliminated slowly, with a half-time of years.

Metallic mercury poisoning is characterized by tremor and nervous symptoms such as anxiety, distress and sleeplessness. At lower exposure levels the symptoms are less pronounced and often difficult to pinpoint. Exposure to metallic mercury may cause immunotoxic effects (see below).

Up to 10% of absorbed mercury compounds (mainly divalent) is absorbed via the gastrointestinal tract and excreted via the kidneys. Inorganic mercury passes the blood–brain barrier to a limited extent only and there have been few reports of brain damage. However, inorganic compounds can result in damage to the critical organ, in this case, the kidneys. Kidney damage is also seen as a result of exposure to metallic mercury vapour. The kidney disease caused by inorganic mercury is nephrosis. It is characterized by greatly increased excretion of protein in urine.

Animal experiments have shown that the immune system is affected by exposure to inorganic and metallic mercury. Effects are seen in the kidneys. It is probable that the same mechanism operates in the development of kidney damage in humans.

More than 90% of absorbed methylmercury is absorbed from the gastrointestinal tract. The absorbed methylmercury is distributed evenly in

the body, and accumulates in the brain. Methylmercury also passes the placental barrier. Therefore, if the mother is exposed, so too is the fetus. About 1% of the methylmercury in the body is excreted daily, giving a biological half-time of around 70 days. Most of it is excreted via faeces; the amount eliminated via the kidneys is insignificant.

There have been several incidents when people have consumed food containing methylmercury over long periods and in high concentrations. Methylmercury has then accumulated in the body and damage ensued. The earliest signs of methylmercury poisoning are non-specific symptoms, including paraesthesia and malaise. Subsequently, constriction of the visual field, deafness, and coordination problems may develop. The fetus is particularly vulnerable and may be poisoned during pregnancy even if the mother herself shows no signs of poisoning.

Biological monitoring of mercury

Biological monitoring of mercury is complicated by the fact that both organic and inorganic forms of mercury occur in the body and can be identified in blood and urine. Mercury concentration in individuals who are not occupationally exposed, and whose fish intake is moderate or low, varies between 0.1 and 7 μg/litre. The lower values are found in urine and the higher in blood.

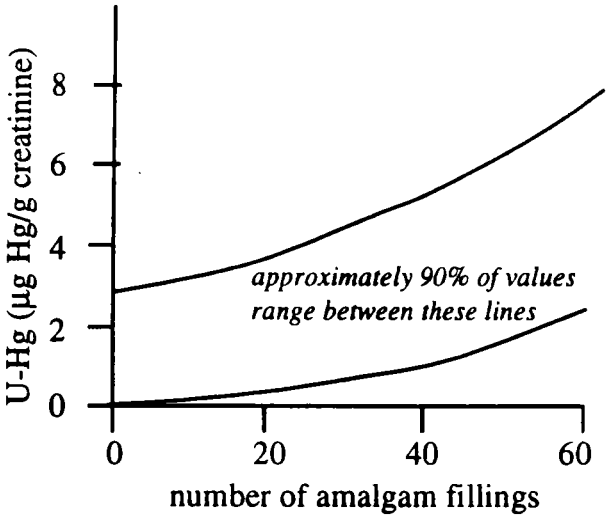
...in urine

The concentration of mercury in urine relates primarily to an exposure to metallic mercury vapour or inorganic mercury compounds. There is a relationship between the number of amalgam fillings and the excretion of mercury in urine (Figure 18). However, for people who are not occupationally exposed, the urinary levels are seldom higher than 10 μg/litre.

In the case of occupational exposure, there is a linear relationship between air and urine concentrations of mercury. Urine concentrations (μg/litre) correspond to air concentrations (μg Hg/m^3) multiplied by 1–2.

