EUROPEAN COMMISSION

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Health and safety

Report

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Preface to the first volume

The evaluation of the exposure of workers to dangerous agents is one of the measures ensuring better health protection. This evaluation is called monitoring.

Two approaches are available for the monitoring:
(i) ambient monitoring already in use for many years and
(ii) biological monitoring of more recent development.

The need for clear definitions and for establishing the respective roles of these two types of monitoring has become necessary recently. In 1980 in Luxembourg at an international seminar organized jointly by the CEC and the US authorities (Occupational Safety and Health Administration and the National Institute for Occupational Safety and Health) on the assessment of toxic agents at the workplace, the following definitions were agreed:

(i) ambient monitoring is the measurement and assessment of agents at the workplace and evaluates ambient exposure and health risk compared to an appropriate reference;
(ii) biological monitoring is the measurement and assessment of workplace agents or their metabolites either in tissues, secreta, excreta, expired air or any combination of these to evaluate exposure and health risk compared to an appropriate reference.

In addition, the term 'health surveilance' was also defined as the periodic medico-physiological examinations of exposed workers with the objective of protecting health and preventing occupation-related disease. The detection of established disease is outside the scope of this definition.

The definitions of biological monitoring and health surveillance separate components of a continuum which can range from the measurements of agents in the body through measurements of metabolites, to signs of early disease. A problem left unresolved concerns the precise place within these definitions of certain biochemical tests such as zinc protoporphyrin (ZPP), delta aminolaevulinic acid dehydrase (ALA-D), delta aminolaevulinic acid (ALA) in the blood and urine, etc., which are, in fact, indicators of metabolic effects which have occurred as a consequence of exposure.

Ambient monitoring is carried out for different reasons, for example:

(a) determining ambient concentrations in relation to an established legal standard or consensus guideline;
(b) determining the relationship, if any, between the concentrations of agents at the workplace and the health of the workers;
(c) ensuring the effectiveness of control measures;
(d) evaluating the need for controls in the vicinity of specific emission sources;
(e) indicating trends in relation to an improvement or determination at the workplace;
(f) providing an historical record.

Biological monitoring measures or evaluates exposure from all routes. It sometimes allows a better evaluation of health risk than ambient monitoring especially in cases where exposure through different routes has to be considered. Biological monitoring takes into account individual variability, the impact of factors such as personal activity, biological characteristics and life style of the individual.

The two types of monitoring are complementary in increasing the protection of workers' health. If both are carried out simultaneously, information should be produced on the relationships existing between external exposure and concentration of the substance in biological samples, and between this concentration and early effects.

Detailed knowledge of the metabolism of the toxic agent in the human organism and of the alterations that occur in critical organ is essential in selecting the parameter to be used as indicator.

Unfortunately, however, such knowledge is usually insufficient and thus limitations exist in most biological monitoring programmes.

The conditions necessary for successful biological monitoring are:

(i) existence of indicators,
(ii) existence of analytical methods that will guarantee technical reliability in the use of these indicators,
(iii) possibility of measuring the indicators on readily accessible biological specimens,
(iv) existence and knowledge of dose-effect and dose-response relationships.

In carrying out a biological monitoring programme, it is indispensable to know exactly what the characteristics and behaviour of the indicators under study are in relation to length of exposure, time elapsed since beginning and end of exposure, and all physiological and pathological factors other than exposure that could give a false interpretation of the results obtained.

Conditions for biological monitoring application include adoption of analytical methods yielding values comparable throughout the different laboratories.

This long-adopted approach has already permitted the CEC to standardize in 1972 a method for erythrocyte ALAD determination and develop programmes for interlaboratory comparisons for lead and cadmium determination in biological media.

The Council of Ministers of the European Communities, in adopting in 1978 the First Action Programme on Safety and Health at Work proposed by the Commission, stressed the need to increase protection against dangerous substances; it emphasized the need to promote new monitoring and measuring methods for the assessment of individual exposure, in particular through the application of sensitive biological indicators.

In August 1982 the Council adopted a directive on the protection of workers exposed to lead. The monitoring of blood lead levels as well as the determination of ALAU, ALAD and ZPP are among the tools to be used for monitoring worker exposure to lead. A comparison of the results with action levels and limit values allows appropriate action to be taken.

Considerable data concerning the biological monitoring of a number of industrial chemicals have been published in international literature.

Nevertheless, the difference in approches used in the research, the variety of analytical methods and the frequent discordances in the results, usually make it difficult to formulate a conclusive synthesis permitting the transfer of literature data into practice.

The aim of this series dedicated to the human biological monitoring of industrial chemicals in occupational health is based on the considerable experience acquired by the authors in the specific topics.

For the draft of the monographs, the following outline, suggested by R. L. Zielhuis and R. Lauwerys, has been used:

(i) a review of metabolism and/or mechanism of action;
(ii) potentially useful biological parameters for evaluation of exposure and/or body burden and/or early reversible effects:
(iii) a critical evaluation of each parameter:
    predictive validity in regard to exposure;
    quantitative relationship between levels of external exposure and internal exposure, and between exposure and effects;
    limitations of the test;
(iv) a proposal for one or several tests for biological monitoring.

Because of the considerable gaps in scientific knowledge it has not been possible to follow this outline strictly in every single one of the monographs. It is hoped that future research will fill these gaps.

It must be recognized that the biological monitoring approach for other toxic agents must still be developed and that considerable research is still necessary.

The Council in the abovementioned action programme and in the directives recently adopted in this field stressed the need to provide adequate information at all levels. It is considered that these monographs will be of benefit to the occupational health physicians, the industrial hygienists, the employers and the trade-union representatives, by giving the scientific rationale on which a number of biological monitoring programmes are based.

The Editors
1983

Preface to the second volume

Last year we published a series of monographs in one volume under the title 'Human biological monitoring of industrial chemicals series' in which benzene, cadmium chlorinated hydrocarbon solvents, lead, manganese, titanium and toluene were discussed.

When preparing these documents each author was asked to pay particular attention to the problem of the quantative relationships between the levels of external and internal exposure and between exposure and effects.

In a number of cases information on the levels of biological indicators which are indicative of current exposure without short-term detectable health effects is available.

However we were already confronted with the impossibility of determining at present if the levels for biological indicators without short-term detectable health effects can also be considered as adequate with respect to longer-term effects.

In preparing the present series of monographs it became apparent that for a number of biological indicators corresponding to biological tests, it is not yet possible to establish if these are indicative of early reversible effects and would thus qualify for the term 'biological monitoring' as defined in the preface of this first volume. For many substances, extensively used in industry, biological indicators are being developed but still require extensive assessment before possible routine application.

As the object of these monographs is to provide up-to-date scientific information, not only for the chemical substances for which biological indicators could be considered routine, but also for the many more substances for which biological indicators are at the early stage of development, it was considered advisable to change the title to the series to 'Biological indicators for the assessment of human exposure to industrial chemicals'.

We hope that this new title will avoid giving the reader the impression that for the substances presented in this volume and the subsequent ones, biological indicators can be already routinely applied.

The Editors
1984

Preface to the third volume

Following the established frequency, we are happy to present the third volume in the series of monographs on 'Biological indicators for the assessment of human exposure to industrial chemicals', which is addressed to occupational health physicians, industrial hygienists and, in general, to all who are concerned with prevention of occupational disease in the workplace.

The original title of the first volume of the series 'Human biological monitoring of industrial chemicals series' was changed in the second volume and this change is now further justified by the four monographs making up the third volume: alkyl lead compounds, dimethylformamide, mercury and organophosphorus pesticides.

As in the previous volumes, the scope of the publication has not been limited to the most widely known and used toxic industrial agents. It was felt that consideration should also be given to other substances, where recent scientific advances have suggested the need to verify how far assessment of exposure using biological indicators is reliable in real industrial situations. One of the aims of this series is, in fact, to stimulate further research, especially applied research, that would have the task of validating, on large groups of workers, preliminary scientific observations that are usually obtained from studies on relatively small groups of subjects and often in controlled experimental exposure situations.

Eighteen monographs have now appeared in this series published by the Commission of the European Communities. The previous two volumes covered 14 monographs on acrylonitrile, aluminium, benzene, cadmium, chlorinated hydrocarbon solvents, chromium, copper, lead, manganese, styrene, titanium, toluene, xylene and zinc.

Highly competent scientists from the following European scientific research institutes have contributed in preparing the monographs: Cattedra di Medicina del Lavoro dell'Università di Parma (Italy), Clinica del Lavoro L. Devoto dell'Università di Milano (Italy), Coronel Laboratorium, Universiteit van Amsterdam (the Netherlands), Institut für Arbeits- und Sozialmedizin der Universität Erlangen-Nürnberg (the Federal Republic of Germany), Unité de toxicologie industrielle et médicale, Université de Louvain, Bruxelles (Belgium).

It is planned in the future to extend cooperation to other scientific institutes and thus involve a wider number of scientists and experts.

The fourth volume, which is already under way, will include the following monographs: 'Aldrin, dieldrin and endrin' by N. J. van Sittert, Shell internationale Petroleum (the Netherlands); 'Non-substituted aliphatic hydrocarbons' by K. N. Cohz, Danish National Institute of Occupational Health, Hellerup (Denmark); 'Arsenic' by V. Foà, Clinica del Lavorno, University of Milan, (Italy); 'Vanadium' by K. H. Schaller, Institut für Arbeits- und Sozialmedizin, University of Erlangen-Nürnberg (Federal Republic of Germany).

The Editors
1986

Preface to the fourth volume

The fourth volume of the series of monographs on 'Biological indicators for the assessment of human exposure to industrial chemicals' of the Commission of the European Communities includes monographs on arsenic, aldrin and dieldrin, endrin, cobalt and vanadium. For the first time some chemical substances widely used in agriculture are also examined; for these substances, in addition to the occupational exposure, particular consideration has to be given to exposure of family members and the general population consuming agricultural products treated with pesticides.

It is evident from these documents that the information on biological indicators resulting from both occupational data relative to users and manufacturers, and from non-occupational data relative to consumers, contributes to the interpretation of the biological tests used to evaluate the exposure and/or the early effects. Occupational and environmental exposure to chemicals represent two situations, with uncertain limits, that tend to get nearer and nearer, and require a common study methodology.

A volume which will include the following monographs: 'Nickel', by P. Grandjean (Institute of Community Health, Odense University, Denmark); 'Aromatic hydrocarbons, nitro and amino compounds', by R. Lauwerys (Department of Occupational Medicine and Hygiene, Catholic University of Louvain, Brussels, Belgium); 'Carbamate pesticides', by M. Maroni (Institute of Occupational Health, Clinica del Lavoro L. Devoto, University of Milano, Italy) is under preparation and should be published in 1988.

The Editors
1987

Preface to the fifth volume

With the fifth volume of the series of monographs published by the Commission of the European Communities on 'Biological indicators for the assessment of human exposure to industrial chemicals', 27 toxic substances or groups of substances widely used in industry and agriculture have been covered.

This volume contains monographs on carbamate pesticides, nickel, aromatic amines and aromatic nitro-compounds, thus giving consideration to chemical compounds that are widely used in agriculture. Carbamate pesticides involve risks not only in the case of occupational exposure but also in the case of intake via the diet in the general population. With the inclusion of aromatic amines and aromatic nitro-compounds, for the first time in this series biological indicators for the assessment of the absorption and early effects of mutagenic and potentially carcinogenic compounds are considered, indicators which could then be used to identify groups at risk of exposure to genotoxic substances. The monograph on nickel examines the problems involved with the exposure to this metal which can frequently cause immunotoxic effects both in the general population and in occupationally exposed subjects and considers the excess incidence of carcinogenic effects in subgroups of refinery workers exposed to certain nickel compounds.

In view of the many requests received, the previous four volumes have been reprinted.

The sixth volume is under preparation and will be published in 1989. It will include the following monographs: 'Carbon monoxide' by P. Grandjean (Institute of Community Health, Odense University); 'Ethylbenzene and cumene' by R. Lauwerys (Department of Occupational Medicine and Hygiene, Catholic University of Louvain); 'Beryllium' by P. Apostoli (Institute of Occupational Health, University of Brescia, Italy); 'Anaesthetic gases' by E. Capodaglio, Institute of Occupational Health, University of Pavia); 'Selenium' by K. H. Schaller (Institute of Occupational and Social Medicine of the University of Erlangen-Nurnberg, (Federal Republic of Germany).

The Editors
1988

Preface to the sixth volume

The sixth volume of this series of monographs of the Commission of the European Communities on 'Biological indicators for the assessment of human exposure to industrial chemicals' includes documents regarding the following substances: beryllium, carbon monoxide, ethylbenzene, methylstyrene, isopropylbenzene, inhalation anaesthetics and Selenium.

Ethylbenzene, methylstyrene and isopropylbenzene conclude the discussion on the principal aromatic hydrocarbons which commenced in 1983 with benzene and toluene in the first volume followed by styrene and xylene in 1984.

In this volume, carbon monoxide is included, a pollutant produced in workplaces by incomplete combustion; this gas can also be present in the atmosphere in large cities and thus largely involves the general population that may also be exposed because of tobacco combustion.

The documents on beryllium and selenium indicate that it is necessary to gain a further insight into the metabolism and early effects of these metals in order to understand the significance of the biological indicators.

The document on inhalational anaesthetics faces the problems concerning the monitoring of workers in operating theatres and for which reliable biological indicators are finally available, in particular the monitoring of nitrous oxide which is the most widely used anaesthetic gas.

With this volume 27 monographs have already been published in this series covering 15 metals, 17 solvents, seven other chemical substances and three groups of pesticides.

The Editors
1989

Preface to the seventh volume

With the publication of this volume, the series of monographs of the Commission of the European Communities on 'Biological indicators for the assessment of human exposure to industrial chemicals' has been enriched by the addition of six documents regarding antimony, barium, tin, thallium, hexane and methyl ethyl ketone.

The number of monographs published since 1983 has thus risen to 33 with 19 metals, 19 solvents, seven other chemical substances and three groups of pesticides having been considered.

Since the first volume was issued, great strides have been made in the field of prevention of occupational diseases, with exposure to the most widely used and most harmful industrial toxic agents steadily decreasing in the workplace. The widespread use of biological indicators in the field of prevention has contributed to this favourable course of events.

When the publication of these documents started such rapid improvement in the workplace situation could not be expected.

In this light it is necessary to carefully examine the current validity of some of the indicators discussed in the early monographs and introduce new indicators when such are available.

The Editors
1993

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Antimony

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Biological indicators for the assessment of human exposure to industrial chemicals

Antimony

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Summary

Antimony (Sb) is a non-essential semi-metal. Sb is mainly used in alloys with other metals to increase their strength, hardness and resistance to chemical corrosion. Sb is employed in various industrial settings and Sb exposure has been studied in Sb smelter and ore-processing plants, in the glass industry, in battery plants, bronze foundries and abrasives plants.

Few data are available on human toxicokinetics; the main route of Sb absorption in occupational environments is through the lungs and the metal can be retained in the lungs for long periods (up to 20 years). Urinary elimination occurs in two phases, a rapid and a slower one.

Chronic occupational exposure to Sb may result in various health effects, such as irritation of the respiratory and gastrointestinal tract, ECG abnormalities, skin lesions ('antimony spots'); a particular form of pneumoconiosis called antimoniosis has also been described. The data on the carcinogenic properties of Sb are inconclusive.

In workers exposed to antimony, urinary Sb (SbU) as well as blood Sb (SbB) levels may be higher than those of non-exposed subjects, and, only for certain Sb compounds for mean exposures ranging from 100 to 1 000 $\mu g/m^3$, a correlation has been demonstrated between the atmospheric Sb concentration and SbU. However, the overall available data do not enable us to consider SbB and SbU as reliable indicators for the biological monitoring of workers, especially for low exposures, both for individuals and groups of subjects. No indicator of effect is so far available.

Introduction

Chemical and physical properties

Antimony (chemical symbol Sb, from the latin Stibium) is a non-essential semi-metal known since approximately 4000 BC. It has a crystalline structure and belongs to the V B subgroup of the periodic table. Arsenic belongs to the same subgroup and has similar chemical and physical properties.

Sb is a silver white, brittle, hard and easily pulverized element. It exists in the trivalent or pentavalent oxidation state, in both inorganic and organic compounds. Pentavalent Sb has a tendency to convert into the trivalent state in acidic media and acts, therefore, as an oxidizing agent. Sb is stable at room temperature but, when heated, it burns giving off dense white fumes of Sb oxide (Sb_2O_3) with a garlic-like smell.

Sb is insoluble in water and organic solvents and soluble in aqua regia. Small quantities of Sb in other metals increase their mechanical strength, hardness and resistance to corrosion. Indeed, it readily forms alloys with arsenic, tin, copper, iron, bismuth, zinc and lead (Gudzovskij, 1983; Weast, 1985; Winship, 1987).

Some data concerning the physicochemical properties of Sb are listed in Table 1.

It must, however, be mentioned that the Sb properties may vary in the different metal compounds.

Production

The amount of Sb in the earth's crust ranges from 0.1 to 10 mg/kg dry weight. The native Sb is rare and often contains arsenic, silver, iron and other metals as impurities. Sb is found in 114 minerals: the most common are stibnite (Sb_2S_3) which can contain up to 70% Sb, kermesite (Sb_2S_2O), valentinite (Sb_2O_3). Other natural sources of Sb are complex sulphide ores of stibnite containing mainly lead, tin, copper, silver, iron and mercury. Sb sulphides and oxides are the most important Sb compounds (Khatamov et al., 1967; Norseth and Martinsen, 1988).

Sources of primary Sb are chiefly China, Bolivia, the Republic of South Africa, and the former USSR; the total world production in 1987 was around 60 000 tonnes and 50% of the total world reserves is in China.

The extracted ore is sorted and crushed, then concentrated by settling and flotation. Free metal is produced by reduction of Sb sulphide with coke or by roasting the sulphide in the air, to obtain Sb tetraoxide which is then reduced with coke. The metal can then be purified by means of electrolytic processes.

Sb can also be extracted as a by-product in the lead electrolytic refining process. Lastly, recycling of non-ferrous scrap (secondary smelting) is also an important source of Sb (Stokinger, 1981; Norseth and Martinsen, 1988).

Exposure to Sb may occur during mining, smelting or refining operations and most of the data on environmental Sb concentrations concern different smelting operations.

Industrial exposure

Sb exposure can also occur because of its numerous applications in industry.

Sb is used in metal alloys (with lead, copper and tin) in the manufacture of printers' type, pewter, metal bearings, munitions, lead shot, lead electrodes, storage battery grids, plumbers' solder and cable sheathings.

However, it must be considered that exposure to Sb has not been widely studied in certain industrial settings because it occurred as an impurity: for example, in mechanical bronze alloys Sb can be found at 0.2–0.3%, whereas in lead-bronze alloys it occurs at at 0.1–0.7%. Moreover, during the casting and finishing of some 'noble' alloys employed in odontotechnical activities, with the use of the particle induced X-ray emission (PIXE) Sb has been found at atmospheric concentrations ranging from 0.5 to 4.1 $\mu g/m_3$, whereas it proved undetectable during operations with other alloys (Apostoli et al., 1988).

Sb and its compounds (oxides, trisulphides, pentasulphides) find applications in the manufacture of non-metal products such as pigments, paints, lacquers, enamels, plastic, rubber, matches, glass and pottery abrasive phosphorus (as a beryllium replacement), and vulcanizing agents. It is also incorporated in munitions, fire-proofing chemicals and textiles. High purity Sb is employed in the manufacture of semiconductors, in the form of intermetallic compounds with alkali or alkaline earth metals, transition metals and elements like aluminium, gallium, and indium.

Sb trioxide and pentoxide are still used in the preparation of chemotherapeutic agents adopted in the treatment of helminthic and protozoal infections (Bradley, 1941; Stemmer, 1976).

Table 2 summarizes the principal studies in which atmospheric Sb concentrations were measured in different industrial settings.

Most of the surveys have been made in ore-processing and smelting plants, whereas a few have been carried out in abrasives, glass or Sb oxides manufacturing plants.

During the study of industrial hygiene carried out in our Institute, environmental Sb concentrations ranging from 1.1 to 9.8 μg Sb/m^3 in a battery factory and from 1.0 to 4.2 μg Sb/m^3 in five bronze foundries were measured (Apostoli and Alessio, 1990).

Environmental exposure

Sb is mainly introduced into the environment by human activities such as mining, smelting, refining and fuel combustion or from municipal discharges. For example, concentration ranges of 36 to 142 mg Sb/kg were reported in dust samples in the furnace of solid urban waste incinerators (Ziemacki et al., 1989).

Moreover, Sb can be found in coal at various concentrations, as Table 3 shows. Figure 1 reports only the calculated mobilization of trace metals whose global emission is less than 1 000 tonnes per year from coal-fired power plants in the European Community countries: Sb represents, in the secondary group, one of the most important elements (about 600 tonnes per year) (Sabbioni et al., 1984).

Ambient air concentrations in US towns such as Chicago were reported to range from 1.4 to 55 ng/m^3, whereas lower levels ranging from 0.4 to 4 ng/m^3 were detected in seven different sites in the UK. At the South Pole the concentration is below 1.7 pg/m^3 (Dams et al., 1970; Peirson et al., 1973; Zoller et al., 1974).

Main exposure to Sb in the general population is through the diet, but the data on daily intake are controversial. Table 4 gives the results from studies carried out from 1971 to 1977 on human Sb dietary intake.

The Sb concentration varies from 3 μg/kg wet weight in fish to 8 μg/kg in milk and potato (Norseth and Martinsen, 1988).

Drinking water usually contains less than 0.5 μg/l and the maximum daily intake has been reported to be 15 μg (Winship, 1987).

The Sb concentration in cigarettes is 0.1 mg/kg dry weight and about 25% is from the paper; 20% is estimated to be inhaled.

Another source of environmental exposure can be dental materials; Molokhia et al. (1985) found concentrations between 2 and 656 μg/kg (up to 1 000 times the normal dental tissue concentration) in non-metallic dental materials currently used in restoration.

Finally, Sabbioni et al. (1981) estimated the Sb daily exposure as μg/kg of 'standard man' proposing the following values: with air, 0.03-0.7; with tobacco smoke, 0.1-0.8; with drinking water, 0.04-0.06; and 7-60 with food.

Effects on humans

It must be remarked that Sb ore contains arsenic as an impurity and consequently there is a small proportion of arsenic in industrial compounds. This fact has complicated the studies on the toxicity of Sb in occupational exposures, as effects observed could have been those of the contaminant rather than of Sb itself.

Indeed, signs and symptoms of acute and chronic Sb poisoning are similar to those of arsenic poisoning.

Sb interferes with cellular metabolism by combining with sulphydryl groups in respiratory enzymes, inhibiting their activity. It also binds sulphydryl groups in serums and affects the protein and carbohydrate metabolism and glycogen liver production (Gudzovskij, 1983).

Acute intoxication is unlikely to occur in industry, but can result from accidental or intentional ingestion. The symptoms of acute poisoning include violent irritation of the nose, mouth, stomach and intestine with abdominal pain, vomiting, haemorrhagic diarrhoea, dehydration, muscle pain, irregular respiration, choking, headache, lowered temperature, convulsions, ventricular tachycardia, collapse and coma, followed by death in a few hours due to circulatory or respiratory failure and hepatic or renal complications (Gudzovskij, 1983; Lauwers et al., 1989).

In industrial occupational settings, most effects are related to chronic exposure to Sb trivalent salts. The most important effects are respiratory, cardiac, skin and suspected carcinogenic and reproductive effects.

Respiratory effects

Rhinitis with septal perforation, pharyngitis, laryngitis, tracheitis, pneumonitis and chronic bronchitis have been reported in workers exposed to unknown concentrations of Sb trioxide dust (Renes, 1953; Klucik et al., 1962).

Acute exposure to $SbCl_3$ at the concentration of 73 mg/m^3 caused irritation of the upper respiratory tract in seven workers (Taylor, 1966). Three cases of pulmonary oedema after acute exposure to unknown Sb concentrations have also been described (Cordasco and Stone, 1973).

The most important effect on the respiratory tract is, however, a particular form of pneumoconiosis called antimoniosis.

Parkes (1982) states that Sb pneumoconiosis must be regarded as a 'benign condition', with no detrimental effect upon health or life expectancy. However, the benignity of this condition is discussed.

Several authors have remarked upon pneumoconiosis-like X-ray pictures obtained from workers with long-term occupational exposure to Sb.

Prevalences of 10-50% of pneumoconiosis have also been reported by some authors in Sb process workers; pulmonary function tests were, however, usually moderately or not affected and post-mortem analysis of lungs usually revealed no fibrosis or inflammatory reactions. Therefore, it seems that the Sb pneumoconiosis is an inert reaction to retained Sb particles (Klucik et al., 1962; Mc Callum, 1963; Cooper et al., 1968; Le Gall, 1969; Dumortier et al., 1974; Cavelier et al., 1979; Daguenel et al., 1979).

In the Yugoslavian smelter studied by Potkoniak and Pavlovic (1983), 51 smelters had been exposed to a total dust concentration of 17-86 mg/m^3 for 9 to 31 years; the dust mainly consisted of Sb trioxide (40-90%) and Sb pentoxide (2-8%), but also of 2-5% free silica. The workers showed X-ray changes indicating antimoniosis, characterized by the presence of numerous small opacities of pin-head type densely distributed in the middle and lower lung fields.

No characteristic pulmonary function abnormalities were noted; an obstructive or a mixed restrictive-obstructive pattern, as well as an increased airway resistance and decreased forced expiratory flow, were detected in some workers.

Symptoms of chronic bronchitis, upper airway irritation and conjunctivitis were also reported. The changes developed after at least one decade of work and massive fibrosis or 'r' type lesions were never seen. The authors also stated that antimoniosis was different from the classical silicosis or other forms of pneumoconiosis due to mixed dusts, because of the particular morphologic and radiologic picture of antimoniosis and the different latency in the onset of the lesions.

Possible Sb pneumoconiosis has been recorded in industrial settings different from smelting as in the case of two chemical workers exposed to Sb trioxide (Guzman et al., 1986).

Finally, it must be remarked that experimental data demonstrated that long-term (up to 14 months) exposure to Sb trioxide concentration ranging from 1.6 to 125 mg Sb/m^3 in different animal species causes lipoid pneumonia, interstitial pneumonitis, fibrous thickening of alveolar walls, focal fibrosis, adenomatous hyperplasia and cholesterol clefts, rather than clear findings of pneumoconiosis (Gross et al., 1955; Watt, 1983).

Cutaneous effects

Dermal effects, the so-called antimony 'spots', have been known for many decades (Oliver, 1933). Sb spot is a rash consisting of itching papules and pustules around sebaceous and sweat glands, especially where skin is exposed to heat or where sweating occurs. The rash is common in persons chronically exposed to Sb and its salts, transient and probably due to a toxic rather than allergic mechanism (Renes, 1953; Mc Callum, 1963; Potkoniak and Pavlovic, 1983).

Cardiovascular effects

Cardiovascular mortality and morbidity and ECG changes were attributed to Sb in workers of an abrasives plant exposed to concentrations of Sb trisulphide ranging from 0.6 to 5.5 mg/m^3 for 8 to 24 months. Sudden deaths ceased upon abandoning the use of Sb, but ECG changes tended to persist after several years (Brieger, 1954). Klucik and Ulrich (1960) reported similar anomalies in workers exposed to Sb_2O_3 and Sb_2S_3.