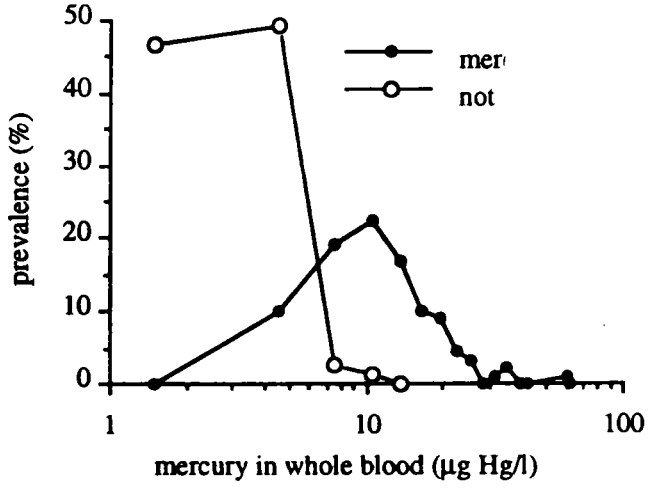
If mercury concentrations in urine exceed 100 μg/g creatinine, the risk of adverse effects in the nervous system becomes significant. Tremor, nervousness, irritation (erethismus mercurialis) and kidney damage with proteinuria may be observed. At exposure levels corresponding to between 50 and 100 μg Hg/g creatinine in urine, these symptoms are less pronounced. Some studies indicate that early signs of adverse effects relating to the nervous system or kidneys can be observed even at urinary levels of between 25 and 35 μg Hg/g creatinine.

Figure 18



Urinary exposure to mercury in persons not occupationally exposed, but with different numbers of amalgam surfaces. (Taken from Langworth et al., 1991.)

Figure 19 SEE ERRATA



Frequency distribution of mercury concentration in whole blood in Swedish workers in the chlorine industry and non-exposed controls (Langworth et al., 1991).

During recent years there have been indications that inorganic mercury can affect the immune system. Animal studies have shown that mercury is immunotoxic. At present, it is not known whether a level exists below which such effects do not occur.

...in blood

Monitoring of mercury in the blood is usually carried out to identify exposure to methylmercury. The concentration of total mercury in blood among people who are not occupationally exposed is influenced by their consumption of fish. Heavy consumers of lake fish have higher blood mercury levels in blood than those who eat fish only rarely. It was recently shown in a Swedish study that people who never eat fish have blood levels of around 2 μg Hg/litre, while the mercury concentrations of those who eat fish three times a week are close to 10 μg Hg/litre (Figure 19).

During long-term constant exposure (several months) to methylmercury in food, there is a linear relationship between daily intake of methylmercury and the concentration of mercury in blood. The mercury concentration in blood (μg/litre) corresponds to the daily intake of methylmercury (μg/day) multiplied by 0.5–1. When exposure is continuous, the blood mercury concentration is proportional to the concentration in the brain, the critical organ for methylmercury. The ratio between the concentration of mercury in the brain and blood is 5–10:1, i.e. the blood concentration of mercury is 5–10 times lower than the brain concentration.

After long-term exposure to methylmercury, at blood levels of about 200 μg Hg/litre, the risk of developing poisoning is significant (5%) for adults.

...in hair

Analyses of methylmercury in hair can be used to make a retrospective estimation of maternal exposure during pregnancy. It has been found that children born to mothers whose hair mercury concentrations ranged between 70 and 640 μg Hg/g, show a considerably higher prevalence of developmental changes than controls.

Studies from New Zealand indicate that adverse effects in children can be correlated with maternal hair levels as low as 10–20 μg/g, corresponding to a blood level of about 40–80 μg Hg/litre. Figure 4 summarizes results from a number of studies; the prevalence of symptoms is related to the concentration of methylmercury in hair.

References: WHO (1990; 1991)

NICKEL

Occurrence

Nickel (Ni) is probably not essential for human beings. But it is used in the production of steel, coins, nickel-cadmium batteries and electronic components.

Exposure

The nickel concentration of water is usually below 5 μg/litre, and below 1 mg/kg in most foodstuffs. Higher concentrations (2–10 mg/kg) are found in some types of nuts and beans. Daily intake is estimated to be about 250 μg/day.

Metabolism

Absorption of nickel from the gastrointestinal tract is about 3%. Absorbed nickel appears to be eliminated relatively quickly, mainly via urine. The biological half-time has been estimated to be between 1 and 2 days. Moderately increased concentrations of nickel have been found in the urine and blood of workers exposed to nickel, even after exposure has long since ceased. Thus a small fraction of absorbed nickel will accumulate in the body and be eliminated only slowly, i.e. with a long biological half-time.

Health effects

Nickel commonly causes allergic effects, particularly contact dermatitis. Occupational exposure may affect the respiratory tract. Cancer of the nose, sinus and respiratory tract has been reported to occur occupationally. Nickel compounds with a low solubility, in particular, cause cancer, but more soluble compounds are also considered to be carcinogenic.

Biological monitoring of nickel

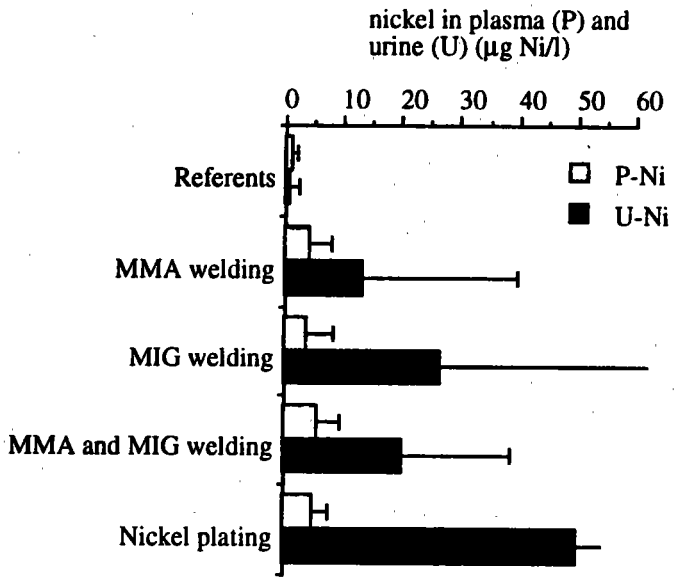
It is difficult to obtain biological samples which are free of nickel contamination. The normal concentration of nickel in serum is probably around 0.1–1.1 μg/litre, while the urinary levels are somewhat higher at 0.5–6 μg/litre. Analysis of nickel in faeces has revealed substantial peroral exposure in workplaces where nickel is used.

Urine and serum/plasma from nickel-exposed workers contains higher concentrations of nickel than that of non-exposed workers (Figure 20). There is substantial individual variation, however, and the correlation between nickel in air on the one hand, and blood and urine on the other, has been found to be weak. Very high nickel concentrations in plasma and urine (>100 and >1000 μg Ni/litre, respectively) have been observed in acute nickel poisonings.

It has not been possible to relate concentrations of nickel in biological samples to specific health risks. The critical effect of nickel is lung cancer.

References: Angerer and Lehnert (1990); Grandjean et al. (1988); Sunderman (1988); Tola et al. (1979)

Figure 20



Concentrations of nickel in urine and plasma during different types of exposure. T indicates the standard deviation. Air concentrations of nickel during MMA and MIG welding ranged between 70 and 100 μg/m³. During galvanization the air concentrations were between 30 and 160 μg/m³.

SELENIUM

Occurrence and exposure

Selenium is an essential trace element. The concentration of selenium in different foodstuffs varies considerably (0.01–1.0 mg/kg), depending on the origin of the food. Grain grown on soil rich in selenium contains high concentrations. In most countries the daily intake of selenium is about 100 μg. There are countries where intake is much lower (including Finland, New Zealand and Sweden (<50–70 μg) and certain areas of China (<20 μg)) and also countries where it is much higher (including Scotland, Venezuela, and certain areas of China (200–700 μg)).