Moreover, experimental studies in dogs demonstrated that sodium Sb and potassium Sb produce a non-reversible decrease in myocardial contractile force and a decrease in perfusion pressure (Bromberger-Barnea and Stephens, 1965).

Other effects

Effects such as pain, nausea, vomiting, diarrhoea, liver enlargement, bitter taste and a higher prevalence of peptic ulcers have been described in Sb exposed workers (Renes, 1953; Brieger, 1954; Gallina and Luvoni, 1958; Taylor, 1966).

Chronic Sb exposure has also been related to symptoms such as headache, muscle pain, vertigo, anorexia and blood changes (Rodier and Souchere, 1955; Gudzovskij, 1983).

It is worth mentioning the haemolytic anaemia and acute renal failure described in the past following acute inhalation of stibine, the volatile hydride of Sb, with a clinical picture that resembles the one deriving from acute exposure to arsine (Stokinger, 1981).

Carcinogenic effects

Experimental data showed a significant increase in lung cancer in female rats following inhalation exposure to Sb trioxide at concentrations ranging from 0 to 45 mg/m^3 or to Sb ore concentrate at 0 to 40 mg/m^3, for seven hours per day, five days per week for up to 52 weeks (Groth et al., 1986). The only epidemiological study reports about a twofold excess of lung cancer in a group of 1 081 workers of an Sb and zircon smelter mainly exposed to Sb trioxide for an average of 22 years (range: 7-43), between 1922 and 1971. Data on Sb exposure refer to 1963 when, after control measures were instituted, the air concentrations were approximately 50 mg Sb/m^3; from 1971 to 1975, they ranged from 0.3 to 56 mg Sb/m^3, with an overall average of 9.5 mg Sb/m^3.

No excess of death from lung cancer has been observed among those employed after 1958 (Stokinger, 1981; Doll, 1985).

The available human data were considered 'inadequate' by the International Agency for Research on Cancer (IARC, 1989): therefore, the overall evaluation classified Sb trioxide as possibly carcinogenic to humans (group 2B). The American Conference of Government Industrial Hygienists (ACGIH, 1989) concluded that production of Sb trioxide should be regarded as a suspected carcinogen (group A2).

Metabolism

Most of the toxicokinetic information arises from experimental studies which have involved the administration of Sb organic derivatives intravenously, intraperitoneally or subcutaneously, because these are some of the routes used for clinical purposes. This fact must be taken into account when inorganic compounds used in industry are considered. Moreover, the biological behaviour is affected by the valence state, as observed in a greater toxicity of trivalent forms.

Absorption

Sb compounds are slowly and poorly absorbed from the gastrointestinal tract in mice (15% of a single oral dose). A prolonged contact with skin can determine a poor absorption. The principal route of absorption in workplaces is through the lungs. Mc Callum et al. (1971) developed an X-ray spectrometry method to measure the inhaled Sb. By calculating from the data they detected in symptomless workers with radiographic lung changes, we found a moderate correlation ($r = 0.55$) between measured lung Sb and period of employment (Figure 2). The authors also found that there was a correlation between length of exposure and X-ray classification.

An experimental model has been proposed by Leffler et al. (1984): in hamsters, after intratracheal instillation of Sb_2O_3 or Sb industrial dust containing Sb at 7.6%, they described a two-phase lung clearance curve (figure 3). The authors also claimed that the observed differences were primarily related to the solubility rather than to the particle size and they also stated that the low solubility in factory dust combined with a long biological half-life may be of importance in explaining the observed Sb lung accumulation in exposed workers.

In rats exposed to Sb_2Cl_3 by inhalation of labelled trivalent Sb salt, Djuric et al. (1962) noticed that a large proportion of the body burden was recovered in blood. A couple of weeks after exposure about 10% of the body burden was found in blood, at a higher proportion than in any other organ.

Distribution

In man, after intravenous injection or oral administration of drugs, the distribution is mainly in the liver, heart, kidneys, thyroid, adrenals and bone (Ozawa, 1956; Abdallah and Saif, 1962).

According to Edel et al. (1983) and to Djuric et al. (1962), if Sb is absorbed through the lungs in rats, it accumulates principally in red cells and to a much lesser extent in the liver and spleen, lungs and heart. On the other hand, localization of Sb in red blood cells was not evident either in rabbits or in dogs intratracheally treated with $SbCl_3$, making it difficult to extrapolate the rat data to man (Norseth and Martinsen, 1988).

Felicetti et al. (1974a) investigated the metabolism of inhaled Sb in Syrian hamsters. The animals were exposed to aerosols of labelled Sb tartrate of trivalent and pentavalent states, which showed the same pattern of metabolism. Whole body clearance of pentavalent aerosols, for example, occurred in two phases (Figure 4). Initial clearance was very rapid, resulting in the elimination of 90% of the initial activity by day 7 post-exposure. Early rapid clearance was followed by a slower phase during which the remaining Sb was eliminated with a biological half-life of about 16 days. Tissue distribution indicated that Sb accumulated mostly in the liver (especially trivalent forms), skeleton (especially pentavalent forms) and skin. In blood, trivalent Sb was concentrated in red blood cells at all sampling times; pentavalent concentrations were higher in plasma at 2-hour post-exposure but at 24-hour post-exposure these forms were also concentrated in red blood cells. Other studies in dogs and rats (Felicetti et al., 1974b; Djuric et al., 1962) demonstrated, however, a long-term whole body retention time of 100 and 200 days respectively.

Gerhardson et al. (1982) found that former (20 years after retirement) smelters exposed to Sb had on an average 12 times higher lung concentrations of Sb (315 μg/kg wet weight compared to non-occupationally exposed subjects (26 μg/kg). There was also no tendency towards decreased concentrations over time (up to 20 years) after cessation of exposure, thus indicating a long biological half-life. Moreover, the antimony concentrations in the liver and kidney cortex did not differ from the values obtained in the reference group.

Sb crosses the placenta in mice, after both parenteral and peroral administration (Gerber et al., 1982).

Excretion

Sb is excreted via urine or faeces. In experimental studies, it has been found that route and rate of excretion are dependent on the valency state of the compound; species differences were also observed. As a general rule, trivalent compounds are excreted via faeces, whereas pentavalent ones are excreted faster via urine (Edel et al., 1983; Norseth and Martinsen, 1988). After intravenous and intraperitoneal injection of pentavalent compounds in mice, 50 to 60% was found in urine after six hours; total excretion was around 70% at 48 hours (Goodwin and Page, 1943). Twenty-four hours after intraperitoneal administration of trivalent and pentavalent compounds in hamsters or rats, 6 to 15% of the former and 65 to 83% of the latter were found in urine, whereas the faecal excretion was 33 to 50% for trivalent Sb and 1 to 10% for pentavalent compounds (Gellhorn et al., 1946; Edel et al., 1983).

Djuric et al. (1962) after a 30-minute inhalation exposure in rats, found that 10 to 30% of the dose was excreted in urine and faeces the first day, decreasing by 1% within a few days. The ratio between urinary and faecal excretion fluctuated around 0.9. An almost similar urine/faecal partition was reported by Felicetti et al. (1974b) in beagle dogs after aerosol inhalation for a non-specified short time; the urine/faeces ratio was about 0.8 with no significant change from day 2 to day 32.

After intramuscular or intravenous injection in volunteers, 80% pentavalent and 25% trivalent Sb was found in urine within 24 hours, a pattern similar to that of animal studies. Other authors (Bartter et al., 1947) found that after intravenous administration the urinary excretion was four times higher than fecal. Rees et al. (1980) recovered 95% Sb in urine after six hours from an intramuscular injection of sodium stibogluconate. Taylor (1966), in seven subjects accidentally intoxicated by $SbCl_3$ found urinary concentration in rapid decrease after exposure. There might however be a long-term component according to the study of Mansour et al. (1967) who studied the urinary excretion in a patient treated for bilharziasis.

Biological indicators

General population data

Concentrations around 0.1 mg Sb/kg wet weight have been detected in the lungs of non-occupationally exposed subjects, whereas the liver and kidneys contain about one third of the lung concentration (Elinder and Friberg, 1986). Lower levels have been measured by Gerhardson et al. (1982), who detected 26.7 and 5 µg Sb/kg wet weight in the lungs, liver and kidneys respectively. Similar values were obtained by Brune et al. (1980). Japanese authors found 60 and 20 µg Sb/kg in the lungs and liver respectively, whereas the highest concentrations were detected in the adrenal glands (70 µg/kg wet weight) or skin (100); no differences between sex or age-groups were noticed (Sumino et al., 1975).

Blood, serum and urinary values in non-occupationally exposed subjects detected in various studies are reported in Table 5.

An upper limit of 1.7 µg/l for urinary Sb (SbU) and of 3 µg/l for blood Sb (SbB) has been proposed for non-occupationally exposed subjects by a working group of the Italian Society of Occupational Health (Abbritti et al., 1985).

Occupationally exposed workers data

The literature reports few reliable data concerning the biological monitoring of subjects occupationally exposed to Sb.

Belyaeva (1967) reported values of SbB up to 200 mg/l in workers exposed to trioxide and pentasulphide and the metal. SbB levels ranging from 0 to 130 µg/l were reported in a group of firearm instructors exposed to Sb-containing dusts, whereas the levels in controls were found to be less than 10 µg/l (Berman, 1980).

Urinary values ranging from traces to exceptionally high values of 600 mg/l were reported by Renes (1953) in workers exposed to concentrations ranging from 0.4 to 70 mg Sb/m^3 and with gastrointestinal symptoms.

In the plant studied by Brieger (1954), SbU levels of 0.8-9.6 mg/l. corresponded to exposure levels of 0.6-5.5 mg Sb/m^3.

In a Milan glassworks (Gallina and Luvoni, 1958), six workers with gastrointestinal effects, probably due to Sb_2Cl_3 poisoning, had SbU values ranging from 30 to 210 μg/l.

In three workers exposed to concentrations of 0.5-36.7 mg Sb/m^3, the SbU levels ranged from 425 to 680 μg/l, while another patient with pneumoconiosis had levels ranging from 55 to 28 μg/l, seven months and four years after retirement (Mc Callum, 1963).

In the group of 272 women in which reproductive disturbances were reported (Belyaeva, 1967), the mean SbU value was 21-29 mg/l (range 5-182); the SbB levels were 10 times higher than those of unexposed women.

In the plant where cancer deaths were detected (Stokinger, 1981), and where exposure levels from 1971 to 1975 ranged from 0.3 to 56 mg Sb/m^3, the mean SbU values in 1971 and 1972 were 0.73 and 0.5 mg/l in 1975.

Cooper et al. (1968) studied 28 subjects occupationally exposed to Sb and found urinary spot values ranging from 7 to 1 020 μg/l; SbU was determined during the period 1962-68, in which Sb exposure levels ranged from 0.08 to 138 mg/m^3.

Le Gall (1969) did not detect Sb in the urine of workers exposed to 3.4-14.7 mg Sb/m^3.

Smith and Griffiths (1982) found considerably higher SbU values (10-200 μg/l) in exposed workers compared with non-exposed subjects (< 1-5 μg/l).

Earlier studies showed that in occupationally exposed subjects, high urinary excretion is present for some years after cessation of exposure (Klucik and Kemka, 1960; Mc Callum, 1963).

Table 6 shows the SbB and SbU values obtained by Ludersdorf et al. (1987) in workers of a glass-producing industry employed in various activities for which the environmental concentrations varied from < 50 to 840 μg Sb/m^3.

Lastly, in a recent study on Sb metabolism, Bailly et al. (1991) evaluated Sb exposure in male workers from a non-ferrous smelter producing Sb pentoxide and sodium antimoniate; the mean airborne Sb concentration ranged from 86 ± 78 μg/m^3 in the wet process to 927 ± 985 μg/m3 in the dry process. The authors found a correlation between the airborne Sb concentration (log value) and SbU (log value) in post-shift urine samples (r = 0.83): the correlation was better (r = 0.86) if the increase in SbU concentration during the shift was considered. On the basis of the regression equation, the authors suggest a tentative biological limit value of 35 μg Sb/g creatinine between the start and the end of the shift.

According to Norseth and Martinsen (1988), blood and urinary Sb concentrations have no value for risk estimation of pulmonary effects. Workers with radiological lung changes were not found to have particularly high SbU values, as compared with workers without such changes.

It must, however, be noted that Mc Callum et al. (1971) in symptomless workers with radiographic changes, detected a correlation between length of exposure and X-ray classification.

Apart from the abovementioned study by Bailley et al. which refers to mean occupational exposures ranging from 100 to 1 000 μg Sb/m^3, a correlation between air concentrations and SbB or SbU values has not been reported so far. SbU measured at the end of a shift has been considered as an indicator of recent exposure, due to the rapid excretion after absorption. Moreover, in biological monitoring, the elimination that can occur years after cessation of Sb exposure should be taken into account.

On the other hand, SbB can be found at higher levels in exposed subjects compared with non-exposed subjects, but the biological significance of SbB has not yet been defined.

It must however be remarked that when interpreting such different results of the above reported surveys, the different analytical procedures should also be considered.

To date no indicator of effect is available.

Conclusions

The studies on effects of Sb in humans seem to show a moderate toxicity of the metal, although Sb exposure has not been studied extensively and most of the data refer to earlier researches.

It must also be remarked that, on the one hand, the classical occupational exposure to Sb such as in smelting and ore processing occurs, rather infrequently and with lower exposures while, on the other hand, exposure to Sb may sometimes be unrecognized or undesired so that it can be easily overlooked.

Moreover, the Sb metabolism has not been thoroughly investigated, either experimentally or in humans and, in particular, the behaviour of Sb in urine and blood is not completely known.

However, for SbU, two phases of excretion have been identified: a rapid one (within hours of exposure), and a slower one, but it is not known whether this latter phase is related to the body burden of the metal.

Significant differences have been detected between SbU and SbB levels in exposed workers with respect to non-exposed control subjects.

However, most of the studies which report such differences are the older ones and the analytical techniques adopted must be considered when evaluating the results.

While the literature refers to a study dealing with the useful adoption of SbU in monitoring workers exposed to concentrations higher than 100 $\mu g/m^3$, it does not appear to be practicable today to use SbU and SbB as indications in the routine biological monitoring of workers exposed to lower Sb concentrations.

Research needs

Further research is required dealing with the following topics:

The development of reliable analytical methods for the determination of SbU and SbB.

The study of occupational environments in which exposure to Sb is considered as a 'minor' or part of a multiple exposure.

The study of SbU and SbB to clarify their significance as biological indicators of exposure and/or internal dose.

The study of the relationship between external exposure (both current and cumulative) and levels of biological indicators in exposed workers.

The study of the relationship between SbU and SbB in exposed workers.

The individuation of biological indicators of effect and of the possible dose/response and dose/effect relationships.

The study of the state of health of exposed workers and of subgroups of subjects with increasing levels of the biological indicators.

Analytical methods and problems of analysis

There are many analytical methods available, but some of them (for example, colorimetry and polarography) are today of little interest for biological matrixes (Smith and Griffiths, 1982). A great variability exists in the literature data, not only because of the analytical difficulties, but also because of the lack of quality assurance programmes.

The most important problems are the contaminations, the losses of Sb due to adsorption or precipitation or volatilization during sample treatment and the difficulties related to the acid digestion, which is necessary for biological samples both to destroy the organic matrix and to assure the conversion of all the Sb forms to the pentavalent oxidation state (Gallorini et al., 1978; Iyengar et al., 1978).

Nowadays, the most utilized methods are those in atomic absorption spectrometry (AAS) and, among them, those with hydride generation (HGAAS) and those with elec-

trothermal atomization (ETAAS). The HGAAS enables a detection limit to be reached in the order of 0.1 μg/l, but there are problems related to the Sb oxidation state and to the matrix interferences. On the contrary, the accuracy of the ETAAS is conditioned by the matrix interferences and from the high volatility of Sb; in spite of the use of the L'Vov platform and matrix modifier such as palladium or magnesium nitrate, the detection limits of HGAAS cannot be reached (Thompson and Thomerson, 1974; Bencze, 1981; Bettinelli et al., 1988). It must also be underlined that the deuterium background correction is not an accurate technique (Fernandez and Giddings, 1981). The methods in ETAAS with metal extraction are largely used: they enable a detection limit of 0.2–1 *g/l to be reached.

Very sensitive methods with neutron activation analysis (NAA) have been adopted, but they are difficult to use and of limited availability (Bettinelli et al., 1988).

Lastly, the inductively coupled plasma mass spectrometry (ICPMS) has been introduced, which enables a detection limit of 0.02 μg/l to be reached (Thompson and Houk, 1986).

Table 1 – Physicochemical properties of antimony

Atomic number	51
Atomic weight	121.75
Melting point (°C)	630.7
Boiling point (°C)	1750
Density (g/cm^3)	6.68
Electronegativity	2.05
Oxidation states	– 3, 0, + 3, + 5

Table 2 – Main studies on occupational exposure to Sb

Author	Year	Type of work	Environmental concentration (range, in mg Sb/m^3)
Renes	1953	Sb smelter	0.4–70.7
Brieger	1954	Abrasives plant	0.6–5.5
Karajovic et al.	1960	Sb smelter	16–248
Klucik and Ulrich	1960	Sb smelter	1.3–237
Mc Callum	1963	Sb_2O_3 production	0.5–36.7
Cooper et al.	1968	Sb smelter ore processing	0.08–138
Le Gall	1969	Sb smelter ore processing	0.3–14.7
Cavelier et al.	1979	Manufacture of Sn and Sb oxides	0.3–0.6
Cortona et al.	1979	Secondary foundry	0.001–0.15
Donaldson and Cassady	1979	Sb trioxide production	0.2–8.7
Stokinger	1981	Sb smelter	0.3–56
Potkoniak and Pavlovic	1983	Sb smelter ore processing	17–86
Ludersdorf et al.	1987	Glass industry	0.005–0.84
Apostoli	1990	Bronze foundries	0.001–0.004
and Alessio		Battery plant	0.001–0.01

Table 3 – Sb content in coal of different countries

Country	Concentration (ppm)		
	No. of coal samples examined	mean	range
United Kingdom	15	3.3	1–10
West Germany	6	3.5	1.8–5
France	2	5.2	–
Belgium	13	2	–
USA	166	1.1	0.1–8.9

(Sabbioni et al., 1983)

Table 4 – Human dietary intake of antimony in various countries

Country	Daily Intake	Reference
	(μg/day)	
Sweden	2.2–15.6	Wester (1974)
United Kingdom	34± 27	Hamilton and Minski (1973)
Germany	23	Schleutz (1977)
USA	247–1 275	Murthy et al. (1971)

Table 5 – Blood, serum and urinary Sb concentrations of non-occupationally exposed subjects

Author	Year	No of subjects	Specimen	Method[1]	Valves (μg/l)
Hirayama	1959	104	Blood	Col.	0.0-135
Mansour et al.	1967	3	Blood	NAA	1.5-5.5
			Urine		2.9-9.1
Kasparek et al.	1972	149	Serum	NAA	2.5 ± 1.37
Hamilton et al.	1973	75	Blood	SSMS	2 ± 0.6
Wester	1973	16	Urine	–	0.5–2.6 (μg/24h)
		8	Serum	NAA	0.75 ± 0.5
Bencze	1981	34	Blood	HGAAS	0.5–6.2
Smith and Griffiths	1982	18	Urine	ETAAS	< 1-5
Fodor and Barnes	1983	2	Urine	HGAFS	2.0–2.6
Blekastad et al.	1984	281	Serum	NAA	< 0.3 ± 0.2
Ludersdorf et al.	1987	51	Blood	HY-AAS	0.3–1.7
		8	Urine		0.2–0.7
Minoia et al.	1990	360	Urine	AAS	0.19–1.1
		27	Blood	NAA	0.03–3.5
		22	Serum	NAA	0.01–1.7

[1] Legend:

Col. = colorimetry
SSMS = spark source mass spectrometry
HGAAS = hydride generation atomic absorption spectrometry
ETAAS = electrothermal atomic absorption spectrometry
HGAFS = hydride generation atomic fluorescence spectrometry
NAA = neutron activation analysis
HY-AAS = hydride atomic absorption spectrometry

Table 6 – Urinary and blood antimony in workers of a glass-producing industry*

Specific activity	No, of subjects	SbU			SbB		
		Min.	X	Max.	Min.	X	Max.
Melter	32	0.2	0.9	2.9	0.4	0.8	1.8
Batch mixer	45	1.5	5.0	15.7	0.5	1.1	2.4
Craftsman	8	0.4	0.9	3.7	0.5	0.7	1.0
Glass washer	24	0.6	1.2	6.3	0.4	1.1	3.1
Total	109	0.2	1.9	15.7	0.4	1.0	3.1

* Modified from Ludersdorf et al., 1987

Sb air concentrations:	
melting area	< 50–5 μg/m^3
batch bunker	40–840 μg/m^3

Min: lowest value; X: median; Max: highest value.

LEGENDS TO THE FIGURES

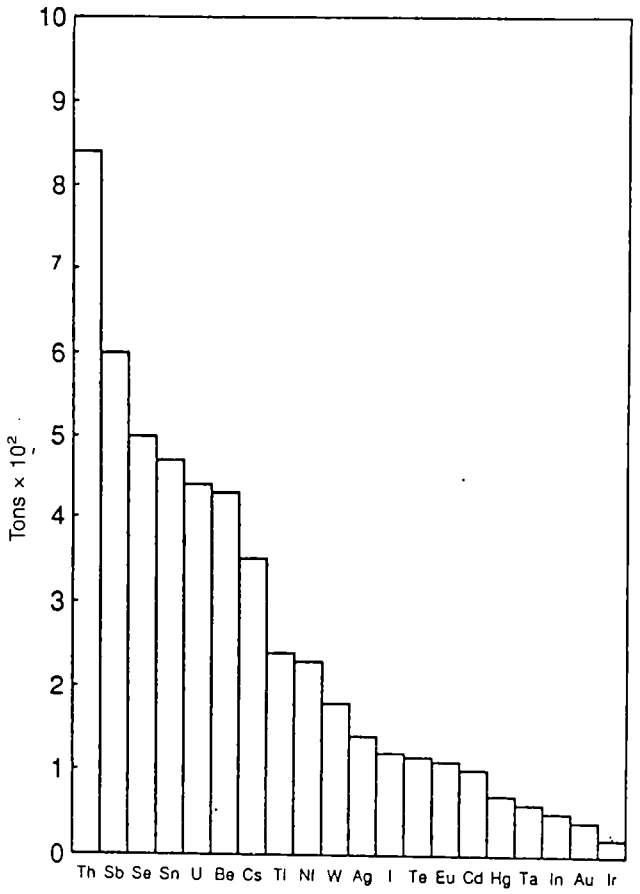

Figure 1 – Metal mobilization from hard coal-fired power plants in the countries of the European Community for the year 1990; second group of elements, with total mobilization below 1 000 tonnes (modified from Sabbioni et al., 1984)

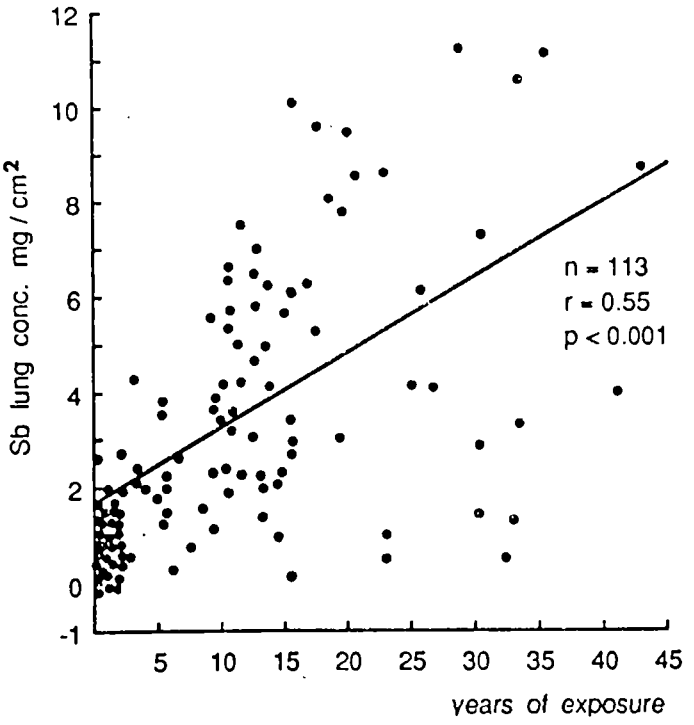

Figure 2 – Correlation between length of exposure and Sb lung concentration in Sb smelters (modified from data by Mc Callum et al., 1971)

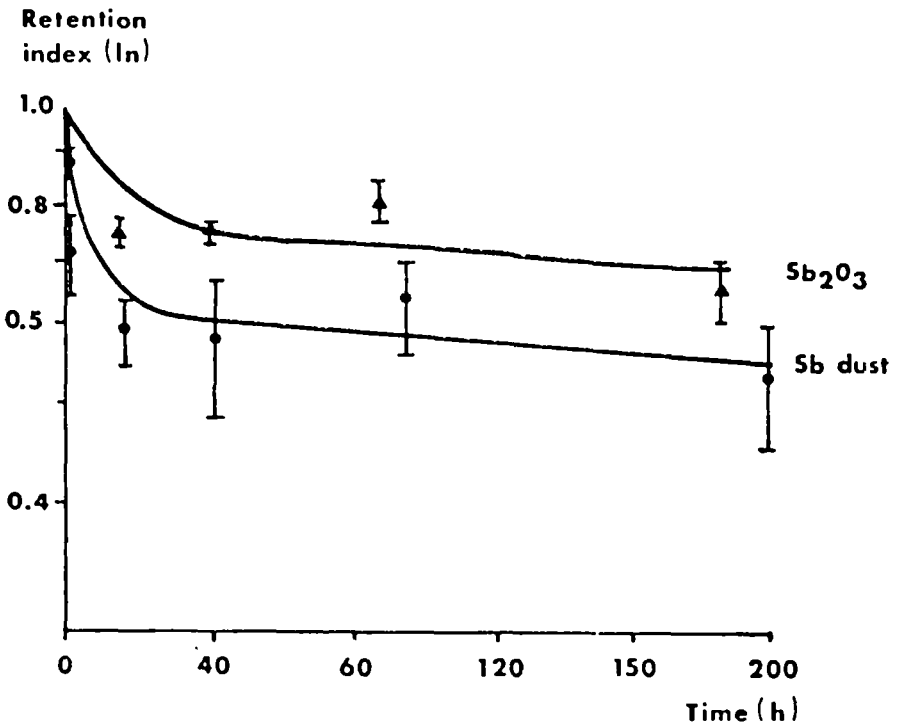

Figure 3 – Lung retention (mean ± standard error of the mean of Sb in hamsters after the intratracheal instillation of antimony trioxide and antimony dust (modified from Leffler et al., 1984)

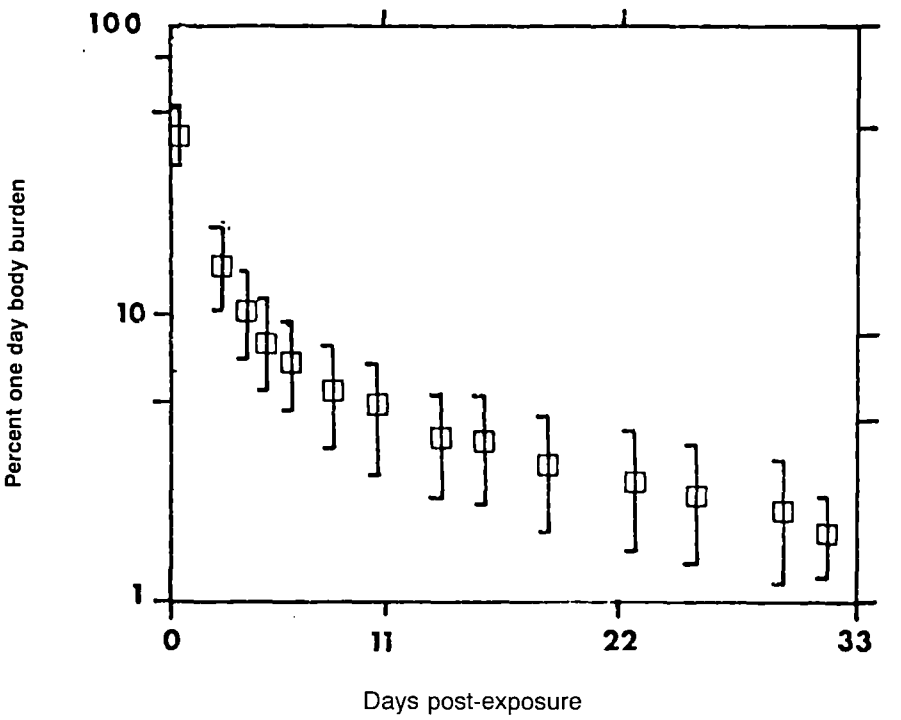

Figure 4 – Whole-body retention following inhalation in hamsters of pentavalent Sb tartrate. Data are plotted as a percentage of one day body burden. Means and standard deviations for each group at each counting date are presented (modified from Felicetti et al., 1974a)

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Biological indicators for the assessment of human exposure to industrial chemicals

Soluble barium compounds

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Summary

Barium (Ba) is a light soft metal. In the earth's crust it is mainly found as a sulphate or carbonate. It is almost always divalent. Ba obviously reduces the passive potassium outward current at cell membranes. Also an indirect action by release of calcium in cells seems to result. Absorption occurs mainly as a chloride, fluoride or carbonate via inhalation or oral ingestion. The main storage is found in the skeleton, high concentrations are also found in eye tissue. The biological half-life is assessed between 2 and 20 hours. Ba is mainly excreted with about 90% in faeces and with only 1 to 10% via urine. Some accumulation after occupational exposure seems to be possible. The critical toxic dose is about 200 mg barium chloride orally administered. In the literature, only a few studies on the external exposure in industries have been published. Some exposure is known in steatite production, in the cosmetic and pharmaceutical industries, and recently also in some welding processes. When welding with high Ba-containing consumables, high external concentrations of soluble Ba up to 200 mg/m^3 can occur (TLV = 0.5 mg/m^3).