Metabolism

Selenium is readily absorbed (40–80%) and is distributed to different tissues. Any excess is excreted rapidly via the urine, partly as methylated selenium compounds. The biological half-time after a high selenium exposure is one or two days. Small amounts of selenium may remain in the body for months.

Health effects

Selenium deficiency is common in animals, but has also been reported among humans. If daily intake falls below 20–30 μg there is a risk of selenium deficiency. Symptoms include lesions in the heart and other striated muscles. If, on the other hand, daily intake is continuously high (above 1000 μg), there is a risk of selenium poisoning. Symptoms include gastrointestinal irritation, nail and skin lesions, hair loss, and eventually, in severe cases, nerve damage. If very high acute exposure occurs, acute liver damage may ensue.

Biological monitoring of selenium

Measurements of selenium in serum and blood are usually taken in order to identify a possible deficiency, rather than to demonstrate toxic effects. For populations receiving sufficient concentrations of selenium in food, the selenium level in serum is usually between 60 and 120 μg/litre. The concentration in red cells is somewhat higher than in plasma. After an above-normal exposure, the selenium concentration increases more in the red cells than in plasma.

The excretion of selenium varies with the daily intake of the metal, and is between 10 and 600 μg/day depending on the type of diet.

Monitoring of selenium in blood and urine provides information on selenium status. In cases of selenium deficiency, the selenium concentration in blood and serum is low (< 40 μg/litre). If exposure to selenium is high, then relatively high concentrations are found in the red cells. Under such circumstances, the urinary excretion is also high. If levels in whole blood exceed approximately 600 μg/litre, there is a risk of toxicity.

Monitoring of selenium in hair may be of value to identify deficiency or poisoning. Selenium deficiency is likely if the concentration in hair is below 0.1 μg/g. There is reason to suspect selenium poisoning if the selenium concentration in hair exceeds 5 μg/g.

References: Magos & Berg (1988); Schaller & Schiele (1989)

TIN

Occurrence, exposure and health effects

The concentration of tin in soil generally ranges from 2 to 200 mg/kg. In fresh water and in most foodstuffs the concentration is low and difficult to measure.

The normal level of tin intake is still uncertain. It is well known, however, that consumption of canned foods may increase the daily intake of tin considerably. Occupational exposure occurs during, for example, tin plating and the production of alloys and solders.

Intake of large amounts of tin, e.g. 100 mg, may cause gastrointestinal symptoms. Long-term inhalation of high concentrations may cause stannosis, a particular type of pneumoconiosis.

Organic tin compounds also exist and are used as stabilizers in plastics and in some pesticides. Some organic tin compounds are very toxic and can cause serious poisonings, affecting the central nervous system. Convulsions and hallucinations may occur.

Biological monitoring of tin

The occurrence of tin in biological media is not known. The extent to which biological monitoring can be used to evaluate exposure or health hazards is uncertain.

Reference: Alessio & Dell'Orto (1988)

VANADIUM

Occurrence

Vanadium occurs in soil in concentrations of between 5 and 140 mg/kg. It is found in fossil fuels and is therefore a component of air-pollutants, particularly in urban areas. The metal is used in the manufacturing of steel.

Exposure

Concentrations of vanadium in water and food are low. Daily intake is probably below 100 μg.

Health effects

Occupational exposure may cause respiratory irritation, nose bleeding, or shortness of breath. Acute asthmatic symptoms have been reported.

Biological monitoring of vanadium

Biological monitoring of vanadium (V) has been carried out to a very limited extent only. The normal urinary concentration is below 2 μg/g creatinine. Urinary excretion increases during occupational exposure. Workers who have been exposed for long periods have been found to have urine levels of 60–70 μg V/g creatinine. It has so far proved very difficult to measure vanadium in blood.