For the determination of Ba in body fluids, electrothermal atomic adsorption spectrometry or inductively coupled plasma emission spectroscopy after dilution of urine or deproteinization of plasma respectively by nutric acid is applied.

The non-occupational exposure from food and water may lead to a greater variation of the Ba concentrations in urine between 0.1 and 75 µg/l and in plasma from 0.1 to 40 µg/l. For the monitoring of occupational exposure the quantification of Ba in plasma or urine is recommended.

Only very few studies are available on internal occupational exposure. In welders with high external exposure the Ba concentrations could be found in urine up to 460 µg/l and up to 75 µg/l in plasma. In the low occupational exposure range there is a wide overlap with the non-occupational load in biological body fluids. Therefore the biological monitoring in occupational medicine can be recommended on a mainly group basis.

Except for hypokaliaemia, no specific early indicators of effect are known. Symptoms of acute poisoning can be any kind of heart arrhythmia, ischemic heart symptoms, hypertension, paralysis of striated and smooth muscles, hypersalivation, abdominal cramps and diarrhoea. No proven long-term effects are known.

Barium

Chemical and physical properties

Barium, chemical symbol Ba, is a soft metallic, silver-coloured element.

Table 1 Physicochemical properties of Barium

Atomic number	56
Atomic weight	137.33
Melting point	710°C
Boiling point	1 537°C
Specific gravity	3.76 g/m^3
Valency status	Strictly divalent (II)

Solubility of barium compounds

The biological effects of Barium strongly depend on its solubility and bioavailability. The solubility of the most important compounds is as follows:

Ba sulphate	Practically insoluble in water, most acids and alkalines; Slightly soluble in concentrated sulphuric acid
Ba carbonate	Practically insoluble in water; very soluble in nitric acid and hydrochloric acid (stomach!), where it forms soluble Ba chloride and nitrate respectively.
Ba nitrate	Very soluble in water:
Ba fluoride	Very soluble in water:
Ba chloride	Very soluble in water:
Ba hydroxide	Very soluble in water and acids:
Ba chromate	Only slightly soluble in water.

Natural resources

About 0.04 to 0.05% of the upper layer of the solid earth's crust consists of barium. It is highly reactive, so it is not found in an elementary status in the earth's crust. Here it mainly occurs as sulphate (baryte = heavy spar) and carbonate (witherit).

Metallic barium is also highly reactive in the air with oxygen, nitrogen and humidity as well as with water, with which it forms alkaline $Ba(OH)_2$. The world mine production of Ba sulphate (baryte) was about 4.5 million tonnes in 1974; the figures indicated for 1985 and 1986 vary between 4.8 million and 5.7 million tonnes (Falbe and Regitz 1989; Machata 1988; Reeves 1986; WHO 1990).

Industrial use

The most widely used Ba compounds are Ba sulphate and Ba carbonate.
Ba sulphate is mainly applied in oil-mining industries to form drill mud. It is also used as a radiation absorber in cement, e.g. in nuclear power plants, as a pigment in colours and lacquers and as a filler material in various chemical recipes (e.g. in lithopone).
Ba carbonate is also applied as a pigment and a filler material, as well as a biocide; in

steel industries it is used as a surface hardener. It also occurs in paper, rubber, ceramics, printing colours, pyrotechnique industries, agricultural additives and as an impurity in soapstone. Ba carbonate is also added in the flux and the coating respectively of some cored wires and rod electrodes in welding technologies.
Ba sulphide is formed from the sulphate by heating with coal. It is mainly applied as a biocide and a depilator. Carbonate as well as various soluble compounds such as hydroxide, acetate, chlorate, chloride and nitrate may occur as a biocide and in paper, rubber, ceramic, prints, and dyestuff industries.
Chloride and fluoride are also used in metallurgy for hardening steels.
Fluoride is also added in some flux cored wires and coated stick electrodes for arc welding.
Ba chromate is used as a pigment in colours, ceramics and glasses.
Organic compounds such as stearate are less important. They may be used as stabilizers in plastic industries and as a lubricant in metal industries (Falbe and Regitz 1989; Stockinger 1981; Spoor 1964; Moreton 1981; Reeves 1986; Machata 1988; WHO 1990).

Effects *in vitro* and in animal trials

Experiments in cell physiology show that Ba can directly inhibit the passive transmembraneous potassium conductivity, mainly for the outward current. It also seems to interact with calcium whether as a substitute with some intrinsic activity or as a messenger to release Ca from the endoplasmatic reticulum of the cells. After extracellular application Ba ions lead to spontaneous depolarization of cells with phasic contractions of striated and smooth muscles with subsequent flaccid paralysis.
At the heart Ba ions lead to a spontaneous depolarization of the cells. In the central nervous system Ba can release various transmitters.
In animal trials after injection of Ba ions into the brain ventricles tonic and clonic cramps could be observed. After injection into respectively the peritoneum and the blood vessels of mammalians the acute symptoms were as follows: Contraction of the arterioles with a rapid increase of the systolic blood pressure only, but not of the diastolic blood pressure; bradycardia, increase of ventricular activation time, increase of QRS-time, confluence of T and U waves in ECG, disorders of repolarization, atrionodular and ventricular premature systoles up to ventricular fibrillation. In the course of an intoxication, contractions of the muscles with subsequent flaccid paralysis of striated muscles including the diaphragm, hypersalivation, fluid diarrhoea and severe hypokaliaemia, even without diarrhoea or before diarrhoea has been observed.
Longterm exposure with parenteral injection of soluble Ba compounds and inhalation of Ba carbonate (13 mg/m^3 over 1 month) additionally revealed the following symptoms: anaemia, leucocytosis, loss of weight, decrease of serum proteins and blood glucose, osteoporosis, lung sclerosis, dystrophy and hyperplasia of liver, spleen and kidneys.
(Argibay et al. 1983; Armstrong and Taylor 1980; Armstrong et al. 1982; Augustine and Eckert 1984; Clement 1981; Cohen et al. 1983; Constanti et al. 1981; Cukierman and de Carvalho 1982; Douglas and Rubin 1964; Eaton and Brodwick 1980; Ehara and Inazawa 1980; Erdélyi 1979; Frank and Rohani 1982; Gallant 1983; Gerasimova and Roszinskin 1980; Hermann and Gorman 1979; Hiraoda et al. 1980; Malavé et al. 1983; Meier and Katzung 1978; Milanov and Stoyanov 1982; Mugelli et al. 1983; Mukai and Takagi 1983; Mukai et al. 1982; Munch et al. 1980; Nachshen and Blaustein 1982; Nagel 1979; Nakazato and Onoda 1980; Naylor and Grindwald 1982; Oliveira-Filho et al. 1978; O'Neill 1983; Osterrieder et al. 1982; Popava 1978; Potreau and Raymond 1980; Roza and Berman 1971; Saeki et al. 1981; Shanbaky et al. 1978 and 1982; Tarasenko and Pronin 1974; Tarasenko et al. 1977; Woll 1982; Yanagihara and Irisawa 1980; Yashuda et al. 1983; Zengel et al. 1980; Zengel and Magleby 1981).

Effects on humans

Barium is not known as an essential trace element for man.
Inhalation of Ba sulphate dust can lead to a benign pneumoconiosis with small nodular opacities in the lungs with general distribution (baritosis). It is often found in workers mining, grinding or bagging baryte, but also in lithopone manufacture and soapstone production.
Pure Ba sulphate is not known to lead to any lung impairment. It is highly unsoluble and therefore not toxic, so it is applied in medicine as a contrast medium.
Barium containing minerals may be contaminated with quartz, which may lead to a mixed pneumoconiosis with subsequent lung function disorders (Seaton et al. 1986; ILO 1983).

Soluble Ba compounds such as chloride, fluoride, nitrate are irritant to the mucosa and the skin. The inhalation as well as the ingestion of water-soluble Ba compounds may lead to severe toxic effects. Also the oral ingestion of Ba carbonate may be toxic, because it is solved in hydrochloric acid of the stomach, where it forms highly soluble Ba chloride.
The miniumum single toxic dose has been evaluated from case reports as about 0.2-0.8 g Ba chloride. The letal dose is estimated between 0.8 and 20 g Ba chloride. Intoxications with soluble Ba compounds occurred due to misclassification of flour, bakery ingredients, due to the external application of depilatories and biocides as well as with suicidal intention.
The prognosis of the intoxication seems to be positively influenced by vomiting and diarrhoea, which may reduce the bioavailable Ba dose.

All symptoms of an intoxication come up acutely with a latency between 30 minutes and some hours.

The following disorders have been observed in man:
Initially: Gastroenteritis including vomiting and diarrhoea and blood in the faeces; tenesmus and cramps of the bowls. Paraesthesia of the face, the neck and the upper arm; headache, dizziness, hyperhydrosis, tremor of the extremities, hypersalivation (sometimes dryness of the mouth); inhibition on the reaction of the pupils on light and of the convergence of the eyes with diplopia. Acceleration of the heart rate up to 140 beats per minute (later on normalization or even subnormal rates); hypertension up to 180/110 mm Hg (later on normalization or even hypotension); reduction of the body temperature. Severe hypokaliaemia with concentrations down to 1.6 mmol per liter serum. Sometimes short fasciculations or spasms of the striated muscles including singultus.
In the further course: paraesthesia of all extremities; diminution of the muscle reflexes; flaccid paresis of the sceletal muscles, mainly developing upwards. Dysarthria, dysphagia. Cardial arrhythmias of any kind; disorders of the electric activation and repolarization of the heart (digitalis-like action of Ba). Excessive leucocytosis: up to 70 000 leucocytes per microlitre blood in WBC. Sometimes disorders of the pyramidal tract.
The final stage: Overall paralysis of striated muscles including the diaphragm; ventricular fibrillations of the heart; cyanosis. Occasional renal disorders with kidney failure are described (may be brought about by therapeutical attempts with intravenous application of sulphates with succeeding deposition of Ba sulphate in the kidneys). No affection of the consciousness. Death due to paralysis of the ventilatory muscles or due to heart failure (Adzhiev 1968; Becker 1951; Berning 1975; Camerer 1943; Dean 1950; Diengott et al. 1964; Domenjoz 1945; Fazekas 1955; Gould et al. 1973; Habicht et al. 1970; International Labour Office 1983; Jeske and Musialowicz 1978; Lacroix 1943; Lecomte 1959; Lewi and Bar-Khayim 1964; Lydtin et al. 1965; v. Marchtaler 1950; Maretic et al. 1957; Morton 1945; Preisz 1956; Rausch 1951; Smith and Gosselin 1976; Talwar and Sharma 1979; Wetherill et al. 1981).

A subchronic intoxication of a part of the population in Si Chuan (China) was found with vomiting, diarrhoea and a reduction of muscle reflexes and flaccid paresis; the cause of this intoxication was a contamination of table salt with soluble Ba salts (ILO 1983; WHO 1990).

No sure long-term effects of Ba are known. Acute intoxications – if not fatal – recover to the *restitutio ad integrum*. Some investigations of cardiovascular risks in correlation with the Ba content of drinking water show conflicting results; no sure impact of Ba on blood pressure, rate of vascular and heart diseases and after long-term exposure can be assessed (Brenniman et al. 1979 and 1981; Kojola et al. 1979; WHO 1990).

Metabolism

Absorption

The absorption of soluble Ba from the airways and the lungs as well as from the gastrointestinal tract, where it is mainly absorbed in the small intestine (Dean 1950), can be estimated from animal trials between 30% and 70% of the applied dose (Cuddihy and Ozog 1973; Cuddihy and Griffith 1972; Cuddihy et al. 1974; Sutton and Shepard 1973; Reeves 1986). No data in man have been established.

In man some reports of cardial disorders like arrhythmias and the impairment of repolarization have been observed after the Ba sulphate enema. This effect is predominantly described in some studies in patients who had been suffering from cardiovascular risks, but not in all studies. The cardial effects are generally explained as vegetative reactions due to the manipulations in the stomach and the gut. It is not clear whether Ba may be involved in these effects after absorption to some degree (La Van et al. 1962; Eastwood 1972; Berman et al 1965; Gibbs et al 1972; Roeske et al. 1975).

Distribution

The half-time of soluble Ba has been studied in man in some trials after intravenous and intramuscular injection of soluble radioactive Ba isotopes. The results are in accordance with those of studies in mammalians. The half-life has been assessed between 2.5 and 6 hours within the first 5 hours and from 28 to 35 hours with a delay of 50 hours after the application, both in blood and in urine (Bauer et al. 1959; Harrison et al. 1966 and 1967; Mc Cauley and Washington 1983; Cuddihy et al. 1974; Cuddihy and Griffith 1972; Erre et al. 1980).
So a two- or even multi-compartment storage system of Ba in the organism can be assumed (Marcus and Becker 1980; Reeves 1986).

After intravenous injection the tissue content reaches its maximum within the first two hours with a subsequent decline afterwards (Harrison et al. 1967).

In man about 22-24 mg Ba is being stored in the organism, about 20 mg of which is found in the skeleton, which means about 90% of the Ba pool of the body. The Ba concentration in bone is about 2 mg Ba/kg bone (wet weight). Even higher concentrations can be found in lung, heart, muscle and pigmented parts of the eye tissue. Age does not seem to affect the overall Ba storage in the organism markedly. Regional differences of storage and distribution in various countries have been described (Schroeder et al. 1972; Harrison et al. 1967; Kojola et al. 1979; Reeves 1986).

Excretion

In man about 90% or even more of the excreted Ba is found in the faeces. Only about 10% or less is being eliminated in urine. Furthermore, the secretion with sweat of about 6% of the excreted Ba is important. The ratio faeces vs urine excretion is estimated as 9:1 on average, some authors give values up to 200:1 (Harrison et al. 1966 and 1967; Kojola et al. 1979; Syed et al. 1981; Schroeder et al. 1972; Sutton and Shepard 1973; Tipton et al. 1969). The ratio is the same after gastrointestinal as well as after parenteral application.
The average excretion of Ba in the faeces varies between 0.3 and 1.2 mg per day and the renal elimination between 0,2 and 30 µg/day, which equals the average daily uptake in ordinary diet (Schroeder et al. 1972; Sutton and Shepard 1973; Tipton et al. 1969; Syed et al. 1981; Havlik et al. 1980; Reeves 1986; WHO 1990). The renal plasma clearance has been calculated very differently by two authors as about 330 ml/day and 10 l/day respectively (Harrison et al. 1966; Schroeder et al. 1972 with reference to the data given by Tipton et al. 1966 and 1969). The cumulative overall excretion of Ba after the uptake is about 70–75% within the first three days and about 85% within the first 10 days (Harrison et al. 1966 and 1967; Reeves 1986).

Biological indicators

Barium concentrations in serum/plasma and urine of non-occupationally exposed persons

Data from the older literature have to be evaluated with precaution. In the last few years analytical methodologies have become more sensitive and specific than the older ones. Table 2 shows the barium levels in serum/plasma as well as in blood and in urine found by various investigators in non-exposed subjects.
The barium levels in plasma samples show a high interindividual variation (Zschiesche et al. 1989 and 1992). Most or all of the barium in blood is found in the plasma fraction (Nagel 1979; Schroeder et al. 1972; Reeves 1986). The concentrations ranged from <1.0 to 38.8 µg/l, most of the values being below 8 µg/l.

The renal barium excretion may also be characterized by high interindividual as well as by intra-individual variations. Over a five days period the levels ranged between <1.0 and 72.3 µg/l and between <1.0 and 78.2 µg/g creatinine. Most of the values were below 20 µg/l or g creatinine respectively. (Zschiesche et al. 1987, 1989 and 1992). The intra-individual behaviour of the Ba concentrations in biological materials was very different even without any occupational exposure. Constantly high as well as constantly low values could be observed, but also a changeable internal exposure. Examples are given in Table 3.

In a recent study of unexposed Italian subjects a mean barium concentration in urine of 2.7 ± 1.5 µg/l (N = 35), in blood of 1.2 ± 0.6 µg/l (N = 25) could be determined. In this study tremendous efforts were made in eliminating errors in the preanalytical and analytical phase (Minoia et al. 1990).

Occupational exposure to soluble barium

In the literature very few studies of Ba exposed workers with regard to biological monitoring have been published. A TLV of 0.5 mg/m^3 has been derived from workers of a plant in the USA with exposure to Ba nitrate (ACGIH 1980 and 1991). This TLV has not been established quite profoundly so far (Stockinger 1981).
Essing et al. (1976) investigated 12 workers in the soapstone industries, who had had a long-term exposure to Ba carbonate with concentrations between 0.17 and 2.3 mg Ba/m3 air. They did not find any radiological disorders of the lungs and the pelvis. Two of them had systolic and diastolic hypertension.
Two workers had a partial block of the right cardial brunch. Seven workers experienced symptoms of chronic bronchitis, three of whom had signs of a obstructive lung disease as well; all of them were smokers. Five workers showed low-grade small nodular and reticular opacities respectively in chest-X-ray (p,s or t 0/1 to 1/0 according to ILO classification 1980). No sufficient signs of a Ba intoxication could be found. An acute paralysis has been described by Shankle and Keane 1988 in a worker who had inhaled Ba carbonate in the chrome plating industry. Within 1h, he experienced abdominal cramps, nausea, and vomiting, and later there was excess salivation, paralysis of the extremities, and renal dysfunction. A serum potassium level of 0.3 mmol/l and a Ba level of 250 mEq/l were reported. After treatment with potassium infusion, complete recovery occurred within 5 days. The potassium and Ba levels reported by the authors would reflect a tremendous internal exposure as well as extreme hypokalemia. Both findings hardly seem compatible with life, so the validity of these data seems uncertain (Zschiesche et al. 1987).

Dare et al. (1984) as well as Oldenburg et al. (1988) and Moreton et al. (1981) had proved that 30% to 90% of Ba in the fumes of some particular, coated stick electrodes and flux-cored wires are soluble in water or 0.1 M hydrochloric acid respectively within some minutes. This meets the requirements of the definition 'soluble' barium compounds.

Dare et al. (1984) as well as Schramel et al. (1985) report on four and five welders respectively who had been exposed to Ba-containing welding fumes. Dare et al. indicate Ba concentrations in urine between 31 and 234 µg/l after shift in an experimental trial with reference values between 1.8 and 4.7 µg/l. Schramel et al. found Ba concentrations of 26-198 µg/l urine in welders and of 4.5 µg/l as reference value. No data on ambient monitoring or medical investigations are being reported.
A major study with the quantification of the internal as well as the external exposure and the evaluation of any possible adverse effects of soluble Ba ions is an experimental investigation of 18 welders by Zschiesche and co-workers (1987, 1988, 1989 and 1992).

In this experimental study eight welders used coated stick electrodes on a nickel basis, 4 mm diameter, length 350 mm each (German DIN standard 85739: E Ni Fe BG 1), the fumes of which contained 37.3% barium on the average. Welding was applied over one working week (five days) in medium-sized shops without local exhaust systems. On average, each welder consumed between 96 and 106 stick electrodes per day with an arc time of about 80% over four hours. This equals a realistic 40% arc time per eight hour shift. Ten welders used self-shielded flux cored wires with a diameter of 2.0 mm (US AWS standard 5.79-80: E 71 T 8 Ni 1). In the mean, between 5.8 and 7.1 kg wire were consumed per welder per day. The average barium content in the fume was 12.4%. Five welders had been working without local exhaust systems, the other five applied a gun-integrated exhaust device offered by the wire producer. The other parts of the study design met the conditions in stick electrode welding.
The external exposure is shown in detail in Tables 4-6. In stick electrode welding the

median barium concentration in the breathing zone was 4.4 mg/m3 air (range 0.1-22.7 mg/m3). Welding with flux cored wires without local exhaust device resulted in a median external exposure in the breathing zone behind the protection shield and mask of 2.0 mg/m3 (range 0.3 – 35.9 mg/m3), when welding with the integrated exhaust system of a median barium concentration of 0.3 mg/m3 (range 0.1 – 1.5 mg/m3). All figures given are mean time weighted average values.
None of the stick electrode workers had applied barium-containing consumables before. Out of the flux cored wire welders three had been welding with barium-containing consumables in the week before the study started, another two some weeks before. The pre-exposure Ba levels in urine and plasma did not show any influence due to this previous exposure.

Each day pre- and postshift urine spot samples and plasma from venous blood samples were taken. An increase of the internal dose in plasma as well as in urine was observed over the one-week study. It was found in the shape of sawteeth with relative maxima after shift and relative minima in the preshift specimens. In stick electrode welders the maximium median concentrations in urine were found on Wednesday after shift, to have a median value of 101.5 µg/l (89.1 µg/g creatinine) and a maximum single concentration of 407 µg/l (370.6 µg/g creatinine). Flux cored wire welders, who did not apply the exhaust device, experienced the highest median barium concentrations in urine, on Friday after shift, with a median of 113.1 µg/l (77.3 µg/g creatinine). In this case the maximum individual concentration was 313.8 µg/l (287.9 µg/g creatinine).
In accordance with the effective reduction of the external exposure by the integrated local ventilation system, the flux cored wire welders using this opportunity had the lowest renal barium elimination. In these the highest values were also found in the Friday postshift urine specimens with a maximum median concentration of 44.3 µg/l (49.2 µg/g creatinine). The maximum individual concentration was 63.2 µg/l (179.5 µg/g creatinine).
The behaviour of the renal barium excretion is shown in Figure 1.
In plasma the interindividual as well as the intra-individual variation of the barium concentrations was lower than in the urine specimens.
Also in this biological fluid there was a sawteeth-like increase to be observed. In all three groups of the welders the highest barium concentrations were found on Friday after shift. At this time in stick electrode welders the median plasma concentration was 24.7 µg/l and the highest single value was 63.4 µg/l.

In flux cored wire welders without the application of local exhaust the highest median concentration was 16.6 µg/l, the maximum individual concentration being 74.0 µg/l. Again, flux cored wire welders, who used the local ventilation system experienced the lowest internal Ba load in plasma with a maximum median concentration of 4.4 µg/l and the highest single value of 7.9 µg/l. The results are shown in Figure 2.

On average there was good correlation between external and internal exposure. The coefficient of correlation was best for the concentrations in plasma after shift of the same day with r = 0.63 (Figure 3). The correlation with the barium concentrations in the postshift urine specimens was less striking with r = 0.44 for the liter-reference and r = 0.47 for the creatinine-reference (Figure 4). Nevertheless, all these correlations were statistically significant (p = 0.05). Even weaker was the correlation of the external barium exposure with the preshift urine concentrations of the next day with r = 0.40 (liter-reference) and 0.36 (creatinine-reference). Also this correlation was significant (p = 0.05).

The correlation of the barium concentrations within both the biological matrices was also good. It shows a coefficient of correlation of r = 0.60 (liter-reference for the urine levels) and 0.62 (creatinine-reference of the urine levels) in the post-shift specimens of the corresponding days. The correlation of the concentrations in plasma after shift and in urine of the next morning was r = 0.74 (liter) and 0.55 (creatinine) respectively. The results are shown in Figure 5.

As can be seen from the course of the barium concentrations in the biological materials, the values on median base do not normalize completely by Monday morning after a free weekend (day 12 of the study). This fact is mainly evident for the plasma values. The differences before and after welding with barium-containing consumables were partly significant (p = 0.05). On the other hand, the preshift Ba concentrations in plasma and urine on Monday after the weekend were within the range of the pre-exposure values. So, a slight accumulation, which is probably not toxically important, may be seen after high long-term exposure to soluble barium compounds.

The biological half life of barium both in plasma and in urine was calculated between 10 and 18 hours in all cases of this study. This is in good agreement with the previous experimental results.

Biological indicators of health effects

In the literature there are only very few studies on health effects in workers occupationally exposed to soluble barium compounds.
The informal notice that no sure health effects were seen in workers, who had been exposed to Ba nitrate led to the evaluation of the TLV in the USA (ACGIH 1980). Essing et al. found some excess of chronic and even obstructive bronchitis in soapstone workers who had been smokers. Both the studies did not involve suitable sensitive and specific methods to detect early effects of soluble barium. The already mentioned study by Zschiesche and coworkers (1989 and 1992) included the following investigations: Anamnesis, neurological investigation, determination of heart beat rate and blood pressure, ECG with limb and precordial tracings each day before and after shift; permanent two channel recording of ECG over 12 days; quantification of electrolytes in serum (Na, K, total and ionized Ca, Mg), acid-base-status each day before and after shift; total protein in serum, protein electrophoresis in serum and sensitive tubular nephrogenic enzymes (N-acetyl-β-D-glucosaminidase, alanineaminopeptidase) before and during the trial.

Out of these parameters only potassium showed a reduction of the plasma level in some welders down to 2.9 mmol/l. Nevertheless, the intra-individual potassium levels of these welders varied markedly and became partly normal again, even if the Ba exposure continued. Furthermore, no dose–effect pattern could be recognized from the values.

All other parameters including detection of premature heart action, disturbance of heart repolarization, sensoric and motoric disorders including dynamometry did not show any newly upcoming impairments, no differences before and after shift and no trends during the trial compared to the basic data collected during two days before when welding with non-barium containing consumables.

Conclusions

Summarizing all data published on biological monitoring, it is obvious that only limited knowledge on the basic barium level in blood and urine respectively of the general population is present. Except for two studies, in particular no reliable serum or blood concentrations have been published.

The data on biological monitoring of the environmental exposure show great variations interindividually as well as intra-individually; to some degree also greater differences between various studies are evident for the urine concentrations. Mainly the study by Zschiesche and co-workers (1989 and 1992) shows a wider range of the Ba concentrations in biological material.
Two other studies by Schramel et al. (1985) and by Minoia et al. (1990) show smaller variations. It is quite evident that the daily uptake of barium as well as the excretion may be strongly influenced by dietary factors, which may particularly affect the concentrations in urine spot samples (Sutton and Shepard 1973; Schramel et al. 1985.).
Taking together the results of all studies available, there seems to be an upper normal limit (upper 95% range, one-tailed) of about 10 to 15 μg Ba/l or μg/g creatinine in urine spot samples in the majority of investigations in Europe. The upper normal limits in serum and blood seem to be somewhat lower (around 5 to 8 μg/l).
There is only one extensive study on biological monitoring of workers who have been occupationally exposed to soluble barium compounds.
In this investigation the overlap of 'normal' values with the results of biological monitoring even after heavy external exposure seems to be wide. Therefore, at the present state of knowledge BM of barium seems preferably applicable on group basis and for the demonstration of any change of exposure in the course of time. Single spot values may probably not be able to demonstrate or disprove an occupational exposure, except where relatively high Ba concentrations are found.

Research needs

Further studies on the environmental internal exposure in various geographical regions;

the evaluation of a correlation between normal barium concentrations in urine and serum/blood and of the external load by drinking water and food;

further studies on the internal exposure of workers who are occupationally exposed to various soluble Ba compounds, such as nitrate, chloride, fluoride or carbonate, whether after long-term exposure or with intermittent exposure;

evaluation of a possible change of biological half-life of barium in different body fluids with regard to duration of exposure;

further studies on acute or chronic adverse effects of soluble barium compounds on occupationally exposed persons;

the evaluation of a minimum toxic dose or concentration after long-term exposure for man.

Analytical methods

Determinations of barium with conventional analytical reagents is unsatisfactory for microquantities. Inductive coupled plasma (ICP)-atomic emission spectrometry and electrothermal atomic absorption spectrometry (ETAAS) are suitable for the determination of barium in biological body fluids (serum/plasma, urine), both in the physiological and occupationally relevant ranges without time-consuming sample processing. Because of the absence of line overlaps at the wavelengths for barium and because of the high spectral resolving power of the commercially available ICP spectrometers, the specificity of the ICP method may be considered certain. ICP-emission spectrometry has a whole range of advantages for barium determination in comparison with atomic absorption spectrometry with electrothermal atomization, which is otherwise frequently used for metal determinations in biological material. Thus, ETAAS is relatively error-prone because barium absorbs at long wavelengths which lie in the range of the emission energies of the graphite furnace. Carbide formation must be expected with barium as well. In addition, the ICP method uses aequous standards for calibration and a standard addition procedure can be avoided (Angerer and Schaller 1988).

For the ETAAS determination of barium the spectrophotometer has to fulfil several optical specifications, especially to measure reliably in the long wavelength ranges (553.6 nm). After dilution of the samples the barium concentrations can be determined by standard addition technique and background correction. The ICP shows a detection limit of around 0.2 µl, the ETAAS of 2 µg/l.

A high risk of contamination must be expected in assays of low barium levels. To prevent exogenous contamination all bottles and tubes used for specimen collection and sample treatment must be specially cleaned with 10% nitric acid and ultrapure water.

Table 2: Plasma or serum, blood and urine barium concentrations of occupationally non-exposed persons found in the recent literature.

Reference	Specimens	No. of Specimens	No. of Subjects	Mean (standard deviation) or Median	Range	Method
Zschiesche et al. 1987 and 1989	Serum	83	18	2.0 µg/l	<1-38.8 µg/l	ET-AAS
Minoia et al. 1990	Blood	25	25	1.2 ± 0.6 µg/l	0.47-2.9 µg/l	ET-AAS and/ or ICP (not specified)
Zschiesche et al. 1987 and 1989	Urine	106	18	9.3 µg/l	<1-72.3 µg/l	ET-AAS
Zschiesche et al. 1987 and 1989	Urine	106	18	7.0 µg/g creatinine	<1-78.2 µg/g creatinine	ET-ASS
Schramel et al. 1985	Urine	25	25	4.5 ± 4.2 µg/l	0.2-12.7 µg/l	ICP
Schramel et al. 1985	Urine	25	25	6 ± 6 µg/day	0.2-21 µg/day	ICP
Dare et al. 1984	Urine	3	3	---	1.8-4.7 µg/l	ET-AAS
Minoiai et al. 1990	Urine	35	35	2.7 ± 1.5 µg/l	0.25-10.1 µg/l	ET-AAS and/or ICP (not specified)

Table 3: Course of the barium concentrations in urine and plasma in some welders in the pre-exposure phase of the study (Zschiesche et al. 1989). Examples are given for generally low, generally high and for variable barium concentrations. All values are given as µg/l.

Welder no.	Material	Day							
		1		2		3		4	
		Pre-shift	Post-shift	Pre-shift	Post-shift	Pre-shift	Post-shift	Pre-shift	Post-shift
1.1	Urine	1.5	2.4	2.3	2.7	-	-	-	-
	Plasma	0.5	0.3	0.2	0.8	-	-	-	-
3.2	Urine	18.4	19.4	7.0	46.8	22.9	47.0	36.1	38.6
	Plasma	6.6	7.0	6.4	38.8	-	-	-	-
1.4	Urine	7.4	4.3	44.3	14.3	-	-	-	-
	Plasma	8.0	1.0	1.5	3.7	-	-	-	-

- = no specimens taken (weekend)

Table 4: External exposure (personal air sampling) of welders when using coated stick electrodes without fume extraction. Given are time weighted averages (TWA) of total fume concentrations in the breathing zone, of barium concentrations and the barium content in the total fume (%).

Welder	Day	Fume total (mg/m³) TWA	Ba-air (mg/m³) TWA	Ba-air (% total fume) TWA
1.1	5	27.5	7.7	28.1
	6	11.6	2.3	20.9
	7	18.9	5.2	27.4
	8	12.6	3.0	24.2
	9	21.5	6.1	28.5
1.2	5	13.8	2.8	20.2
	6	15.8	3.3	19.2
	7	72.6	19.2	26.4
	8	29.2	6.1	21.0
	9	16.7	4.4	26.1
1.3	5	5.3	4.5	84.7
	6	9.1	4.4	48.6
	7	0.8	0.1	16.7
	8	8.3	3.5	42.4
	9	8.7	2.1	24.6
1.4	5	11.5	5.4	46.4
	6	14.1	6.1	43.6
	7	37.0	15.1	40.9
	8	58.7	13.9	23.7
	9	81.7	18.4	22.5
1.5	5	n.w.	0.6	-
	6	1.5	0.2	10.0
	7	31.6	12.2	38.7
	8	48.0	10.9	22.7
	9	4.5	17.0	22.8
1.6	5	8.7	4.4	50.3
	6	16.2	1.7	10.2
	7	57.8	15.3	26.5
	8	151.4	14.9	9.8
	9	88.7	15.8	17.8
1.7	5	67.3	22.7	33.7
	6	61.0	20.6	33.8
	7	n.w.	3.1	-
	8	n.w.	1.2	-
	9	8.3	2.5	30.4
1.8	5	n.w.	0.1	-
	6	6.0	0.2	4.0
	7	n.w.	0.9	-
	8	8.7	1.8	20.6
	9	15.6	4.1	26.2

Table 5: External exposure of welders (personal air sampling) when using flux cored wires without fume extraction. Given are time weighted averages (TWA) of total fume concentrations in the breathing zone, of barium concentrations and the barium content in the total fume (%).

Welder	Day	Fume total (mg/m^3) TWA	Ba-air (mg/m^3) TWA	Ba-air (% total fume) TWA
2.1	5	3.1	0.3	10.7
	6	0.6	0.2	24.8
	7	1.1	0.2	19.7
	8	2.9	0.5	16.5
	9	3.6	0.5	13.7
2.2	5	2.6	0.2	8.6
	6	1.9	0.2	8.8
	7	1.4	0.2	12.2
	8	2.7	0.3	9.9
	9	4.4	0.6	12.8
2.3	5	2.4	0.2	7.1
	6	0.8	0.1	18.1
	7	2.6	0.4	15.2
	8	1.3	0.1	11.0
	9	4.8	0.5	10.6
2.4	5	1.9	0.2	9.5
	6	3.0	0.4	12.4
	7	1.3	0.2	14.8
	8	5.3	1.0	19.3
	9	3.1	0.4	14.3
2.5	5	1.9	0.1	6.2
	6	4.2	0.3	7.3
	7	1.5	0.2	12.1
	8	2.7	1.5	56.5
	9	4.3	0.6	13.2
3.1	5	7.8	1.4	17.4
	6	7.8	1.7	22.1
	7	8.1	1.1	13.8
	8	12.2	2.3	18.5
	9	23.5	3.8	16.1
3.2	5	35.4	5.0	13.8
	6	21.8	3.2	12.5
	7	18.4	1.9	10.4
	8	5.5	0.3	6.2
	9	13.7	2.0	14.5
3.3	5	14.1	2.0	13.4
	6	9.4	2.4	25.2
	7	4.3	1.6	35.9
	8	6.4	0.7	11.5
	9	15.8	2.3	14.8
3.4	5	10.5	1.2	9.2
	6	24.7	3.5	14.1
	7	6.2	1.1	17.7
	8	5.7	0.5	9.0
	9	16.0	2.3	14.4
3.5	5	31.2	4.9	15.9
	6	42.1	6.0	14.3
	7	12.3	1.7	15.6
	8	4.2	0.4	10.5
	9	16.6	2.4	14.6

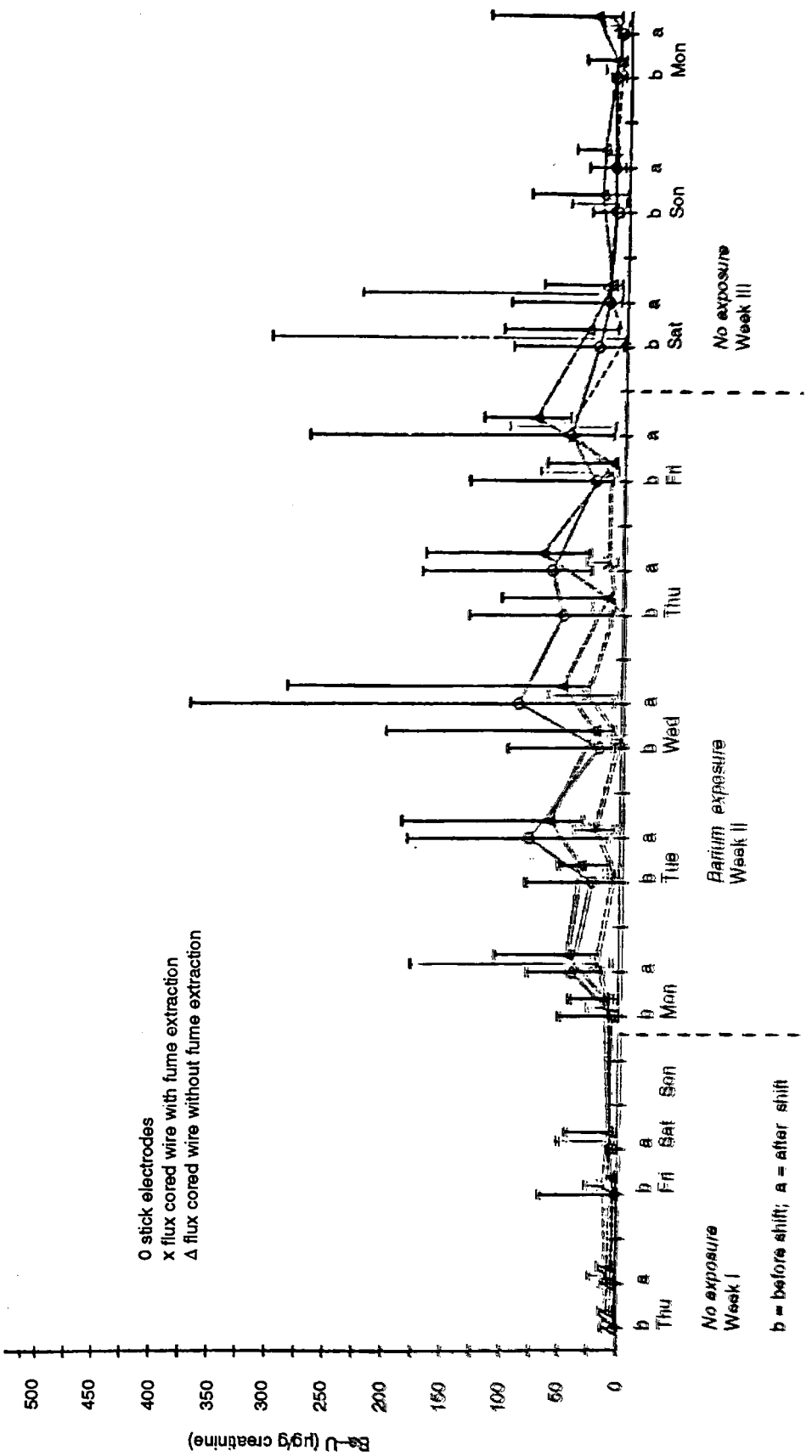

Fig. 1 Barium concentrations in urine (µg/g creatinine) before, during and after barium exposure. Given are the medians (connected dots) and ranges of every sampling time for each group of welders [b = before shift; a = after shift] (from Zschiesche et al. 1992).

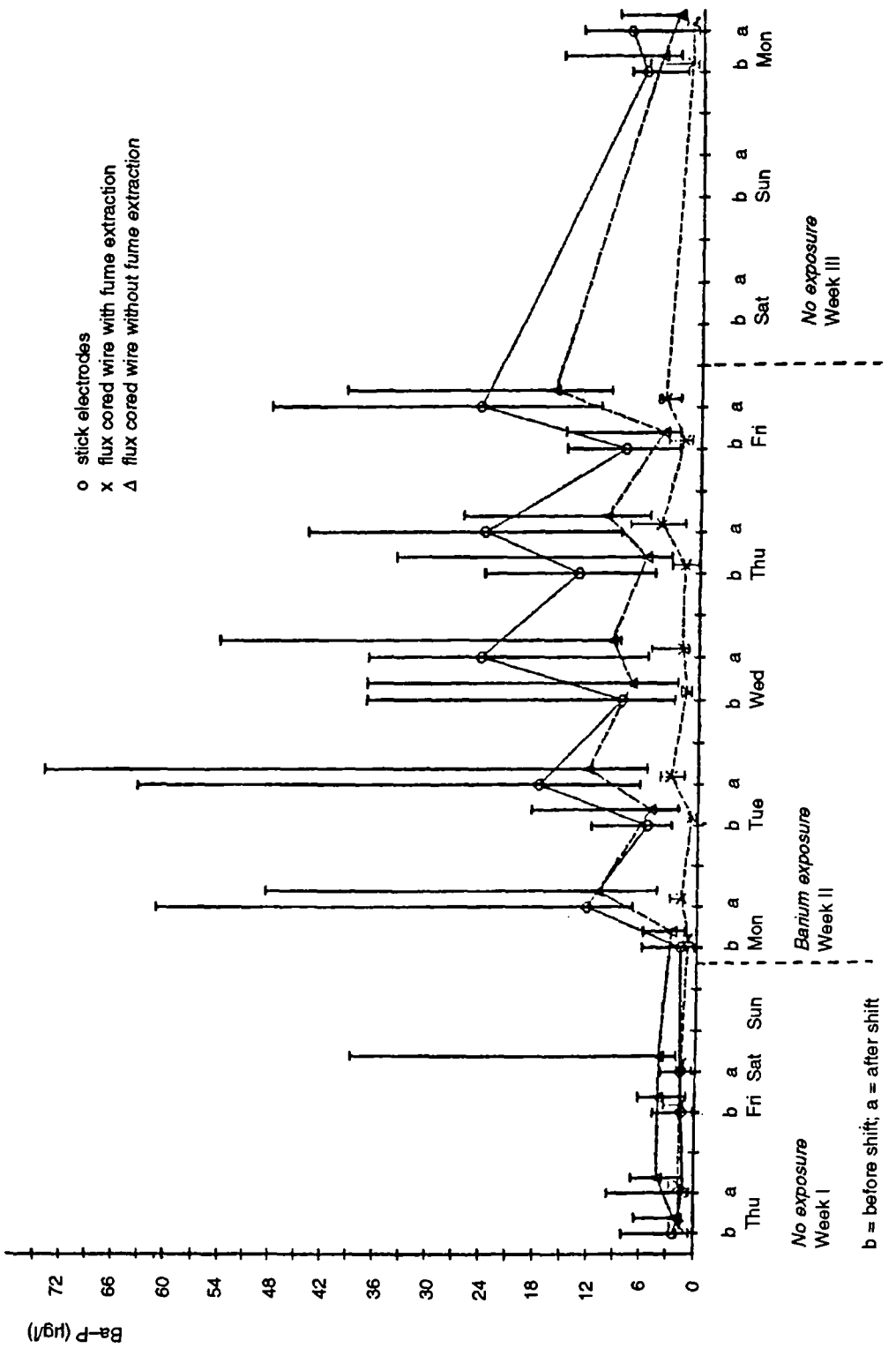

Fig. 2 Barium concentrations in plasma (µg/l) before, during and after barium exposure. Given are the medians (connected dots) and ranges of every sampling time for each group of welders [b = before shift; a = after shift] (from Zschiesche et al. 1992).

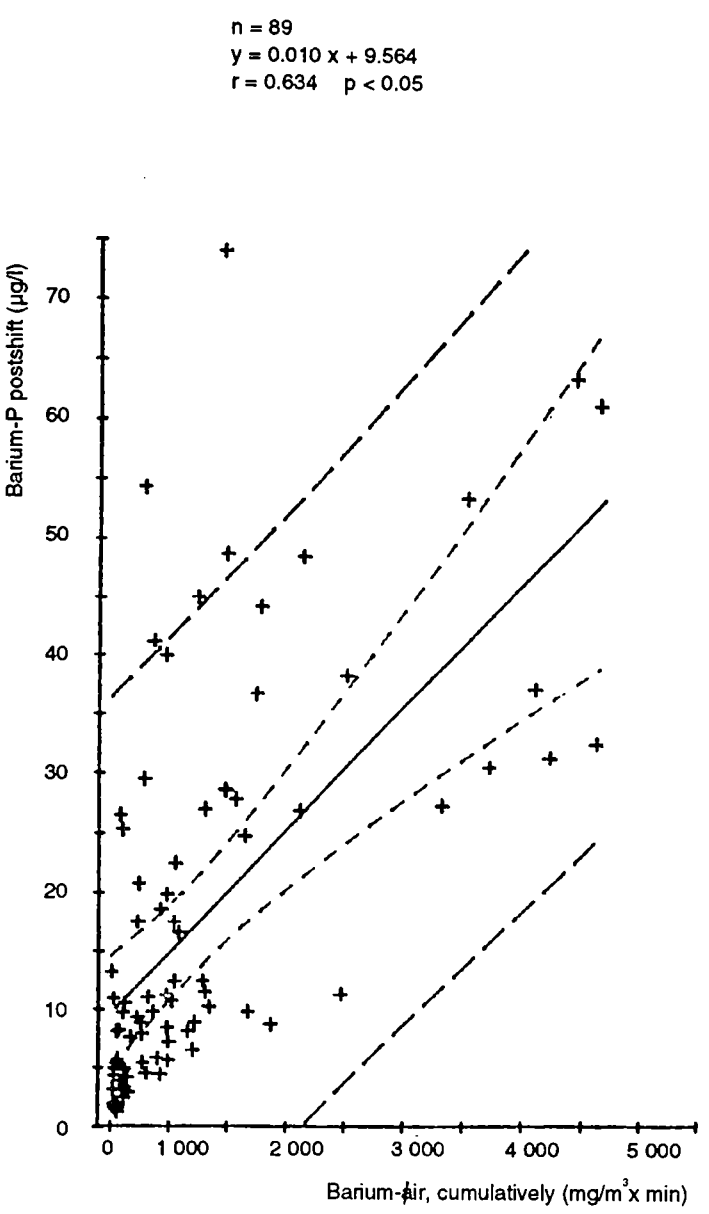

Fig. 3 Correlation between the external barium exposure in personal air sampling and the internal barium concentration in plasma of the corresponding day after shift of each welder and each day. The external Barium concentration is expressed cumulatively as concentration multiplied by the duration of exposure each day in minutes (from Zschiesche et al. 1992).

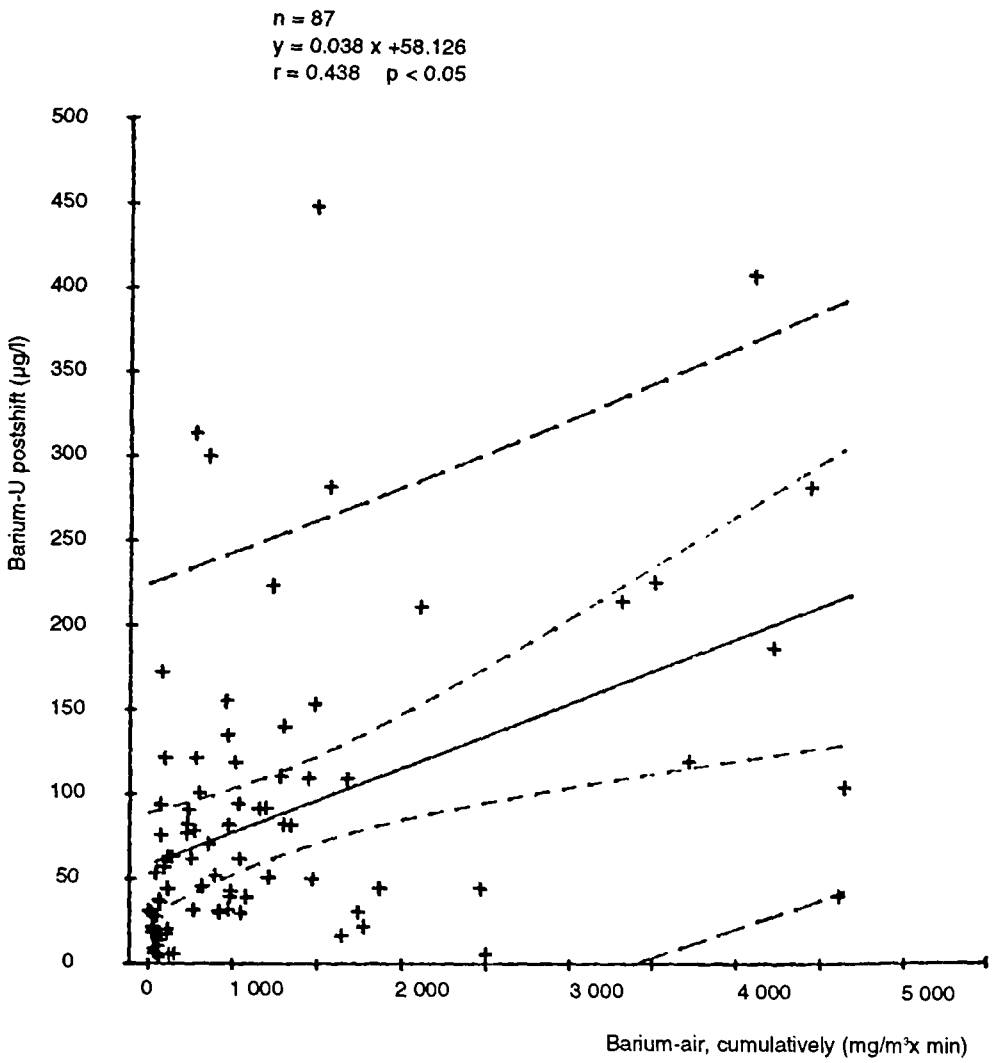

Fig. 4 Correlation between the external barium exposure (personal air sampling) and the internal barium concentration in urine of the corresponding day after shift of each welder and each day. The external barium concentration is expressed cumulatively as concentration multiplied by the duration of exposure each day in minutes (from Zschiesche et al. 1992).

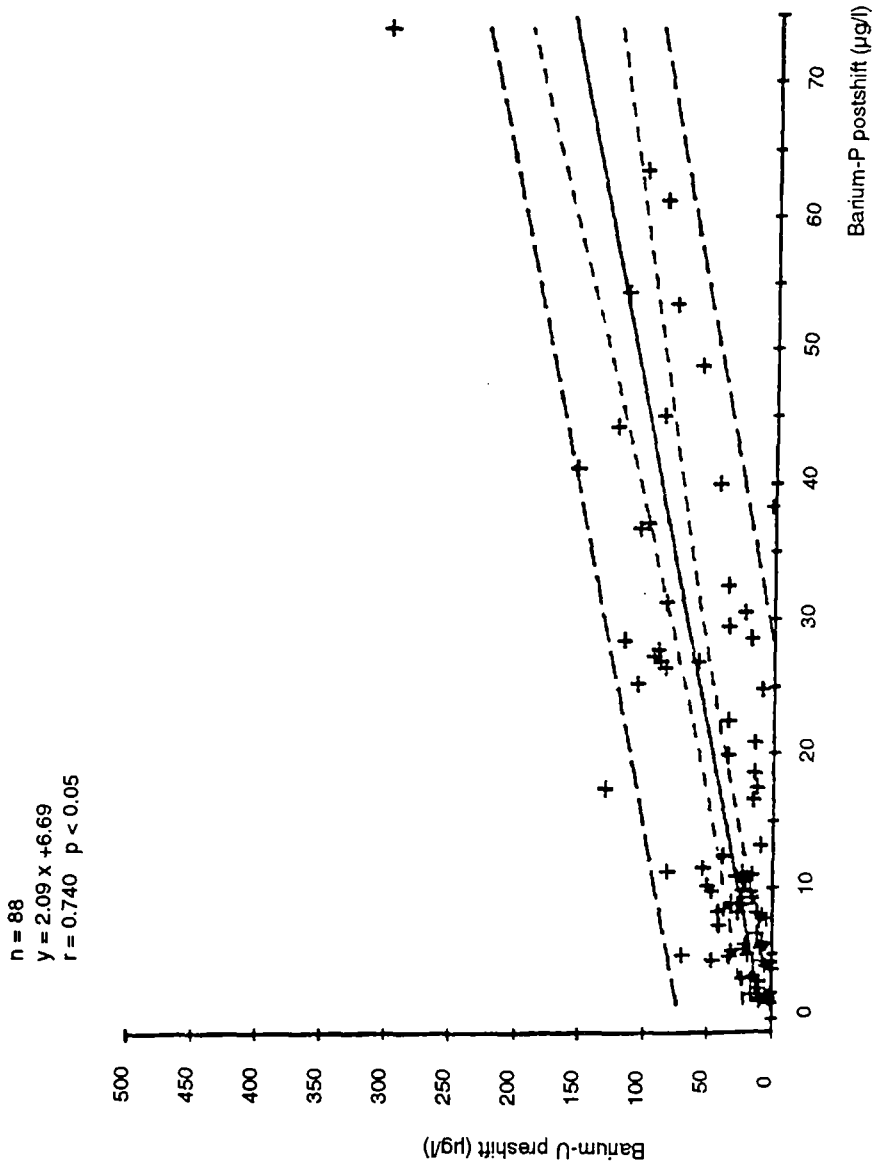

Fig. 5 Correlation between the internal barium exposure in plasma postshift samples versus urine barium concentrations before shift of the following day (from Zschiesche et al. 1989 and 1992).