References: Alessio et al. (1988); Kiviluoto et al. (1981); Schaller & Triebig (1987)

6. Conclusions: Possibilities and Problems

For some metals it is possible to estimate the absorbed dose by monitoring indicator media such as blood or urine (biological monitoring), and thus to evaluate exposure and/or risks. Biological monitoring is a complement to the routine surveillance of metals in environmental media such as air and food.

Biological monitoring of metals is valuable in several respects. It measures the total exposure from different media and takes into consideration inter- and intra-individual variations in uptake due to differences in metabolism and physical workload. It can therefore be used to identify individuals or groups of individuals subject to high exposure and risks. Furthermore, since many metals are retained in the body for long periods, biological monitoring can provide information concerning not only recent exposure, but also exposure that occurred a considerable time ago.

Health monitoring is also carried out using body fluids as indicator media. The purpose of such monitoring is to identify early biological effects and should not be confused with biological monitoring of the metals themselves. Health monitoring does not prevent biological effects but is often necessary for documenting that adverse effects have not occurred. In effect it can serve as a control to ensure that exposure is sufficiently low.

One of the basic prerequisites for meaningful biological monitoring is knowledge of the metabolism of the metal and the relations between exposure, dose, effects and responses. Only when concentrations can be evaluated against such information is a quantitative evaluation meaningful. Uncritical multi-element analysis of trace elements should therefore not be carried out when such information is lacking.

During biological monitoring great care must be taken to ensure that neither contamination nor loss of metal occurs during sampling, or storage of samples, and that the analyses are carried out using accurate methodology and adequate quality control procedures. There have been many instances of serious error in these respects. It is essential that parts of the report are devoted to analysis and quality control.

The quality of the analysis is naturally of central importance. Most laboratories are prepared to provide their customers with information about quality control methodology and results of quality control analyses. It is recommended that customers make arrangements with the laboratory about such information at an early stage.

The potential for biological monitoring is summarized in Table 2.

Table 2. Tabular presentation of the value and possibilities of the biological monitoring of metals

Metal or metal compound	Media	Exposure assessment[3]	Health effects[4]
aluminium[1]	B	+ +	+ +
aluminium[2]	U	+ +	?
antimony	B	+	?
arsenic (inorg)	U	+ +	+ +
cadmium	B,U	+ + +	+ + +
chromium	U	+ +	+
cobalt	U	+ +	?
lead (inorg)	B	+ + +	+ + +
lead (org)	U	+	+ +
manganese (inorg)	B,U	--	?
manganese (org)	U	+ +	?
methylmercury	B,H	+ + +	+ + +
metallic mercury	B,U	+ + +	+ + +
nickel	B,U	+ +	?
selenium	B,U	+ +	+ +
tin	B,U	?	?
vanadium	B,U	+	?

[1] patients with kidney disease
[2] aluminium welders
[3] B = blood, plasma or serum
U = urine
H = hair
[4] - no relationship
+ some information available and/or weak relationship
+ + relationship exists
+ + + a well-established relationship; used on a routine basis
? relationship unknown

Biological monitoring is used widely to evaluate both exposure and risks, particularly for lead, cadmium and mercury. For several other metals biological monitoring may also be a valuable complement to the more conventional monitoring of environmental media.

For some metals, particularly mercury and arsenic, it is important to differentiate between different metal species. An indicator medium that is suitable for evaluation of exposure and risks for one metal compound, may not be useful for another metal compound. Sometimes it is necessary to analyse both the total concentration of the metal and the concentration of different metal species.

The review in the present paper is short and somewhat simplified. Nevertheless, it can serve as a basis for the interpretation of analytical results under different exposure conditions, and as an introduction to the possibilities and pitfalls of biological monitoring. More information on this subject can be found in the extensive international documentation listed in *Biological Monitoring of Toxic Metals* (Clarkson et al., 1988).

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