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Biological indicators for the assessment of human exposure to industrial chemicals

Hexane and methyl ethyl ketone

A. Mutti

I–Hexane

Summary

Hexane is a major component of the rubber solvent fraction distilled from petroleum. Occupational exposure occurs in a number of activities but especially in the production and use of glues, paints, varnishes and printing inks. Shoemakers, however, make up the main occupational target group.

Several outbreaks of hexane-induced peripheral neuropathies have been reported; neurophysiological changes have also been found in subjects exposed to relatively low airborne concentrations.

Inhalation is the main absorption route; the lung uptake is about 20% of inhaled hexane. Percutaneous absorption may also occur, but it is thought to be very low. About 10% of the total uptake is excreted unchanged through exhaled air, trace amounts being detectable in urine.

Biotransformation involves the mono-oxygenase system, giving rise to 2-hexanol, 2,5-hexanediol, 5-hydroxy-2-hexanone, and 2,5-hexanedione (HD). Such metabolites are conjugated in part with glucuronic acid, and then excreted in urine.

Hexane concentrations in blood, alveolar air and urine are correlated with current exposure. Time-weighted average exposure is better mirrored by the urinary excretion of metabolites, among which HD seems to be the best indicator for monitoring purposes. In fact, urinary HD is both correlated with exposure and is thought to play a pathogenetic role in hexane-induced neuropathy.

Owing to its relatively long half-life, HD tends to accumulate over the working week. Such a behaviour is toxicologically important and should be considered when implementing biological monitoring programmes.

Urinary levels of 3 mg/g creatinine and 5 mg/l (hydrolysed samples) would correspond to 8h–TWA concentrations of 50 ppm of hexane in the air.

Very recently, it has also been suggested that hydrolysis might lead to the formation of interfering substances thus artefactually increasing 2,5-HD levels in urine samples from subjects exposed to low hexane concentrations. About 200 μg/l of 2,5-HD in samples undergoing simple extraction would correspond to hexane airborne concentrations of 50 ppm.

Hexane

Older name: n-hexane
Synonym: hexyl-hydride

Chemical and physical properties

Colourless, flammable *liquid*		
Boiling point		: 68.7 °C
Melting point		: 95.6 °C
Vapour pressure	(15.8 °C)	: 100 mmHg (13.3 KPa)
	(20 °C)	: 124 mmHg (16.5 KPa)
Vapour density		: 3.0 (air = 1 at the boiling point of hexane)
Flash point		: –30 °C
Solubility		: insoluble in water (0.014 g/100 ml at 20 °C); soluble in ether and chloroform, 50 g in 100 ml ethanol
CAS-Number		: 110-54-3
Formula		: C_6H_{14}
		CH_3-CH_2-CH $_2$-CH_2-CH_2-CH_3
Molecular weight		: 86.20
1 ppm = 3.52 mg/m^3		
1 mg/m^3 = 0.284 ppm		

Production

Hexane is produced by distillation of petroleum. Commercial hexane also contains four isoparaffinic isomers (2-methylpentane, 3-methylpentane, 2,2-dimethylbutane, 2,3-dimethylbutane) as well as methylcylopentane, cyclohexane, and minor amounts of other hydrocarbons in the C_5-C_7 range. Certain solvent mixtures also include aromatic or chlorinated hydrocarbons and ketones.

Industrial exposure

Hexane is widely used in food-oil extraction and as a solvent of glues, paints, varnishes and printing inks. Pure hexane is used as a laboratory reagent, mainly for high performance liquid chromatography.

An estimated 2 500 000 workers are potentially exposed to hexane in the United States, where 500 million pounds were used annually in 1985 (Dunnick et al., 1989). Although its use has been reduced in recent years, hexane is still ubiquitous in the shoe and leather industry. Table 1 summarizes the typical levels of exposure recorded during field surveys or metabolic studies on occupationally exposed workers. Over recent years, there has been a tendency towards a reduction of exposure to hexane in industry, achieved either by exhausting vapours generated during adhesive drying or by substituting it with less harmful solvents, or both.

Table 1: Exposure to hexane in the shoe industry

No. of samples	Median (mg/m^3)	Range (mg/m^3)	References
41	160	32-500	Perbellini et al., 1981
58	350	50-780	Mutti et al., 1981
30	59.6	15-195	Imbriani et al., 1984
10	243	8-1143	Mutti et al., 1984
20	59.0	7-232	De Rosa et al., 1981
128[1]	35	7-102	Ahonen and Schimberg, 1988

[1] Four workplaces

The NIOSH has recommended that the permissible exposure limit (PEL) be reduced from 500 to 100 ppm (350 mg/m^3), with a ceiling level of 510 ppm (1 800 mg/m^3) averaged over a 15-minute period (Mackinson et al., 1981). The current ACGIH-recommended threshold limit value (8h-TWA) is 50 ppm (180 mg/m^3).

Effects on humans

Like many other organic solvents, which by definition are inert chemicals, hexane has long been considered to be a relatively safe substance and for that reason it has been introduced in the shoe industry as a substitute for the much more toxic benzene. For the same reason, nearly 400 cases of 'shoemakers' polyneurophathy' occurring in Italy over the 15 years up to 1976 (published cases reviewed by Abbritti et al., 1976) were attributed to other agents, mainly tri-ortho-cresyl-phosphate (TOCP), the possible role of hexane exposure being systematically overlooked.

Neurotoxic effects

In 1967, the earliest cases linking hexane exposure to peripheral neuropathy were reported in Japan (Yamada, 1967). Later, an additional 93 cases involving sandalmakers exposed to 500-2 500 ppm of hexane for several months were reported (Yamamura, 1969).

Little attention was paid to these reports, until a similar neuropathy involved 86 workers exposed to methyl-n-butyl ketone (MnBk) and methyl-ethyl ketone (MEK) in a plastic coating and printing plant (Billmaier et al., 1974). MnBk has been identified as an aetiological agent, but it is likely that MEK also played a potentiating role (Saida et al., 1976). It became thus apparent that hexacarbons could induce peripheral neuropathy, possibly through the formation of a common reactive metabolite. Since then, hexane has been recognized as the probable cause of peripheral neuropathy in hundreds of cases involving shoemakers, mainly home workers, in various countries.

Abuse of commercial glues and hexane-containing solvents has also been associated with peripheral neuropathy (for review, see O'Donoghue, 1985). In either cases, axonal degeneration has been recognized as the underlying pathological change, characterized by a central-peripheral distal distribution. The typical lesion is the 'onion bulb' or focal axonal swelling 'giant' axons being formed by paranodal accumulation of neurofilaments and mitochondri. Myelin damage has usually been regarded as secondary effect of axonal swelling (Spencer and Schaumburg, 1977).

The clinical course is insidious and develops over several weeks to months, leading to bilateral, symmetrical, sensorimotor peripheral neuropathy. Sensory changes show a glove and stocking distribution and involve loss of touch, vibration and temperature sensation. In more severe cases, motor disturbances are apparent, involving either hands or feet, or both. Muscle weakness makes it difficult to grasp objects, e.g. glasses or cups, and to go upstairs. Subjective symptoms include headache, tiredness, nausea, anorexia. Following removal from exposure, the progression of clinical signs may continue for several weeks. The prognosis is usually good, but mild to moderate cases require several months for recovery (Cianchetti et al., 1976).

Exposure-response relationship

Whereas exposure levels under conditions of abuse are very high – the air concentration exceeding thousands ppm – and are repetitive in order to achieve and maintain an euphoric state, much lower levels usually occur in industry (Table 1). Because of their retrospective nature, almost no case reports include exposure conditions in their description. Furthermore, most reported cases occurred before the possible aetiologi-

cal role of volatile substances was suspected. As a result, it is very difficult to link a definite exposure pattern and/or level to the outcome. However, though limited, evidence about the occurrence of an exposure-response relationship and the existence of a threshold does exist.

Exposure in industries where cases of polyneuropathy have been reported were usually in the range of 500 to 1 500 ppm and lasted several months. Co-exposure to other compounds with unpredictable interactions with hexane metabolism also occurred. However, a couple of reports refer to levels ranging from 60 to 240 ppm and 30-1 150 ppm (105-4 060 mg/m^3) (Table 2). This table is of course aimed at showing the difficulties in establishing a threshold rather than at estimating the incidence of hexane-induced polyneuropathy, which is certainly much greater than that arising from cases published in international journals. For example, respectively 678 and 119 additional cases of subclinical and clinical neuropathy due to hexane were diagnosed in six Italian occupational health institutes during the period 1976-80 (Chiesura, 1981). Over the same period, exhaustion systems were lacking in some 40% of Italian plants, where exposure levels exceeding the ACGIH-recommended TLV (180 mg/m^3) were found in a similar proportion, i.e. 37.7% (De Rosa et al., 1981).

In a cross-sectional study on currently exposed workers, a significant reduction in median nerve motor conduction velocity was detectable in workers exposed to levels giving rise to a cumulative exposure (hygienic effect x years) exceeding 20 when the TLV was set at 360 mg/m^3 (Mutti et al., 1981). In a subsequent survey, neurological complaints and changes in motor nerve conduction velocity (MCV) were found in workers exposed to median values of 362 mg/m^3. Abnormal findings were also significantly over-represented in a subgroup of workers with median exposure levels of 173 mg/m^3 (Mutti et al., 1982a, 1982b). In a small group of heavily exposed subjects (median levels 448 mg/m^3) with peaks up to 5 000-7 000 mg/m^3 (when exhausters had broken down), abnormal somatosensory evoked potentials and/or nerve conduction velocities were found in 6 out of 15 workers (Mutti et al., 1982c). The latter study was carried out three months after substantial improvements in the working environment lowered exposure to trace amounts. Thus, hexane-induced electrophysiological changes should be regarded as chronic or slowly reversible effects. According to the above findings, the current ACGIH-recommended TLV (180 mg/m^3) should be regarded as a relatively safe exposure level. However, Sanagi et al. (1980) were able to show mild subclinical changes in muscle strength and nerve conduction velocity in a small group of workers exposed to 186 mg/m^3 on average, although they concluded that hexane vapour levels of less than 100 ppm for eight hours per day were not likely to produce a clinical neuropathy.

Table 2: Exposure in industries where cases of hexacarbon-induced polyneuropathy had been reported

No of cases	Solvent mixture	Exposure duration	level, ppm	Clinical findings	Reference
6	Hexane 64% Methyl-pentanes and cyclopentane	3-10 months	2 500	Sensorimotor polyneuropathy	Wada et al. 1965
93	Hexane 70% Toluene	6 months	500-2 500	Sensory in 100% Motor in 43% Optic in 3% MCV reduced in 50%	Sobue et al. 1968
3	Hexane 16% Acetone, methyl-pentanes, methyl cyclo-pentane	6-10 months	650-1 300	Sensorimotor Fibrillations at the EMG	Herskowitz et al. 1971
86	MnBk 10% MEK	Several months 9–36 months	331-516	Sensorimotor MCV slowing Progression after removal from exposure	Billmaier et al. 1974

No of cases	Solvent mixture	Exposure duration	level, ppm	Clinical findings	Reference
4	Hexane 12.5% Many others	5-7 months	60-240	Sensorimotor Fibrilations at EMG	Takeuchi et al., 1974
8	Hexane	?	30-1 150	Sensorimotor	Paulson et al., 1976

In a single published study, both biological monitoring and electroneurographic measurements were simultaneously performed, giving rise to some information about the dose-response relationship (Governa et al., 1987). A more detailed discussion of this study is given in the section dealing with the definition of biological limit values. It ought to be noted that electrophysiological measurements, especially nerve conduction velocities, may underestimate the occurrence of neuropathy when axonopathy is the underlying mechanism.

Mechanism of action

Excellent reviews covering experimental studies are available (O'Donoghue, 1985; Spencer et al., 1980). Thus, only a brief discussion will be reported here. Inhibition of glycolysis by 2,5-hexanedione (2,5-HD), the metabolite common to hexane and MnBk thought to be responsible for their neurotoxicity, may impair axonal transport functions (Spencer et al., 1980). Several enzymes involved in glycolytic and phosphorilative processes have been found to be inhibited by 2,5-HD (glyceraldehyde-3-phosphate dehydrogenase, fructose-6-phosphate kinase, and enolase). Inactivation of thiamine pyrophosphate was also suggested as the underlying mechanism of the 'dying-back' process (Shoental and Cavanagh, 1977).

Paranodal accumulation of neurofilaments has been attributed to 2,5-HD-induced formation of pyrroles and subsequent cross-links of cytoskeletal components (Saida et al., 1976). However, a negative relationship has been found between the potency of neurotoxic hexacarbons (in terms of latency) and the number of axonal swellings, thus suggesting that the latter phenomenon is a secondary effect and not a requirement for axonal neuropathy (Krasavage et al., 1978).

Recently, Abou-Donia et al. (1988) confirmed the involvement of cytoskeletal proteins in the molecular pathogenesis of hexacarbon neuropathy, the inhibition of phosphorylation of neurofilament protein being an associated change. Whatever the mechanism underlying the dying-back process, the formation of a Γ-diketone is an essential step. In fact, whilst A, B and Δ diketones were ineffective, other Γ-diketones could experimentally induce peripheral neuropathy in animals (Spencer and Schaumburg, 1977). More importantly, a relationship has been found between the relative neurotoxicity of hexane metabolites and blood levels of 2,5-HD achieved in rats treated by gavage (see Fig. 1, from Krasavage et al., 1980).

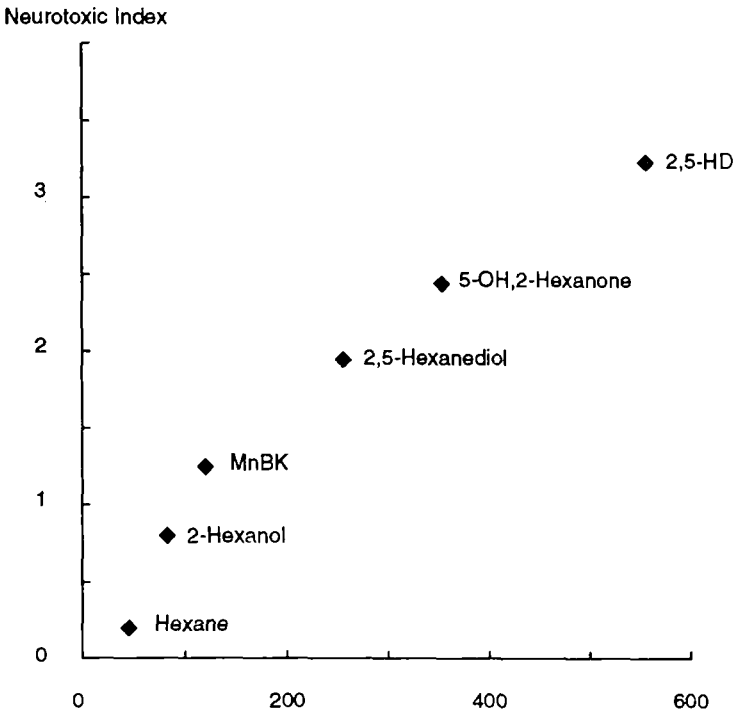

Fig. 1. Relationship between the peak serum levels of 2,5-hexanedione and the severity of neurotoxic changes following the administration of hexane metabolites. (Adapted from Krasavage et al., 1980.)

Metabolism

Absorption

Uptake of hexane occurs primarily through inhalation of vapours. Although percutaneous absorption has been suggested as the major route of entry in man (Nomiyama and Nomiyama 1974), experiments in guinea pigs contradicted such an assumption (Jacobson et al., 1982). On the other hand, cases of polyneuropathy have frequently been reported in subjects not having direct contact with glues or solvents, which indicated the aetiological role of volatile substances dispersed in the working environment under poor hygienic conditions (Abbritti et al., 1976). Despite the toxicological importance of the respiratory route, pulmonary retention of inhaled hexane is relatively low, figures from 16.4 to 25.2% (median 20%) having been consistently found by using different methods (Veulemans et al., 1982; Brugnone et al., 1983; Mutti et al., 1984). A value as low as 5.6% was found by Nomiyama and Nomiyama (1974).

Distribution

Data of distribution are mainly derived from *in vitro* experiments aimed at evaluating the solubility and the tissue/blood partition coefficient. Hexane is poorly soluble in blood, whereas it is highly soluble in fat, the fat/blood partition coefficient being 130 (Table 3).

Table 3: Solubility of hexane in blood and human tissues (From Perbellini et al., 1986)

Tissues	Air/tissue partition coefficient	Tissue/ blood partition coefficient	Relative mass of the organ	Relative blood supply, per cent of body weight	Half-life (minutes)
Blood	0.8	6.4			
Brain	5.0	6.2	2.3	0.14	7.3
Liver	5.2	6.5	2	0.24	3.7
Kidney	3.0	3.7	0.5	0.22	0.6
Muscle	5.0	6.2	43	0.15	90
Heart	2.8	3.5	0.4	0.04	3
Lung	1.0	1.2	1.6	-	-
Fat	104	130	20	0.05	3 440

The distribution of solvents also relies on physiological parameters and is a dynamic phenomenon where a key role is played by perfusion. Whereas after single exposures the adipose tissue is expected to contain a relatively small fraction of absorbed hexane, repeated exposures lead to accumulation of the solvent in fat, owing to its long half-life in this compartment (Perbellini et al., 1986). On the contrary, vessel-rich organs (including the brain) receive relatively large amounts of hexane, which are, however, rapidly cleared from the tissue even without considering the proportion undergoing metabolic transformation.

Biotransformation

Hexane is metabolized by microsomal enzymes giving rise to several oxidation products. Probably due to steric hindrance at other sites of the molecule, 2-hexanol is the predominant oxidation product and is further oxidized to MnBk or 2,5-hexanediol, which are then transformed into 2-hydroxy-5-hexanone and subsequently into 2,5-hexanedione (Fig. 2). Other compounds have been found in urine from hexane-exposed subjects, e.g. γ-valerolactone and 2,5-dimethylfuran, but these sustances are thought to be formed during the gas chromatographic analysis from a precursor (Di Vincenzo et al., 1976).

Metabolic interferences

Metabolic interactions between hexane and other solvents occurring in commercial mixtures have been reported (Altenkirch et al., 1977). There is also evidence suggesting that methylethylketone (MEK) co-exposure potentiates hexane and MnBk neurotoxicity in various systems and models. Whereas attempts at inducing peripheral neuropathy in animals treated with MEK alone have been unsuccessful (Saida et al., 1976), hexane-induced neuropathy appeared sooner and in more animals when exposure to 9 000 ppm of hexane (eight hours per day, seven days per week for periods up to 19 weeks) was combined with 1 000 ppm of MEK (Altenkirch et al., 1978). *In vitro* models also demonstrated that combined MEK:hexane exposure of murine spinal cord explants shortened onset of neuropathological changes and lowered the threshold of dose-response relationship for hexane (Veronesi et al., 1984).

The mechanism by which MEK potentiates MnBk/hexane neurotoxicity is still unclear. MEK could act as a microsomal enzyme inducer (Couri et al., 1977). Such a hypothesis is, however, inconsistent with separate experiments showing that the recovery of hexane metabolites is actually reduced to one quarter rather than being increased after MEK co-exposure (Iwata et al., 1983b) and that 2,5-HD levels in the sciatic nerves of rats acutely exposed to hexane:MEK mixtures are actually lower than in nerves taken from animals exposed to equimolar concentrations of hexane alone (White and Bus, 1980). A tempting hypothesis has been put forward by Ralston et al. (1985) and has also been suggested by Ladefoged and Perbellini (1986) to explain similar effects due to acetone co-exposure.

According to these authors the lower recovery of 2,5-HD during co-exposure to acetone would be associated with a concomitant slowing in body clearance. However, it is more likely that toxicodynamic rather than toxicokinetic factors account for MEK potentiation of hexane neurotoxicity. It has been suggested that MEK competes with 2,5-HD for the same binding sites (Ralston et al., 1985). The question then arises as to whether MEK binding to noncritical sites may actually increase 2,5-HD binding to

critical sites unavailable to MEK. Other interactions have been investigated. Toluene and xylenes showed antagonistic effects (Takeuchi et al., 1983; Nylen et al., 1989) which would be easily explained by metabolic interferences greatly reducing the biotransformation of administered hexane (Perbellini et al., 1982b).

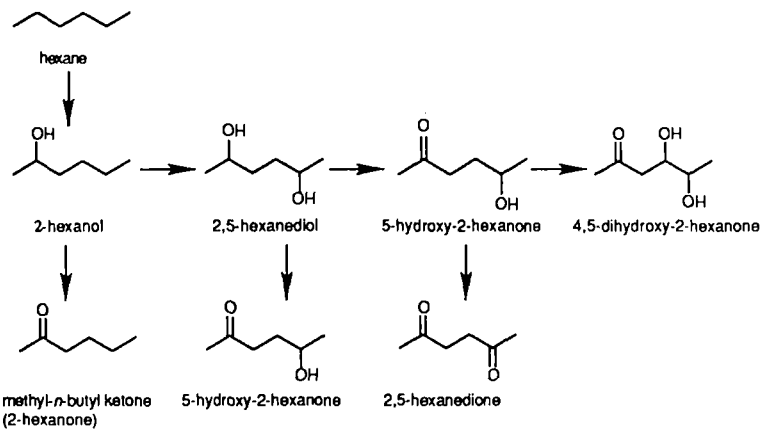

Fig. 2. Main hexane metabolites in mammals.

Excretion

About 15% of absorbed hexane is excreted unchanged through exhaled air during the post-exposure period (Fig. 3). Hexane concentration in the alveolar air during the post-exposure period follows a biphasic course with half-life of 11 and 99 minutes, respectively. These two phases might account for the clearance of hexane from the vessel-rich organs and from the muscle group, respectively. A third compartment gives a very small and undetectable contribution, owing to the slow release of the solvent from the adipose tissue where it tends to accumulate over the working week, the calculated half-life being approximately 60 hours (Table 3). Trace amounts of the solvent are recovered in the urine (Imbriani et al., 1984). Most hexane taken up is oxidized to alcohols and ketones.

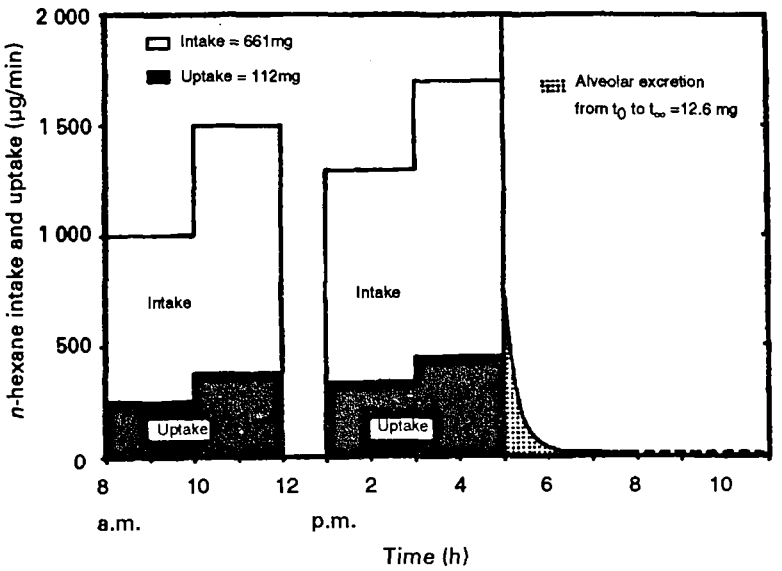

Fig. 3. Time course of total respiratory intake and absorption of hexane during eight hours of exposure (left) and of alveolar excretion during the post-exposure period (right) in a worker exposed to 243 mg/m^3 of hexane in the air (mean daily exposure). (Adapted from Mutti et al., 1984.)

Phase 2 of biotransformation involves the conjugation of these metabolites with glucuronic acid and possibly with other unidentified substances, since acid hydrolysis yields additional recovery of metabolites when it is performed after enzymatic hydrolysis with ß-glucuronidase/sulphatase (Fedtke and Bolt, 1986).

Since altogether the urinary excretion of the main metabolites (Fig. 2) accounts for a small fraction of absorbed hexane, one should conclude that most of the latter is either fragmented into smaller volatile substances or tightly bound to its target or carrier macromolecules in the body.

Biological indicators

The biological tests proposed for evaluating hexane exposure are the following:

- 2,5-hexanedione in urine;
- 2-hexanol in urine;
- hexane in expired air;
- hexane in blood;
- hexane in urine.

The reader should refer to the report on benzene in this series for a critical appraisal of methods of expressing results of analyses performed in urine (Lauwerys, 1979). One exception to such standardization procedures is represented by hexane in urine, which is thought to dynamically change in bladder depending on blood levels. As a result, it should not be either adjusted to constant specific gravity or expressed as a function of creatinine.

2,5-Hexanedione in urine

The gas chromatographic analysis of urine subjected to acid hydrolysis both preceded and not by enzymatic hydrolysis with ß-glucuronidase/sulphatase has been used by several authors (Perbellini et al., 1981; Iwata et al., 1983a; Mutti et al., 1984; Fedtke and Bolt, 1986; Ahonen and Schimberg, 1988).

A comparison between various gas chromatographic conditions and preparation procedures is also available (Perbellini et al., 1990; Kawai et al., 1990). Recently, reverse phase high performance liquid chromatography has also been proposed as a reliable method to measure 2,5-HD in urine (Marchiseppe et al., 1989). Although cumbersome, both these techniques may now be used for the routine monitoring of hexane exposure.

Reference values

Trace amounts of 2,5-HD are detectable in the urine of persons not occupationally exposed to hexane. They have been revealed by gas chromatography-mass spectrometry following extensive acid hydrolysis and subsequent extraction. The source of 2,5-HD is unclear. It might be originated either by an endogenous production of hexane, e.g. by lipid peroxidation, or by atmospheric contamination (Fedtke and Bolt, 1986).

According to the recent report of Kawai et al. (1990), however, 2-acetylfuran would confound 2,5-HD analysis in hydrolysed urine samples. Using a DB-1 column (60 m in length, 0.25 mm inner diametre, 0.25 μm in film thickness), these authors were able to separate 2,5-HD from a much greater amount (about four times) of acetylfuran, which showed the same retention time in a DB-WAX column (30 m in length, 0.25 mm inner diametre, 0.25 μm film thickness). Thus, although detectable, the levels of 2,5-HD in urine samples from subjects not occupationally exposed to hexane are actually very low and measurable only after extensive hydrolysis. In view of its confounding effects at very low exposure levels, such a practice should be avoided or carefully monitored.

It is now well established that 2,5-HD is the neurotoxic metabolite of hexane. Furthermore, the peak serum level reached after administration of precursors is correlated with the severity of neurotoxic changes, i.e. with the critical effect (Fig. 1). Thus, serum levels of 2,5-HD indicate not only exposure, but also internal dose, i.e. the effective dose at the critical organ. The measurement of 2,5-HD in serum is too elaborate and time-consuming for routine applications. The same concepts may, however, be easily extrapolated to urinary 2,5-HD. In fact, the peak level in serum has been found to occur in various mammalian species a few hours after exposure, with a time-lag similar to that necessary for the appearance of peak values in urine (Perbellini et al., 1982a).

Biological limit values

A single, though very interesting, report is available concerning the dose-response relationship between 2,5-HD in urine and the prevalence of electroneuro-myographic (ENMG) abnormalities (Governa et al., 1987). In this study, a statistically significant nonparametric correlation was found between end-of-shift 2,5-HD in urine and ENMG scoring (Kendall's T 0.4179, $p < 0.01$). The predictive validity of 2,5-HD-U with regard to the concomitant presence for ENMG abnormalities also suggested that this marker may be a useful substitute for ENMG for early detection of neurotoxic lesions at pre-clinical states (Table 5).

Although the threshold of 7.5 mg/l for 2,5-HD shows a high predictive validity (1.68), significant ENMG changes were found in three subjects (out of 40 examined) with 2,5-HD values of 3.0, 3.3, and 4.5 mg/l, respectively. Thus, the authors concluded that their data 'are not adequate to set any permissible urine concentration of hexane metabolites.' Similar findings have recently been reported by Bartolucci et al. (1990), who found that 2,5-HD levels of 5 mg/l or greater are associated with electrophysiological changes. These authors pointed out the high specificity and negative diagnostic value of urinary 2,5-HD with regard to ENeG abnormalities.

Table 5: Urinary concentration of 2,5-HD in post-shift urine spot samples as a predictor of ENMG abnormalities. The threshold for 2,5-HD was arbitrarily set at 7.5 mg/l (adapted from Governa et al., 1987)

Post-shift urinary concentration of 2,5-HD	Electroneuromyographic scoring		Total
	< 3	> 4	
< 7.5 mg/l	21	3	24
> 7.5 mg/l	5	11	16
Total	26	14	40

Sensitivity: 0.79
Specificity: 0.90
Validity: 1.69
Positive predictive value: 0.69
Negative predictive value: 0.84
Diagnostic value: 1.53

Good relationships between hexane concentrations in the working environment (8h-TWA) and the urinary excretion of 2,5-HD have been found by independent investigators (Perbellini et al., 1981; Iwata et al., 1983a; Mutti et al., 1984; Ahonen and Schimberg, 1988), though somewhat lower correlation coefficients have been reported by Kawai et al. (1990), who recommend hydrolysis be avoided to prevent artefacts. According to these authors, the best predictor of hexane exposure would be 2,5-HD obtained by simple extraction from urine: some 0.2 mg/l would correspond to exposure levels near the TLV. One should recognize, however, that such a method can only be applied if a mass-selective detector coupled with a gas chromatograph equipped with a capillary column is available.

The differences in the slopes of the regression lines reported by different authors may be accounted for by several reasons. The first one is the variable composition of commercial mixtures that may contain, or not, solvents interfering with hexane metabolism. In fact, the slope of the above relationship may be modified by co-exposure to MEK or to toluene. The second reason may be the different day of the week during which urine collection took place, since the ratio 2,5-HD in urine/hexane in air tends to increase over the working week. Thus, 100 mg/m^3 (8h-TWA) would correspond to about 1 mg/l of urinary 2,5-HD at the end of the first shift on Monday and to about 3 mg/l on Friday, intermediate values having been observed at the end of the other working days (Perbellini et al., 1985).

The study by Ahonen and Schimberg (1988), though involving only four subjects, offers some interesting data pointing to the first explanation. In fact, these subjects were exposed to mixtures containing different proportions of hexane and excreted different fractions of 2,5-HD with regard to absorbed hexane. The authors concluded that there was a non-linear accumulation at higher doses. However, the highest exposure levels were associated with the lowest exposure to interfering substances. A similar conclusion may be drawn from the comparative analysis of all published data (Table 6).

Finally, different preparation procedures might affect the proportion of 2,5-HD hydrolysed from urine. According to Kawai et al. (1990), the 2,5-HD would account for less than one quarter that estimated by common analytical procedures applied to hydrolysed urine samples from subjects non-exposed to hexane. If so, the most critical point for the slope of the relationship between air hexane concentrations and urine 2,5-HD levels would be the exposure interval examined by the various authors. In fact, con-

founding levels of 2,5-HD are likely to reduce the slope obtained when evaluating a limited range including only low exposure levels. Under these conditions a much greater proportion of 2,5-HD would be attributable to background excretion as compared to that affecting samples obtained from heavily exposed workers.

Table 6: 2,5-HD in urine/hexane in air ratio and possible metabolic interference from other components of the solvent mixture

Author	2,5-HD levels corresponding to 180 mg/m³ hexane in air		Other components of the mixture (interference suspected)
	mmol/l	mmol/mol creatine[1]	
Perbellini et al., 1981	48	3.2[2]	Hexane isomers. Six other solvents not including toluene and MEK found at low concentrations (no)
Iwata et al., 1983a	16	1[2]	Toluene and MEK, accounting for 67% of the mixture (yes)
Mutti et al., 1984	40[2]	3	Hexane isomers, heptane and cyclohexane (no)
Ahonen and Schimberg, 1988	14	1	Toluene and acetone

[1] 1 mmol/mol creatinine = 1 mg/g. [2] extrapolated value.

According to Perbellini et al. (1981) an 8h-TWA exposure to 180 mg/m³ would correspond to an average concentration of 5.3 mg/l of 2,5-HD in urine. This value is in reasonable agreement with that of 3.0 mg/g of creatinine proposed by Mutti et al. (1984). Somewhat lower values have been proposed by Iwata et al. (1983a) and by Ahonen and Schimberg (1988). According to these authors, the urinary concentration corresponding to the same exposure levels would be 16 (s.g. 1016) and 14 (s.g. 1024) mmol/l, respectively (about 1.8 and 1.6 mg/l, respectively), probably because of simultaneous exposure to toluene and/or ketones, which were not found in the mixtures examined by Perbellini et al. (1981) and Mutti et al. (1984).

Ahonen and Schimberg also examined several sampling times and alternative ways to calculate exposure-related values for 2,5-HD, namely the daily increase, the peak value, the 24 total excretion, the peak increase over baseline, etc. Of all additional procedures, the evaluation of the 'next morning' spot sample seems to be practical enough and useful when exposure is limited to a few hours over the working shift. Owing to the time-lag of the peak values, the end-of-shift sample might actually under- or overestimate the 8h-TWA exposure levels.

Various mathematical models have been applied to calculate biological exposure indexes equivalent to airborne exposure limits (Leung and Paustenbach, 1988). Physiologically based models suggest that the time-lag for peak values and the relatively long half-life of 2,5-HD (14.2 h) result in a progressive rise of urinary levels corresponding to the same hexane exposure over the working week, with a threefold increase in Friday post-shift values as compared to the corresponding time on Monday (Perbellini et al., 1986 and 1990). Fig. 4 shows the progressive rise of 2,5-HD baseline (i.e. prior to exposure) levels during the working week. One major objection to such an approach is that, whereas exposure limits represent conditions to which nearly all workers may be exposed without adverse effects, pharmacokinetically extrapolated values are usually based on the parameters of the 'average man', i.e. of the 50th percentile of a normal population. One should recognize, however, that such an error is probably not greater than those associated with the definition of exposure limits, the most widely used of which, i.e. the ACGIH-recommended TLVS have recently been the subject of some controversy (Roach and Rappaport, 1990; Castleman and Ziem, 1988).

Urinary levels of 3 mg/g of creatinine and 5 mg/l in samples collected at the end of the working week seem to be appropriate standards for practical purposes. On the one hand, such values would correspond to about 180 mg/m³ of hexane in air (8h-TWA). On the other hand, they are well below the threshold of the dose-response relationship shown by Governa et al. (1987). However, one must be aware that such values might underestimate actual exposure levels to mixtures containing MEK, toluene and acetone. Interactive effects of MEK may be dangerous, since toxic effects might be expected in a significant proportion of workers showing urinary 2,5-HD below the above levels.

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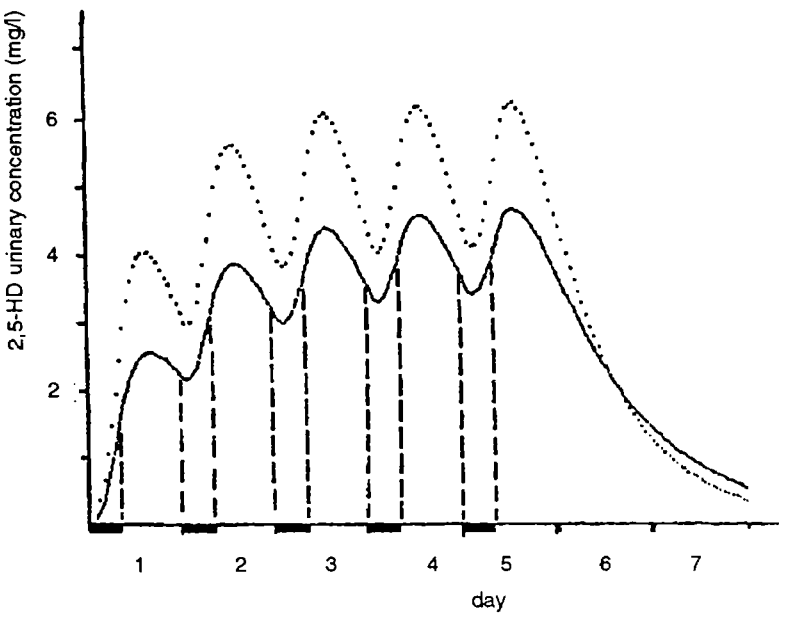

Fig. 4. Urinary excretion rate of 2,5-hexanedione suggested by a mathematical model with a simulated exposure to hexane to 360 mg/m^3 for eight hours for five days a week. The total amount of 2,5-hexanedione daily excreted is also shown. (Adapted from Perbellini et al., 1986). More recently, the same authors reported somewhat higher values for 2,5-hexanedione, urinary concentrations ranging from 3.3 to 4.3 mg/l (prior to subsequent exposure) and from 3.4 to 4.1 mg/l (end of shift) being associated with exposure to 180 mg/m^3 of hexane (Perbellini et al., 1990.)

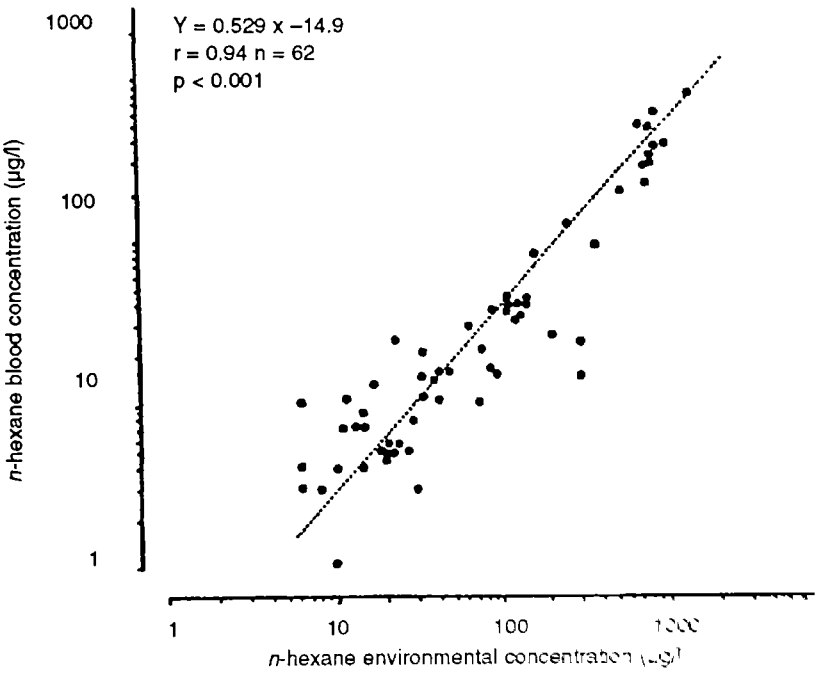

Fig. 5. Relation between environmental and venous blood concentrations of hexane. Data obtained at the end of a four + four hours' workshift. (Adapted from Perbellini et al., 1986)

Hexane in blood

Hexane blood concentrations are closely correlated with the airborne levels measured in the air simultaneously collected by grasp sampling, the slope of the regression line being about 0.5 (Fig. 5).

Somewhat higher values have been obtained by Veulemans et al. (1982) who exposed volunteers to 360 mg/m^3 of hexane. In this experiment, the steady-state level was quickly achieved and values of 200 mg/l were recorded at rest, the corresponding figures for workloads of 20, 40, and 60 W being 230, 260 and 290 mg/l, respectively. Owing to the short half-life of the solvent in blood, its evaluation seems not to offer substantially better information as compared to simple and non-invasive environmental monitoring.

Hexane in alveolar air

Alveolar air is in dynamic equilibrium with arterial blood. It is thus useful to estimate the amount of solvent taken up and it offers a non-invasive means to evaluate the respiratory excretion during the post-exposure period.

During exposure, there is reasonable agreement between the alveolar retention coefficients reported by various authors, the retention data ranging from 0.164 to 0.252, median 0.20 (Brugnone et al., 1978; Mutti et al., 1984; Veulemans et al., 1982). Thus, alveolar levels are about 80% (75-84%) of the inhaled concentration. Owing to the short half-life and hence the rapid equilibrium with inhaled air, hexane concentration in this compartment cannot be used to assess 8h-TWA levels, but perhaps just to monitor short-term or peak exposures. Nor is it likely to be detectable in pre-shift samples (Fig. 6).

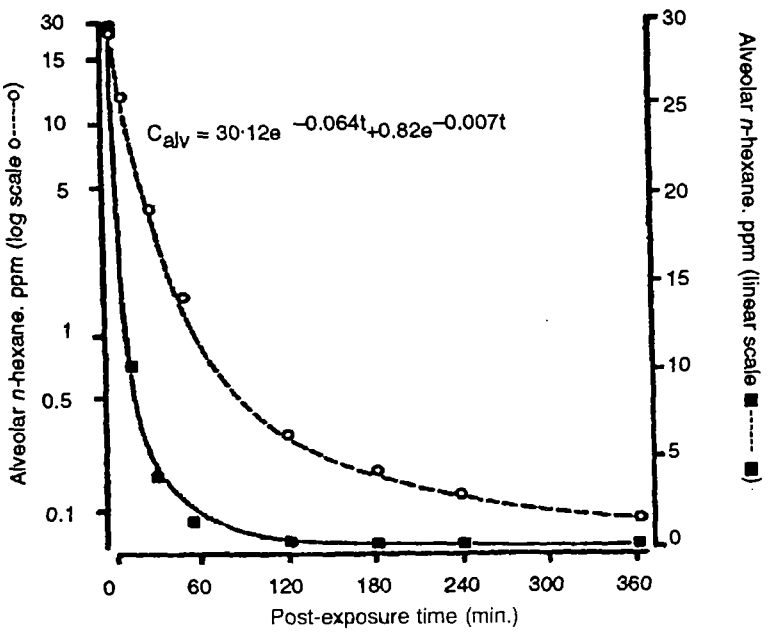

Fig. 6. Time course of alveolar concentrations of hexane during post-exposure period in the same subject as in Fig. 3. Measured values were plotted versus time both on linear (continuous line) and on lin-log scale (dashed line). Experimental curve was obtained by extrapolation to zero time. Fast phase (first hour) was calculated by subtracting slower component at each sampling period. (Adapted from Mutti et al., 1984.)

Hexane in urine

The concentration of hexane in urine has been measured by gas chromatography/mass selective detector (phragmentography) by Imbriani et al. (1984). According to these authors, urinary hexane levels are highly correlated with 8h-TWA levels of 180 mg/m^3. Urinary hexane is thought to reflect blood levels. The permselectivity of the bladder probably accounts for the fact that the corresponding figures for blood hexane are 15 times greater.

Research needs

The following are recommendations for further research:

- standardization of analytical techniques for 2,5-hexanedione in urine;
- development of practical methods to measure 2,5-hexanedione in serum;
- further investigations on dose-effect/response using the urinary excretion of 2,5-HD as an indicator of the internal dose by comparing its levels with neurophysiological parameters;
- studies on factors influencing hexane biotransformation, particularly the metabolic interactions with other solvents contained in commercial mixtures;
- better characterization of the pharmacokinetics of hexane and its metabolites, in order to clarify both the meaning of biological tests and the risk associated with repeated exposures at the workplace.

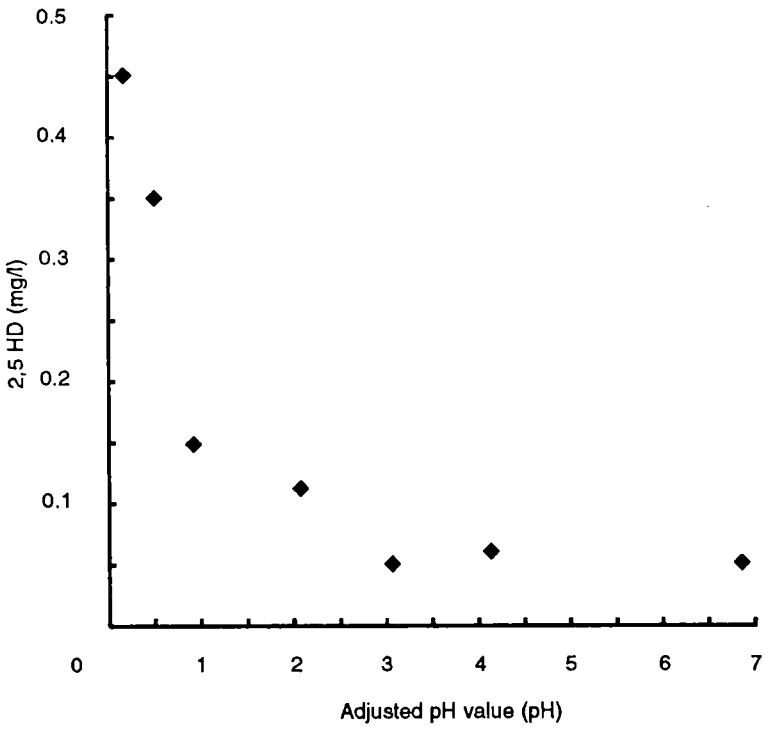

Fig. 7. Effect of pH on release of 2,5-hexanedione during acid hydrolysis. Increasing amounts of 3.6 *N* HCl were added to 1 ml of urine from one subject to obtain the indicated pH value. Water was added to reach the final volume of 1.6 ml for each sample, followed by heating at 100°C for 30 min. (Adapted from Fedtke and Bolt, 1986.)

Practical Recommendations

The measurement of 2,5-HD in urine samples collected at the end of a working week seems to provide the best information about both exposure and neurotoxicological risk. Urinary levels of 3 mg/g creatinine and 5 mg/l (hydrolysed samples) would correspond to 8h-TWA concentrations of 50 ppm of hexane in the air. The preparation of samples is a critical step. According to Fedtke and Bolt (1986), the amount of 2,5-HD in the urine extracts depends on the pH-value adjusted prior to acid hydrolysis (Fig. 7). However, very recently, it has been suggested that hydrolysis might introduce artefacts, i.e. the formation of interfering substances overlapping 2,5-HD during gas chromatographic analysis, thus increasing the background level of urine samples from subjects exposed to low hexane concentrations (Kawai et al., 1990). Two alternative approaches may overcome this problem. In our laboratory, urine samples undergoing acid hydrolysis are adjusted to pH 2.0, i.e. to a value at which artefacts are minimized (Fig. 7). Alternatively, simple extraction without previous hydrolysis may be used (Kawai et al., 1990), though it is likely that the latter solution amplifies the analytical error associated with the extrapolation of exposure levels from biological monitoring data, owing to the much lower slope of the regression line between hexane in the air and 2,5-HD in urine. About 200 μg/l of 2,5-HD in samples undergoing simple extraction without previous hydrolysis would correspond to hexane airborne concentrations 50 ppm (8h-TWA). No data are available to suggest no-observed-effect levels on the basis of the relationship between the internal dose estimated in this way and early neurotoxic effects as revealed by electrophysiological changes.

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II–Methyl ethyl ketone

Summary

Methyl ethyl ketone (MEK) is a major component of mixtures currently used in several industrial applications, mainly as solvent of glues, rubbers, lacquers, varnishes, and plastics.

Adverse effects on the central and peripheral nervous system have been reported, most often following exposure to MEK-containing solvent mixtures. MEK is known to potentiate the toxicity of several other solvents. Although the neurotoxicity of MEK is still controversial, there is evidence of its synergistic interaction with hexacarbons, hexane- and methyl-*n*-butyl ketone-induced neuropathy being potentiated by MEK co-exposure.

Some 50% of inhaled MEK is taken up. Only a minor fraction of absorbed MEK is excreted unchanged via exhaled air (3-10%) or urine (0.1%). Biotransformation involves hydroxylation to 3-hydroxy-2-butanone (acetyl methyl carbinol) and subsequent reduction to 2,3-butanediol, which are excreted in urine together with the parent compound. However, the urinary excretion of such substances within the 24 h following exposure apparently accounts for a small fraction (less than 10%) of absorbed MEK. Nevertheless, available data suggest that their concentrations in the end-of-shift urinary spot samples are closely correlated with the 8-h time-weighted average MEK concentration in the air and may thus be conveniently used as biological indicators of exposure. Current exposure may also be monitored by measuring MEK in blood or alveolar air.

The urinary excretion of MEK is probably the most practical approach for monitoring purposes, urinary levels of about 2 mg/l corresponding to an average airborne concentration of 200 ppm.

Methyl ethyl ketone

Synonyms: 2-butanone, MEK

Chemical and physical properties

Colourless, volatile liquid with acetone-like odour

Boiling point	:79.6°C
Melting point	:– 86°C
Vapour pressure	:20 mmHg (at 20°C)
Vapour density (air = 1)	:2.41
Flash point	:21°F
Solubility	:soluble in water
CAS-number	:78-93-3
Formula	:CH_3-CO-CH_2 -CH_3
Molecular weight	:72
1 ppm = 2.94 mg/m3	
1 mg/m^3 = 0.34 ppm	

Exposure

MEK is a colourless, volatile liquid with an acetone-like odour. It is readily soluble in water and in nonpolar fluids, the ratio between its water/air and oil/air partition coefficients being close to 1.0 (Sato and Nakajima, 1979). As a result, it increases the miscibility of polar and nonpolar substances. This property, together with its high volatility and low toxicity, accounts for its use as a major component of solvent mixtures, especially with acetone, ethyl acetate, and hydrocarbons in the C5-C7 range, mainly hexane and toluene. Such mixtures are used as solvents for glues, rubbers, lacquers, varnishes, and plastics. Industrial uses include the manufacture of shoes, colour printing, plastic coating, paint removing. It is also used to de-wax lubrificating oils, but MEK is seldom used alone. In 1979, the production volume was estimated to be 343 000 tons in the USA (Chemical Manufacturers Association, 1982, quoted by O'Donoghue et al., 1988).

Adverse effects

Since MEK exposure seldom occurs alone, it is difficult to ascribe to MEK exposure those effects that have usually been observed in workers exposed to MEK-containing solvent mixtures. There are, however, a few exceptions. In subjects exposed to 100-200 ppm of MEK for a few minutes, irritation of eyes, nose, and throat was observed (Nelson et al., 1943). A longitudinal study among steel workers exposed to MEK concentrations exceeding 150 ppm (150-450), associated with much lower concentrations of other solvents not affecting the exposure conditions, showed a progressive improvement in simple reaction times after some changes in the working environment resulting in better hygienic conditions and exposure levels lowered to 31-105 ppm (Anshelm Olson et al., 1981). Furthermore, whereas at the first examination reaction times were correlated with exposure intensity, no such relationship was observed at the follow-up, thus proving that the effects were both exposure-related and partially reversible. Such

findings are in agreement with experimental studies showing no behavioural effects of exposure to MEK at 200 ppm for four hours (Dick et al., 1984 and 1989).

Evaluating the role of MEK co-exposure in subjects exposed to MEK-containing hexacarbon mixtures known for the neurotoxic properties of some components, e.g. hexane and methyl-*n*-butyl ketone, is a much more difficult task. Although neurotoxic effects have been ascribed to MEK exposure (Dyro, 1978), experimental studies aimed at inducing peripheral neuropathy in animals treated with MEK alone have been unsuccessful (Saida et al., 1976; Altenkirch et al., 1978). However, several independent investigators have consistently found that MEK co-exposure potentiates the neurotoxic effects of methyl-*n*-butyl ketone and hexane (Abdel-Rahman et al., 1976; Couri et al., 1977; Altenkirch et al., 1978; Ralston et al., 1985). There is also evidence that MEK co-exposure increases the hepato- and nephrotoxicity of haloalkanes (Brown and Hewitt, 1984; Brondeau et al., 1989; Hewitt et al., 1986) and that it reduces the elimination rate of ethanol, thus enhancing ethanol-induced behavioural effects (Cunnigham et al., 1989).

Ames assays gave negative results and did not demonstrate significant mutagenic activity (O'Donoghue et al., 1988). However, MEK was found to induce aneuploid in *Saccaromices cerevisiae* strain D61.M at relatively high concentrations (Zimmermann et al., 1985).

Metabolism

Absorption

Although it may be absorbed through the skin (Wurster and Munier, 1965), MEK is primarily taken up via the respiratory route. In a field study, Perbellini and co-workers (1984) monitored the environmental concentration of MEK during 4-h exposure periods, during which alveolar air was also sampled (time of sampling unspecified). Since MEK concentration in the alveolar air was about 30% of its breathing zone level, the pulmonary retention was estimated at around 70%.

During experimental exposure of volunteers, Liira et al. (1988a) estimated the relative pulmonary uptake to be about 41% (exposure to MEK alone) and 45% (co-exposure to xylene). In a different experiment, the same authors introduced three exercise periods (10 min/100 W) in the protocol. The pulmonary retention turned out to be somewhat higher (53%) than previously reported even under sedentary conditions (Liira et al., 1988b). Although the relative uptake was similar under sedentary conditions with exercise periods, the estimated total pulmonary uptake increased by one third, owing to the increase in the pulmonary ventilation during the exercise (from 11 to 35 l/min). Such inconsistencies may be explained by the different methods used to estimate absorption. In fact, whereas Perbellini et al. (1984) calculated the uptake on the basis of alveolar air samples (end of tidal volume), Liira and co-workers estimated absorption from the difference between inhaled and exhaled concentrations. As recognized by the authors, the latter may artefactually vary according to the breathing technique, since hyperventilation may readily increase the deadspace air and thus the exhaled concentration.

Distribution

As expected on the basis of its similar solubility in oil and in water, MEK showed estimated tissue/blood partition coefficients close to 1 for all tested tissues. Table 1, adapted from Perbellini and co-workers (1984), lists the tissue/air and the calculated tissue/blood partition coefficients. It can be inferred that MEK supply to the different tissues during exposure depends on their blood flow. Despite its volatility, MEK is expected to be retained owing to its high solubility in blood.

Biotransformation

With regard to the metabolism of MEK, oxidation and reduction products, i.e. 3-hydroxy-2-butanone, 2-butanol and 2,3-butanediol, were identified in serum of guinea pigs treated with MEK (Di Vincenzo et al., 1976). After an oral dose of 1690 mg/kg in rats, such a metabolic pathway led to transformation into 2,3-butanediol, accounting for

some 30% of administered MEK (Dietz and Traiger, 1979). In this experiment, the maximum MEK and 2,3-butanediol blood concentrations occurred respectively after 4 and 18 hours, thus suggesting that MEK biotransformation is much slower than that of other solvents. Its solubility in blood probably accounts for the relatively slow biotransformation and disappearance rate.

Table 1. Methyl ethyl ketone solubility in human tissues (adapted from Perbellini et al. (1984)

Tissues	Tissue/air	Tissue/blood
Blood	183 ± 12	1
Kidney	197 ± 17	1.05
Liver	180 ± 15	0.98
Brain	168 ± 26	0.92
Fat	161 ± 14	0.88
Muscle	212 ± 30	1.16
Heart	254 ± 25	1.39
Lung	147 ± 10	0.80

Excretion

Conflicting results have been obtained in humans. Volunteers ingesting 375 mg of MEK in gelatin capsules excreted about 30% of the ingested dose by exhalation (Munies and Wurster, 1965). In subjects exposed to 65-333 ppm for two hours, MEK concentration in the expired air was about 10% of the inhaled concentration. According to Liira et al. (1988b), only 2 to 3% of the inhaled dose was exhaled unchanged after the exposure. The urinary excretion of MEK and its known metabolites also accounts for a minor fraction of absorbed dose. Only 0.1% of absorbed MEK would be excreted unchanged in urine (Miyasaka et al., 1982). The amount of MEK and its metabolite acetylmethylcarbinol eliminated by the kidneys correspond together to 0.1% of the alveolar MEK uptake (Perbellini et al., 1984). Finally, only about 3% of the absorbed MEK would be excreted as 2,3-butanediol (Liira et al., 1988b). Since the recovery of absorbed MEK is very low, one must conclude that its excretion should occur chiefly through uncharacterized metabolites, possibly acetate or acetoacetate (Liira et al., 1988b).

Metabolic interactions

Earlier studies failed to show any metabolic interactions, so that the synergism between MEK and hexacarbons was attributed to a possible competition between MEK or its metabolites and gamma-diketones for binding to non-critical targets (Ralston et al., 1985). Perbellini and co-workers (1985) were able to show that the slope of the linear regression between hexane exposure and the urinary excretion of 2,5-hexanedione, its putative neurotoxic metabolite, was enhanced in shoemakers simultaneously exposed to MEK as compared to subjects exposed to hexane-containing MEK-free mixtures. Such a notion received experimental support by Robertson et al. (1989) who, at variance with earlier findings of the same group (White and Bus, 1980), were able to demonstrate that in rats exposed to hexane, MEK co-exposure resulted in higher levels of 2,5-hexanedione both in plasma and in peripheral nerves. *In vitro* experiments by Veronesi and colleagues (1984) also showed that the threshold for hexane neurotoxicity was shifted towards lower levels by MEK co-exposure with a monotonous trend depending on MEK concentrations in the medium.

Experimental coexposure to *m*-xylene and MEK in man resulted in inhibited xylene metabolism, whereas it did not cause any change in the concentration of MEK in blood or the excretion of 2,3-butanediol in urine (Liira et al., 1988a). The experiment on MEK/ethanol interactions during acute exposure in man by Liira et al. (1990b) deserves a more detailed description. Ethanol administration either before or after MEK exposure inhibited the primary oxidative metabolism of MEK, thus causing an increase in the blood concentrations of MEK (Fig. 1) and 2-butanol (Fig. 2) as compared to those measured during and after exposure to MEK alone. These changes appeared shortly after ethanol administration, which took place either before or after exposure. Serum concentrations of 2,3-butanediol were decreased initially, but there was an increase eight hours after exposure.

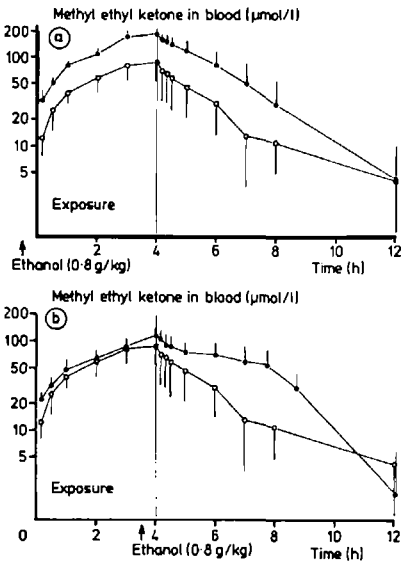

Fig. 1. MEK in blood (mean and SD) during and after exposure to 200 ppm of MEK for four hours (open circles) and same exposure with (a) preceding (b) following ethanol ingestion (closed circles). (Adapted from Liira et al., 1990b)

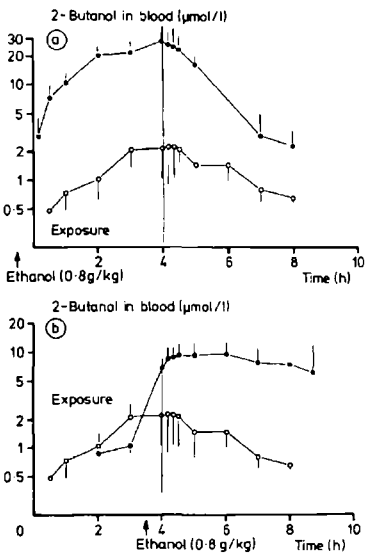

Fig. 2. 2-Butanol in blood (mean and SD) during and after exposure to 200 ppn of MEK for four hours (open circles) and same exposure with (a) preceding (b) following ethanol ingestion (closed circles). (Adapted from Liira et al., 1990b)

In the same experiment, the amount of MEK excreted unchanged in the urine and exhaled air turned out to be increased by alcohol administration (Fig. 3), independently of whether ethanol was administered prior to (a) or after (b) exposure. The recovery of 2,3-butanediol from urine was much greater when ethanol was administered before exposure than following exposure to MEK alone or ethanol administration after MEK exposure (Fig. 4).

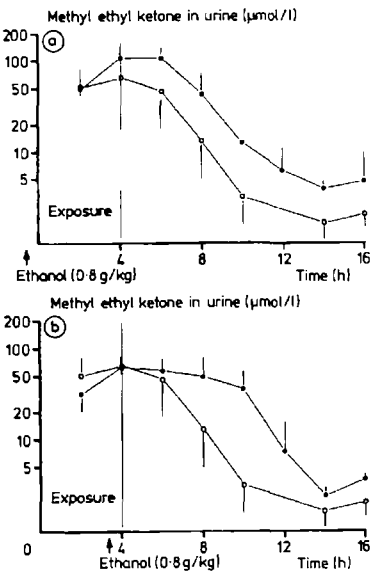

Fig. 3. Concentration of MEK in urine (mean and SD) during and after exposure to 200 ppm of MEK for four hours (open circles) and same exposure with (a) preceding ethanol ingestion (0.8 g/kg) (closed circles) and (b) ethanol ingested at end of exposure (closed circles). (From Liira et al., 1990b.)

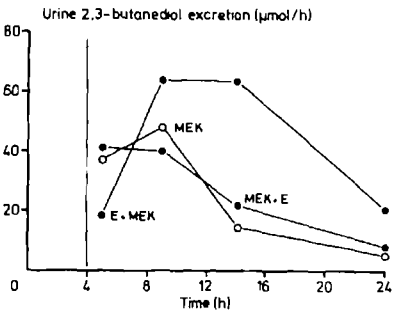

Fig. 4. Excretion of 2,3-butanediol in urine after exposure to 200 ppm of MEK (MEK, open circles) for four hours and same exposure with preceding ethanol ingestion (E+MEK, closed circles) and with ethanol ingested at end of exposure (MEK+E, closed circles). Data points were obtained from pooled urine samples from five subjects. (Adapted from Liira et al., 1990b.)

In any case, the time course of the urinary excretion of MEK and its metabolites seems to follow that of serum levels, thus suggesting that metabolic interferences actually take place during Phase 1 of biotransformation. It ought to be noted that an important role is played by the schedule of administration, the effects of previous ethanol intake being much greater than those caused by ethanol ingestion at the end of the exposure period.

Finally, in volunteers experimentally exposed to acetone:MEK mixtures to assess possible neurobehavioural effects, co-exposure reduced respectively MEK and acetone serum levels by 50% and by one third as compared to the concentrations reached following exposure to each solvent alone (Dick et al., 1989).

Table 2. Summary of metabolic interactions between MEK and other solvents reported in the literature.

Species	Coexposure to	Effect of MEK	Effect on MEK metabolism	References
Rat	Hexane	+ toxicity	Not studied	Takeuchi et al., 1983
Rat	Hexane	- metabolism	Not studied	Iwata et al., 1983
Rat	Ethanol	- excretion	Not studied	Cunningham et al., 1989
Rat	Hexane	+ metabolism	Not studied	Robertson et al., 1989
Man	Hexane	+ metabolism	Not studied	Perbellini et al., 1985
Man	m-Xylene	- metabolism	No effects	Liira et al., 1988a
Man	Acetone	- serum acetone	- serum MEK	Dick et al., 1989
Man	Ethanol	Not studied	- metabolism	Liira et al., 1990b

+ = increased or synergystic effect - = reduced or inhibitory effect

In summary, various metabolic interactions between MEK and other solvents have been described (Table 2). Most of such interactions may be accounted for by cytochrome isoenzyme induction, which may be of the additive, synergistic, or competitive type, as demonstrated by Raunio et al. (1990). However, metabolic interactions continue to be unpredictable on the basis of the chemical structure of the parent compounds. As a result, caution has to be exercised in extrapolating any conclusions from similar situations and in making assumptions not supported by empirical evidence.

Biological indicators

The biological tests that have been proposed to monitor exposure to MEK include:

MEK in urine;

3-hydroxy-2-butanone (acetyl methyl carbinol) in urine;

2,3-butanediol in urine;

MEK in blood;

MEK in alveolar air.

The reader should refer to the report on benzene in this series for a critical appraisal of methods of expressing results of analyses performed in urine (Lauwerys, 1979). One exception to the use of standardization procedures is MEK in urine, which is thought to dynamically change by simple diffusive mechanisms regulated by the relative solubility in various compartments and hence by the partition coefficient rather than by renal handling, thus essentially depending on the arterial blood levels reached before sampling. From a practical point of view, only MEK in urine seems to be suitable for routine monitoring of exposure.

MEK in urine

Simple and reliable head space techniques may be used for the gas chromatographic analysis of MEK in bodily fluids, namely in blood and urine. Although only a minor fraction (less than 1%) of absorbed MEK is excreted unchanged in the urine, the urinary excretion of MEK has been proposed as a biological index to monitor occupational exposure to this solvent, owing to the good relationship between airborne and urinary concentrations of the solvents (Brugnone et al., 1983). Furthermore, such an approach shows inherent practical advantages from the analytical point of view. In fact, the 'head-space' method is rather simple and quick, expecially if compared to much more time-consuming extraction and derivatization techniques necessary to measure MEK metabolites in biological fluids. However, such an indicator has been recommended for use on a group basis, because of the great interindividual variability and limited experience (Myiasaka et al., 1982). In their paper, Ghittori et al. (1987) proposed the concept of BEEL.

Table 3. Linear regressions between airborne and urinary concentrations of MEK following occupational or experimental exposure.

Authors	No of subjects	r	Urinary MEK corresponding to exposure to 200 ppm
Miyasaka et al., 1982	62	0.74	5.3 mg/l uncorrected
		0.75	3.3 mg/l, s.g. 1 016
		0.60	3.4 mg/g creatinine
Perbellini et al., 1984	27	0.69	2.1 mg/l uncorrected
Ghittori et al., 1987	65	0.91	2.2 mg/l uncorrected 2 mg l (BEEL[1])

[1] BEEL: biological equivalent exposure limit (95% lower confidence limit of the regression equation).

The biological equivalent exposure limit) serves to compare each single urinary concentration value with the chosen threshold, in order to make a decision of compliance or non-compliance. Thus, the lower 95th percentile of each determination (starting from the coefficient of variation of the method and assuming a normal distribution) was recommended in a decision of non-compliance for values exceeding the BEEL; conversely, it was advised to employ the upper 95th percentile in a decision of compliance biological exposure for urinary concentrations below the BEEL.

Similarly, Myiasaka et al. (1982) reported the 95% confidence intervals for the statistical parameters of the regression between environmental and biological data. In both cases, it was recognized that like TLVs, biological limit values should protect 'nearly all' exposed workers over a working lifetime. Both the above proposals were thus aimed at translating into statistical terms the concept of 'nearly all' workers.

Although obtained by using the same technique, quite inconsistent limits have been proposed by these authors (Table 3). Such inconsistencies remain when the lower 95% confidence limit is calculated from the regression parameters proposed by Japanese authors (4.0 mg/l). Although the values found by Perbellini et al. (1984) are supported by similar findings obtained by independent investigators (Ghittori et al., 1987), some feelings of uncertainty remain with regard to the possibility of extrapolating urinary MEK concentrations corresponding to 8h-TWA exposures to 200 ppm of MEK (current ACGIH-recommended TLV).

It should also be recognized that such an approach to the definition of biological limit values assumes that the corresponding TLV has actually been validated. Unfortunately, the standard recommended by ACGIH for MEK is among those that have recently

been subject to some controversy. In fact, the standard chosen was found to be inconsistent with the documentation quoted to support its validation (Roach and Rappaport, 1990).

It is therefore prudent to recommend the lowest value proposed thus far, i.e. 2 mg/l. One should also be aware that, even below this limit, complaints about nose and throat irritation may be reported by workers exposed to 100 ppm or more. However, according to individual values reported in the literature thus far, such a condition is unlikely to occur in current industrial settings.

MEK metabolites in urine

In man, the urinary excretion of MEK accounts for less than 0.1% of the absorbed dose (Myiasaka et al., 1982). Another minor fraction of the solvent taken up undergoes metabolic transformation and may be recovered in the urine in the form of 3-hydroxy-2-butanone or acetyl-methyl-carbinol (less than 0.1%) or 2,3-butanediol (about 2-3%). In both cases, analytical techniques are time-consuming. Previous enzymatic and acid hydrolysis is required to measure 3-hydroxy-2-butanone (Perbellini et al., 1984), whilst extraction and derivatization is necessary to determine 2,3-butanediol (Liira et al., 1988a). As a result, although correlated with exposure, these indicators seem to be impractical for routine biological monitoring of occupational exposure to MEK.

MEK in blood

Owing to the solubility of the solvent, MEK blood concentrations are widely scattered depending not only on exposure levels, but also on physical exercise and duration of exposure, the saturation of this compartment being not easily achieved as is usually the case for less polar solvents. Nevertheless, experimental data show close relationships between blood MEK and both airborne and alveolar levels measured on simultanously collected samples (Perbellini et al., 1984; Liira et al., 1988a). Although the venous blood concentration during and after the exposure period turned out to parallel that found in expired or alveolar air, its evaluation seems not to offer substantially better information as compared to simple and non-invasive air sampling procedures.

MEK in alveolar air

Alveolar air is in dynamic equilibrium with arterial blood. It is thus useful to estimate the amount of solvent taken up during exposure. Furthermore, it offers a non-invasive means to evaluate the respiratory excretion during the post-exposure period.

During exposure, the estimated pulmonary absorption reported by various authors ranges from 41 (Liira et al., 1988b) to 70% (Perbellini et al., 1984), the variability being accounted for by sampling techniques, which have been designed to evaluate exhaled or alveolar air, respectively, and by exposure levels, much higher in experimental than in field studies.

From a practical point of view, owing to the short half-life (respectively of 30 and 81 minutes for the two phases characterizing the time course during the post-exposure period) and hence the rapid equilibrium with inhaled air, MEK concentration in this compartment cannot be used to assess 8h-TWA exposure levels, but just to quantify absorption and perhaps to monitor short-term or peak exposures. Nor is it expected to be measurable in pre-shift samples, in order to provide reliable estimates of exposure during the preceding workshift.

Conclusions

MEK is a major component of many commercially available solvent mixtures. Despite its low toxicity, MEK is toxicologically important because of its interference with the metabolisms and toxicity of other components of such mixtures.

Although only a minor fraction (less than 1%) of absorbed MEK is excreted unchanged in the urine, the urinary excretion of MEK has been proposed as a biological index to monitor occupational exposure to this solvent, owing to the good relationship between airborne and urinary concentrations of the solvents. End-of-shift levels of about 2 mg/l would correspond to an average airborne concentration of 200 ppm.

Needs for further research

The following are recommendations for future research:

- to better define the toxicological properties of MEK, with special emphasis on its interactions with the metabolism and toxicity of other organic solvents;
- to better characterize MEK metabolism and kinetics;
- to better define the relationships between external dose and biological indices of exposure/internal dose;
- to validate analytical methods simple and reliable enough to be applied for the routine biological monitoring of exposure to MEK.

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Biological indicators for the assessment of human exposure to industrial chemicals

Thallium and tin

G. Kazantzis

I–Thallium

Summary

Thallium is a highly reactive metal forming monovalent thallous and trivalent thallic salts. It is widely distributed in the earth's crust in low concentration and is present in emissions from coal-burning power plants and from copper, lead and zinc smelters. It has been extensively used as a rodenticide and more recently in the production of photovoltaic cells, in electronic circuitry, as a catalyst in organic synthesis and in myocardial imaging.

Thallium is highly toxic, giving rise, in acute poisoning, to a characteristic pattern of gastroenteritis followed by sensory and motor neuropathy with involvement of the cranial nerves, and central nervous effects. Where survival extends beyond a week or so the neurological features progress and are followed by a marked alopecia. Following long-term, low-level occupational exposure, subjective symptoms including asthenia, anorexia, irritability and pains in the limbs may be followed by peripheral neuropathy and by loss of hair.

Water-soluble inorganic salts of thallium are rapidly absorbed following ingestion, inhalation or skin contact, and absorption may be complete following ingestion. Following rapid absorption, thallium is widely distributed in the body, the highest concentration being found in the kidneys. In blood thallium is found predominantly in the red cells, but concentrations are low, indicating a rapid equilibration with tissues. Thallium ions are transported across cell membranes in a similar manner to potassium. Thallium is excreted in both urine and faeces and in small part via hair and into milk. Excretion in both urine and faeces may persist for many weeks despite low blood levels in poisoned patients. With time the concentration of thallium increases in hair, which may contain the major part of the body burden, thus providing an important additional route for slow excretion.

In normal unexposed subjects the highest tissue concentrations of thallium have been found in hair, followed by nails and the wall of the colon. The most recent studies have shown both urine and blood levels of thallium in unexposed subjects to range below 1 μg/litre.

Thallium concentration in urine is the most reliable indicator of thallium exposure. When estimated with appropriate safeguards, it is of value in biological monitoring of population samples following both occupational and environmental low-level exposure.

Thallium concentration in hair may provide a useful indicator of cumulative absorption of thallium provided external contamination can be excluded.

A urinary thallium concentration of 300 μg/litre has been suggested as the threshold for thallium poisoning until an agreed figure is established. However, following low-level exposure, subjective symptoms have been reported which require further evaluation with regard to their relevance as early indicators of effect. At present there are no reliable data on dose-response relationships for thallium indicative of an earliest adverse health effect.

Introduction

Chemical and physical properties

Thallium (chemical symbol Tl) shares group IIIa of the Periodic Table with indium, gallium, aluminium and boron. It is a blue-white metal of tetragonal crystalline form; atomic number 81; atomic weight 204.4; melting point 303.5 °C; boiling point 1457 °C, and with oxidation states of +1 and +3. It is a highly reactive metal, readily soluble in acids, which forms a series of monovalent thallous and trivalent thallic salts, the latter being less stable. The principal salts of industrial significance are thallous oxide (Tl_20), thallous hydroxide (TlOH) and thallous sulphate (Tl_2S0_4). Thallous oxide can be prepared by heating thallium in air to about 350 °C, the hydroxide produced by dissolving the oxide in water, and the sulphate by dissolving thallium in hot, concentrated sulphuric acid.

Production and industrial uses

Thallium is widely distributed in the earth's crust with an overall concentration of the order of 1 mg/kg. It is found in the USA and Brazil in the minerals lorandite and crooksite. In seawater it has an average concentration of the order of 0.01 μg/litre. For industrial purposes thallium is more often recovered from the roasting of pyrite ores from lead and zinc smelters, the flue dust being treated to render the thallium content soluble. It has also been obtained from residues in the production of sulphuric acid by the lead-chamber process. Total world production is unlikely to have exceeded a few thousand tons per annum.

Thallous sulphate has been extensively used as a rodenticide. In many countries it has been replaced by other less toxic compounds, but with the development of resistance, the use of thallium is increasing again. Thallium is used increasingly in the electronics industry and is used also in photoelectric cells, in infrared spectrometers, in other optical systems and for colouring glass. In the chemical industry it is of use as a catalyst in organic synthesis, for the oxidation of hydrocarbons and olefins, for polymerization and for epoxidation (Wade and Banister, 1973). More recently, thallium as thallous chloride, Tl^{201}, has been increasingly used in myocardial perfusion imaging.

Environmental and occupational exposure

The dietary intake of thallium has been estimated to be of the order of 2μg/day, but data are sparse (Carson and Smith, 1977). Polluted atmospheres may contribute as much, or more, thallium to daily intake, as a normal diet. The principal exposure sources in the general population are air emissions from coal-burning power plants and copper, zinc and lead smelters. Iron and steel production, and also emissions from cement factories represent a significant source of environmental contamination. Emissions from cement factories were found to originate from thallium-bearing roasted pyrite, added to ground limestone for the production of special types of cement (Ewers, 1988). The contamination of vegetables and fruit grown in private gardens with thallium containing dust fallout from a cement plant has been shown to give rise to markedly increased urine and hair thallium levels in the local population (Brockhaus et al., 1981). The use of thallium-containing rodenticides has led to the accidental contamination of food giving rise to many cases of poisoning in humans, in particular in children, in domestic and wild animals and in birds. Thallium has been used in the past as a depilatory agent in the treatment of ringworm of the scalp, again causing many cases of poisoning some with a lethal termination (Munch, 1934).

In the working environment inhalation of thallium and absorption giving rise to milder forms of poisoning has followed the handling of flue dusts, the extraction of the metal and the handling and manufacture of thallium-containing rodenticides. Absorption has also followed ingestion from contaminated hands and food and as a result of skin contact.

Effects on humans

Acute poisoning has been reported most frequently following accidental, homicidal or suicidal ingestion of a thallium salt, and rarely observed following occupational exposure. Thallium compounds are extremely toxic, the critical organ being, in general, the central nervous system, although the system primarily affected is in part dependent on

the length of survival following absorption. The triad of gastroenteritis, polyneuropathy and alopecia has been generally regarded as the classic syndrome of acute thallium poisoning (Gastel et al., 1978). The minimum lethal dose of thallium has been reported to be of the order of 12–20 mg/kg in adults and 2–10 mg/kg in children. While a single dose of ingested thallium may be rapidly fatal, thallium is a cumulative poison following low-level, longer term exposure.

Acute thallium poisoning most commonly presents with gastroenteritis. Nausea, vomiting, diarrhoea and abdominal pain develop within hours of absorption, with in some cases pains in the limbs, cardiovascular and respiratory involvement. In other cases of acute poisoning paraesthesia has been the presenting symptom. (Wainwright et al., 1988). After a few days, involvement of the nervous system becomes apparent, with paraesthesia, exquisitely painful and tender extremities, muscle weakness, mental confusion or delirium, convulsions with circulatory and respiratory involvement followed by death. Where the period of survival extends beyond one week or so a varied neurological picture may develop involving the central, peripheral and autonomic nervous systems with persistent headache, both sensory and motor neuropathy, cranial nerve involvement with retrobulbar neuritis, ataxia and tremor. Tachycardia, cardiac arrhythmias and hypertension may also develop.

In survivors the neurological features progress with a steady proximal spread to involve cranial nerves, eye muscle innervation and respiratory muscles, which may mimic the pattern of Landry's ascending paralysis, or of Guillain-Barré polyneuritis. After an interval of one to three weeks marked alopecia develops, in which the head hair can be readily pulled away. Further details on the clinical features and treatment of acute thallium poisoning and on the pathological features of the disorder are given by Kazantzis (1986). Less common features have included a syndrome mimicking systemic lupus erythematosus (Alarcon-Segovia et al., 1989) and dermatological involvement with an acneiform eruption and eczematous lesions (Heyl and Barlow, 1989). As a sequel to thallium poisoning, severe deterioration of intellectual function has been reported (Thompson et al., 1988).

The diagnosis is usually established during life by the detection of thallium in urine. Nerve conduction studies have shown evidence of a distal sensorimotor neuropathy, affecting primarily the conduction velocity of the faster fibres, in one reported case of acute poisoning with a urinary thallium concentration of 3.5 mg/litre. (Yokoyama et al., 1990). The peripheral nerve lesion is primarily a distal axonopathy, and it has been stressed that in the less severe cases this may be missed if the plantar nerves of the foot are not examined (Dumitru and Kalantri, 1990). Hair from poisoned patients shows a characteristic black zone filling the root and hair shaft near the root, the intensity corresponding to the degree of severity of the intoxication (Metter and Vock, 1984).

Occupational exposure to thallium has occurred mainly in the course of extraction of the metal and in the manufacture of thallium salts and thallium containing products. Occupational thallium poisoning has been uncommon, and no deaths have been reported. Poisoning has followed long-term, low-level exposure from the inhalation of thallium containing dust or fume, via ingestion from contaminated hands or food or as a result of percutaneous absorption. The clinical course has been characterized by subjective symptoms with fatigue, anorexia, pains in the legs and feet and paraesthesia. In 12 non-fatal cases of industrial thallium poisoning the principal symptoms were reported to be fatigue, limb pains and loss of hair (Munch, 1934). Objective signs where present, have consisted mainly of evidence of polyneuropathy, weakness and slowing of pupillary reflexes and changes in tendon reflexes. Polyneuropathy has in some cases been followed by loss of hair after an interval. In four cases where absorption was thought to follow skin contact in rodenticide manufacture, minor degrees of polyneuropathy and of alopecia were noted, with a maximal urinary thallium excretion of 380 μg/litre (Glomme and Sjostrom, 1955). The diagnosis of occupational thallium poisoning is usually made from the occupational history, from the subjective symptoms detailed above, together with any objective evidence of neurological involvement, from loss of hair and from the thallium concentration in urine.

The underlying biochemical mechanisms of toxicity have been considered by Fowler (1988). Swollen mitochondria and alterations in the endoplasmic reticulum in a number of tissues have been observed following acute *in vivo* exposure to thallium. Mitochondrial swelling and stimulation of succinate oxidation with uncoupling of oxidative phosphorylation is indicative of the inhibitory action of thallium on cellular energy production (Melnick et al., 1976). Delta-amino laevulinic acid dehydratase and ferrochelatase, enzymes of the mitochondrial haemo-biosynthetic pathway are also affected by thallium. A close correlation has been shown with disruption of the hepatic endoplasmic reticulum and these haemo-dependent enzyme activities (Woods and Fowler, 1986).

Thallium has been shown to substitute for potassium in the activation of adenosine triphosphatase of liver plasma membranes. In the presence of sodium, such activation is obtained with thallium concentrations only 10% of those of potassium, while in all other respects the sodium potassium activated and the sodium thallium activated adenosine triphosphatases were identical (Favari and Mourelle, 1985).

Metabolism

Absorption

Water-soluble compounds of thallium are rapidly absorbed following ingestion, inhalation or skin contact. Studies in the rat have shown almost complete absorption following ingestion. In a study in the rat in which ^{204}Tl as a thallous nitrate solution was administered by six different routes, the body burden, as a proportion of the administered dose was found to be similar whatever the route of administration (Lie et al., 1960). It was deduced from this study that complete absorption had occurred from the gastrointestinal tract following ingestion and from the respiratory tract following intratracheal instillation.

Distribution

Following rapid absorption, thallium is widely distributed in the body; in animal studies the highest concentration is found in the kidney, followed by salivary gland, testis, muscle, bone, lymph nodes, gastrointestinal tract, heart, spleen and liver, all of which had relatively small differences in concentration between them (Lie et al., 1960). Thallium concentration in blood remained low indicating rapid equilibration with tissues. In the blood, thallium was located predominantly in the red blood cells. Observations have been limited in humans. In a fatal case reported by Cavanagh et al. (1974) the concentration of thallium in the kidney was found to be 20 mg/kg, heart 13 mg/kg, brain 10 mg/kg, with concentrations between 5–6 mg/kg in skin, liver, bone and muscle.

Experimental evidence suggests that thallium ions are transported across cell membranes by the same mechanism as for potassium. The rapid cellular uptake of thallium in a manner analogous to potassium correlates well with regional perfusion of the myocardium and thus delineates areas of ischaemia or infarction when administered as Tl^{201} in myocardial imaging. However, once inside the cell, thallium is released less readily than potassium. Studies on the interaction between thallium and potassium have been reviewed by Kazantzis (1986).

Excretion

Thallium is excreted in both animals and man via the intestine and the kidneys, the total faecal excretion exceeding urinary. In studies on the rat, thallium has been observed in urine and faeces within one hour of oral administration of thallous sulphate. About two thirds of the body burden of thallium is eliminated in faeces and about one third in urine. However, in severe poisoning constipation commonly occurs, which may reduce faecal elimination to zero, and with renal involvement urinary excretion is also reduced. In human poisoning thallium excretion has been observed in both faeces and urine persisting for many weeks despite low plasma levels. In unexposed persons, the highest tissue concentration of thallium has been found in hair. In the long term, hair and, to a lesser extent, nail provides an important additional route for the slow excretion of thallium from the body. Thallium is also excreted in milk by nursing mothers.

Data are inadequate for the estimation of the biological half-life of thallium in humans, but observations in a single case of severe thallium poisoning, based on the urinary excretion of thallium over a three-month interval, were consistent with a half-life of 30 days (Gastel et al., 1978). In animal studies the toxicokinetics of thallium can be described in terms of a three-compartmental model consisting of:

(i) a fast exchange compartment comprising blood and well perfused peripheral organs;

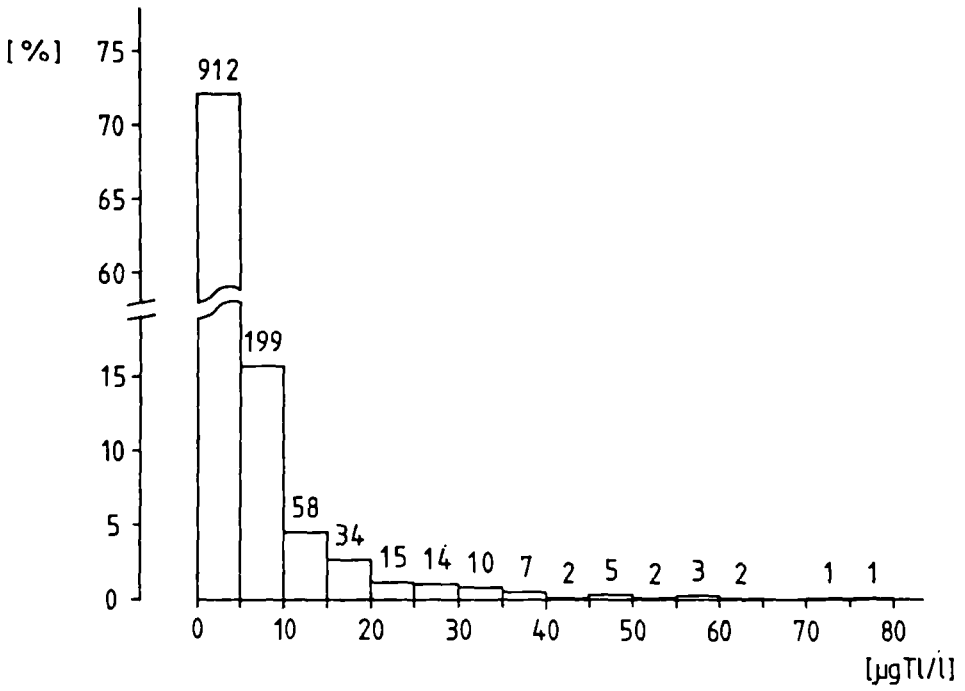

Figure 1: Frequency distribution of thallium concentrations in 24-hour urine samples of a population (N = 1265) living near a cement plant emitting thallium containing dust (Brockhaus et al. 1981)

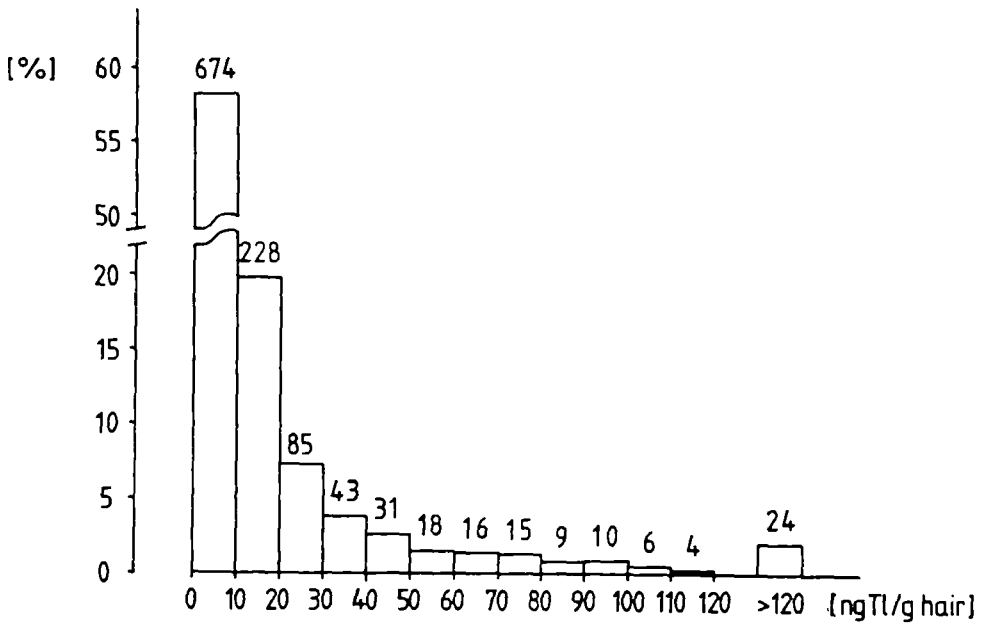

Figure 2: Frequency distribution of thallium concentrations in hair samples of a population (N = 1163) living near a cement plant emitting thallium containing dust (Brockhaus et al. 1981)

(ii) a slow exchange compartment comprising brain as the target organ for neurotoxicity;

(iii) a compartment comprising intestine in which there is an extensive entero-enteral cycle.

This three-compartment model has been shown to be applicable to humans (de Groot and van Heijst, 1988). The elimination half-life after a toxic dose of 10 mg thallium/kg body weight has been estimated to be about 4 days in the rat and 6.5 days in the dog. A total body clearance of about 75 ml/min has been calculated for humans. Because of impaired excretion in both faeces and urine, in severe thallium poisoning half-lives of 9.5 days and 15 days have been reported for patients with impaired elimination (Koshy and Lovejoy, 1981) corresponding with a total body clearance of 20–35 ml/min.

Biological indicators

Indicators of internal dose

Only limited studies have been performed on thallium concentrations in blood and urine in unexposed persons. In one study, the concentration of thallium in whole blood was estimated by atomic absorption spectrophotometry in 320 inner city children in New Jersey between the ages of 1 and 5 years. Values ranged between non-detectable (less than 5 μg/litre) and 80 μg/litre, with a mean concentration of 3.0 μg/litre. About 80% of the children showed no detectable thallium in blood, 17.5% had between 5 and 20 μg/litre, while five children had levels between 40 and 80 μg/litre, although all were without any evidence of thallium toxicity (Singh et al., 1975). The authors stressed that thallium content of blood is not a reliable indicator of body burden of thallium or thallium intake.

Thallium concentration in early morning urine samples in nine non-exposed subjects ranged from 0.13 to 1.69 μg/litre (Weinig and Zink, 1967). Smith and Carson (1977) gave a range of 0.6 μg/litre to 2.0 μg/litre with a mean urinary thallium concentration of 1.3 μg/litre.

Twenty-four hour urine samples and hair samples from over 1 000 subjects living in the vicinity of thallium emitting cement plants together with samples from a reference population were estimated for thallium concentration by electrothermal atomic absorption spectrometry equipped with a heated graphite furnace atomizer (Brockhaus et al., 1981). The mean thallium urinary level in the reference group from the rural area was 0.4 μg/litre ± 0.2 μg/litre, range < 0.1–1.2 μg/litre, and from the urban area 0.3 μg/litre ± 0.2 μg/litre, range < 0.1–0.9 μg/litre. By contrast, in the population living in the vicinity of the cement plant, mean urinary thallium concentration was 5.2 μg/litre ± 8.3 μg/litre with a range from < 0.1–76.5 μg/litre (Geometric mean 2.6 μg/litre.) Hair thallium levels were estimated only in the exposed populations with a mean value of 20.3 ng/g ±42.7 ng/g (Geometric mean 9.5 ng/g.) The frequency distribution for urine and hair thallium concentrations is shown in Figs 1 and 2. A questionnaire was also completed by each subject which included questions on health effects that could be related to increased thallium intake. No control subjects were taken and no objective tests performed. From the replies to the questionnaire a clear dose-response relationship was found between thallium in urine and the prevalence of sleep disorders, tiredness, weakness, nervousness, headache, paraesthesia and muscle and joint pain. A similar exposure-response relationship was found when hair thallium was taken as the indicator of exposure. However, a negative correlation was found between urine and hair thallium levels and hair loss. The thallium content of the pyrite additive used in the cement plants was about 400 ppm, giving rise to a total thallium emission of about 5 kg/24 hours.

From September 1979 the use of thallium additives containing more than 2 ppm was prohibited and the local population was advised to avoid the consumption of home grown foodstuffs. Follow-up studies were performed on the local population together with a health questionnaire as given above, special attention being paid to children attending a kindergarten in the vicinity of the cement plant (Dolgner et al., 1983). As compared with their reference population with a mean urinary thallium level of 0.3 μg/litre ±0.14 μg/litre, thallium excretion fell over a three-month period from a mean of 5.2 ±8.3 μg/litre to a mean of 3.0 ±5.6 μg/litre, with a range from 0.2 to 37.7 μg/litre. Almost 20% of the population studied still had a urinary thallium concentration above

5 μg/litre. No clear evidence of adverse health effects was reported in this study. The authors concluded that there was no likely causal relationship between thallium and the occurrence of congenital malformations in the children identified.

Spot samples of urine were collected for thallium estimation together with a medical history and physical examination from 128 male workers from the cement plants referred to above (Schaller et al., 1980). In contrast to the population sample who had ingested thallium containing locally grown foodstuffs, the thallium levels in the urine of the workers were only slightly or moderately elevated, with a range of less than 0.3–6.3 μg/g creatinine, where an upper normal limit of thallium excretion in urine was computed at 1.1 μg/g creatinine. The investigators reported no evidence of symptoms or signs characteristic of thallium poisoning, but gave no details of the examinations performed.

In a further study on the cement plant workers, 36, selected at random, had thallium levels estimated in blood, urine and hair together with a neurological examination and electrophysiological investigation including motor and sensory nerve conduction velocities, evoked potentials and electroencephalography (Ludolph et al., 1986). One half of the examined workers suffered from concurrent disorders, including diabetes mellitus. While multiple symptoms and signs of neurological disorder were detected, no correlation was found between the electrophysiological findings and thallium levels in blood, urine or hair. Urinary thallium levels were increased above 5 μg/litre in five of the examined workers, blood thallium levels above 2 μg/litre were found in 16 workers and hair thallium levels above 20 μg/kg in four workers. The investigators concluded that more thorough epidemiological techniques would be required to reveal a possible causal relationship between chronic low-dose thallium exposure and neurological deficits.

Urinary thallium was estimated in a group of non-exposed individuals and in workers from two cement factories and two cast iron factories using a sensitive ETA-AAS method with a L'Vov platform and deuterium background correction. (Apostoli et al., 1988) While thallium was not detectable in the materials examined or in air samples from the factories, significantly higher thallium levels were found in the workers compared with the reference sample.

Table 1: Urinary thallium concentrations in workers with suspected thallium exposure (From Apostoli et al., 1988).

Groups	Number	Mean exposure length (years)	Tl Urine μg/litre	
			Mean and SD	Range
Not exposed	72		0.22±0.14	0.06–0.61
Cement factories	30		0.38±0.30[2]	0.08–1.22
Cement workers I	20	14.3±9.3	0.40±0.34	0.08–1.22
Cement workers II	10	11.7±7.4	0.33±0.16	0.09–0.60
Cast iron foundries	21		0.33±0.27[1]	0.06–1.04
Cast iron foundry W1	12	15.4±8.2	0.29±0.21	0.06–0.70
Cast iron foundry W2	9	16.8±7.8	0.38±0.29	0.10–1.04

[1] $P < 0.001$. [2] $P < 0.05$.

A study has recently been completed on unexposed healthy subjects living in three provinces of North Italy with the aim of determining trace element concentrations in urine, whole blood, serum (or plasma) and of determining reliable reference values for a series of elements, including thallium (Minoia et al., 1990). The collection, handling and storage of samples was carried out under rigorous standardized protocols. Analytical procedures included electro-thermal atomic absorption spectroscopy (ETA-AAS), inductively coupled plasma atomic emission spectrometry (ICP-AES) and neutron activation analysis (NAA). The subjects selected for this study were from both urban and rural areas and were screened by means of a questionnaire, clinical examination and a haematological and biochemical series of tests to exclude subjects outside the normal range. Those with a history of occupational exposure to metal compounds, heavy smokers, those under physiological stress and those with certain defined disease categories were excluded. The values obtained for thallium are shown in Table 2.

Table 2: Thallium concentration in 24-hour urine samples, blood and serum of healthy Italians (From Minoia et al., 1990).

Thallium concentration μg/litre

Sample	Number of subjects	Mean ± σ mt[1]	Expl[1] range ($X^L - X^M$)	Reference values (range)	Range of uncertainty	Upper limit metabolic anomalies
Urine	496	0.42±0.09	(0.06–0.82)	0.07 –0.7	> 0.7–0.82	> 0.82
Blood	418	0.39±0.05	(0.1–1.1)	0.15–0 .63	> 0.63–1.1	> 1.1
Serum	360	0.18±0.009	(< 0.05–0.4)	0.02–0.34	> 0.34 0 0.4	> 0.4

[1]Mean value ± σ mt where σ m is $\sigma/n^{1/2}$, σ is the standard deviation, n is the number of observations, and t is the Fischer coefficient for n-1 (p = 0.05).

Hair thallium levels were estimated by inductively coupled argon plasma (ICAP) emission spectroscopy in 199 children and 322 adults from a non-exposed population in a study which sought an age-dependent excretion in hair of a series of metals (Paschal et al., 1989). In adults a geometric mean of 0.056 μg/g hair compared with a geometric mean of 0.066 μg thallium/g hair in children, showing no significant difference.

In a group of 39 workers engaged on the manufacture of alloy anode plates for use in magnesium seawater batteries where one of the magnesium alloys included 5% thallium, 29 workers had urinary thallium levels below 50 μg/litre, seven workers had levels between 50 and 100 μg/litre, while three had values up to 236 μg/litre with a median value of 28.0 μg/litre (Marcus, 1985). Urinary thallium estimation was carried out using the colorimetric method of Jacobs but no details were given. Following the introduction of a code of practice and of atomic absorption spectroscopy (Wall, 1977) for thallium estimation, urinary thallium levels fell to a median value of 0.5 μg/litre, with a highest outlying value of 5.2 μg/litre. Random environmental samples using Casella personal monitors showed a maximum level of airborne thallium of 0.022 mg/m^3. All the workers were without evidence of thallium poisoning, as ascertained through a review of their existing medical records.

It has been proposed (Glomme, 1983) that a urine thallium level of 300 μg/litre should be considered the threshold for thallium poisoning until an agreed figure is established. The ACGIH (1977) stated that despite extensive studies on thallium poisoning, no satisfactory data exist from which to derive an airborne threshold limit value for thallium. The current value of 0.1 mg/m^3 had been based largely on analogy with other highly toxic heavy metals. Marcus (1985), using accepted physiological parameters, considered that 40 hours per week exposure to thallium at an airborne concentration of 0.1 mg/m^3 would correspond to a concentration of thallium in urine of about 100 μg/litre. He considered a level of 300 μg/litre for thallium in urine to be too high and suggested the alerting level requiring action should be no more than 50 μg/litre. It should, however, be pointed out that the purpose of the 300 μg/litre limit proposed by Glomme was considered to be the threshold for thallium poisoning, and not the level at which effective preventive action should be taken.

Indicators of effect

Following long-term, low-level exposure, as has occurred in particular in the occupational environment, a pattern of symptoms and clinical signs compatible with a diagnosis of early or subacute thallium poisoning requires evaluation with regard to a differential diagnosis. In particular paraesthesia requires careful evaluation as an indicator of neurotoxicity. Thallium poisoning should be considered in all cases with unexplained neurological symptoms or signs, in particular where accompanied by painful extremities, and the urine screened for thallium without waiting for hair loss to occur.

Experimental *in vivo* studies have demonstrated inhibition of delta-aminolaevulinic acid dehydratase and ferrochelatase following thallium exposure. Alterations in haemo- and haemo-dependent enzyme activity has been shown to be closely related to disruption of the hepatic endoplasmic reticulum (Woods and Fowler, 1986). It has been suggested that estimation of porphyrins in blood and in urine may prove to be a useful early indicator for evidence of thallium cellular toxicity (Fowler, 1988). Abnormal liver function, in particular raised transaminase levels and abnormal renal function evidenced by proteinuria may also be regarded as indicators of effect.

Conclusions

There are numerous reports of acute thallium poisoning, and the clinical and pathological features of this condition have been extensively described. The adverse health effects of lower level, long-term exposure to thallium require further investigation. It has not as yet been possible to relate subjective symptoms in thallium exposed workers to indicators of internal dose, and no dose-response relationship has been identified. Furthermore, from the nature of the effects produced, in particular on the central and peripheral nervous system, thallium is likely to be a metal with a continuum of toxicity in which clinically apparent effects have their asymptomatic, subclinical precursors. Such biological markers for thallium have yet to be identified.

Estimation of the concentration of thallium in urine is of value in monitoring subjects with occupational exposure.

Data are inadequate for the evaluation of the relationship between occupational exposure levels and thallium concentrations in blood. However, because of rapid disappearance of thallium from blood, it is unlikely that blood levels would be of value for biological monitoring.

Hair and nail clippings, and tissue samples, are of value in the diagnosis of acute thallium poisoning. However, with regard to occupational exposure external contamination of hair may invalidate this approach.

Research needs

The use of urine samples for biological monitoring, in particular with regard to exposure levels in the working environment, requires further evaluation.

The estimation of thallium levels in hair and in nail requires further investigation with regard to their usefulness in monitoring for past exposure, in particular in situations where long-term, low-level exposure may occur.

The estimation of porphyrin levels in blood and in urine requires further study to evaluate the usefulness of this approach in detecting specific early evidence of thallium toxicity.

Because of the occurrence of paraesthesia as an early symptom of thallium poisoning, detailed electrophysiological studies, including both sensory and motor nerve conduction velocity should be performed on thallium exposed workers.

Analytical methods

Simple colorimetric methods are available for the determination of thallium in urine. In the 'rhodamine B method' (Bank et al., 1972), thallous ions are oxidized by adding bromide reagent and complexed with rhodamine B which is extracted with benzene, giving a fluorescent red colour at 254 nm under ultraviolet light. The detection limit for this screening test, which can be applied to one drop of urine, has been given as 0.03 μg/ml.

The routine estimation of thallium in urine and other biological samples is by means of flame or graphite furnace atomic absorption spectroscopy. The methods in current use are sensitive, specific and accurate and these have been reviewed by Leloux et al. (1987a). However, wet digestion and extraction methods have to be used as pretreatment to reach detection limits of 6×10^{-5} g/kg. Using graphite furnace methods detection limits of 5×10^{-6} g/litre can be achieved without additional preconcentration steps. Stabilized temperature platform furnace technology enables isothermal atomization, which can result in higher sensitivity and which is less time consuming than extraction method. (Leloux et al. 1987 b).

Thallium in hair and nail clippings has been estimated by means of neutron activation analysis (Henke and Fitzek, 1971). The detection limit of the method has been given as 0.1 μg/kg. More recently thallium levels in hair have been estimated by ICAP emission spectroscopy (Paschal et al., 1989).

Radiochemical neutron activation analysis has been developed for the estimation of thallium at the cellular level in metabolic studies (Sabbioni et al., 1988).

The need for a rigorous, standardized protocol to minimize contamination of biological samples during collection, handling and storage has been addressed by Minoia et al. (1990).

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II–Tin

Summary

Inorganic tin, predominantly in tetravalent form, is widely but unevenly distributed in the earth's crust and present in many foodstuffs. Mono-, di-, tri- and tetra-organic tin compounds have been synthesized for use in the chemical industry, for use as stabilizers and as biocides. A number of these are environmental pollutants and have produced gross disturbance of ecosystems.

Inorganic tin compounds are of a low order of toxicity. Ingestion of high concentrations of soluble tin salts in canned foods and fruit juices may cause gastroenteritis, while inhalation of tin oxide dust has given rise to a benign pneumoconiosis, without pulmonary fibrosis. In contrast, certain organic tin compounds, in particular trimethyl and triethyl tin, are highly toxic giving rise respectively to cell damage and oedema in the central nervous system. Dibutyl and triphenyl tin cause bile duct damage and liver damage, respectively, and many of these compounds are skin and eye irritants. Immune system suppression has been demonstrated in experimental animals, with thymic atrophy and lymphopenia.

Inorganic tin is poorly absorbed, the highest concentration being found in bone with lower levels in kidney and liver. High concentrations have been found in the lungs which can be considered to be the critical organ in those occupationally exposed to tin oxide. The average concentration of tin in whole blood is of the order of less than 2 ng/ml to 5ng/ml. Excretion occurs via urine and bile. Average urine levels have been variously reported between one and 20 μg/litre, with an increased excretion following an increased daily intake. The biological half-life in human bone has been estimated of the order of 400 days.

With regard to the organic tin compounds, absorption, distribution and metabolism are highly influenced by both number and type of covalently bound radicals. Thus gastrointestinal absorption increases with increasing number of radicals and decreases with size. Absorption also occurs through the skin. Excretion occurs mainly into urine and, to a lesser extent, in faeces via bile. While the central nervous system is the critical organ for organic tin compounds, data on availability and on critical organ concentration are lacking.

Blood and urine are likely to be the most appropriate indicators of internal dose and most useful for biological monitoring for both inorganic and organic tin compounds, although data are inadequate for such monitoring at present in part due to analytical difficulties at low levels. Data are also lacking on indicators of effect.

Both inorganic tin and lead are deposited in bone and inhibit δ-aminolaevulinic acid dehydratase. Both triethyl tin and triethyl lead influence mitochondrial function, the activity of glutathione transferase and the utilization of ATP for sodium and calcium transport.

Research is required in particular to ascertain whether significant interference with the haemo-synthetic pathway occurs in humans and whether this may be of value as an early indicator of effect. Further work is required on analytical procedures to establish the relationship between exposure, concentration in blood and urine and possible health effects. It is necessary to investigate the possible effects on the immune system

of low-level exposure to organic tin compounds in those occupationally exposed, in view of the suppressive effects observed in experimental animals.

Introduction

Chemical and physical properties

Tin (chemical symbol Sn) is a soft, lustrous white metal of tetragonal crystalline form, which converts slowly to grey tin, of cubic form, and which converts further, on heating to over 200 °C to a brittle, white rhombic form. Tin is of atomic number 50, melting at 231.9 °C and boiling at between 2 260–2 270 °C. Tin has oxidation states at +2 and +4, giving rise to a series of stannous and stannic compounds, the latter being more covalently bound. The principal salts of industrial significance are tin oxides, in particular stannic oxide, stannic and stannous chloride, fluorides and halogenated sodium stannates. Tin forms one to four covalent bonds with carbon, giving rise to mono-, di-, tri- and tetraorganic tin compounds, those more commonly encountered being the methyl, ethyl, butyl and octyl organic tins in mono- to tetra-forms, and triphenyl and tricyclohexyl tin. The complex chemistry of tin is considered in detail by Harrison (1989).

Production and industrial uses

Tin is extracted most commonly from stannic oxide; occurring as cassiterite in the earth's crust. A small proportion of tin is recovered from secondary smelting operations. The metal is most used for tin plating, acting as a protective coating for other metals, and because of its pliability and ready combination with other metals, it forms a large number of useful alloys, in particular alloyed with copper to produce bronze. Inorganic tin compounds are used in ceramics and in the textiles industry. A wide range of organic tin compounds have increasing uses as catalysts and in organic synthesis in the chemical industry. The dialkyl tins are used as stabilizers for PVC plastics, the trisubstituted organic tins are widely used as biocides, with in particular tributyl tin used in anti-fouling paints for the protection of ships' hulls from molluscs, and triphenyl tin in agricultural pesticides. Tin is a component of dental amalgam, and tin porphyrins are being developed for their potential use as chemotherapeutic agents.

Environmental and occupational exposure

Tin is widely but unevenly distributed in the earth's crust with soil concentrations between about 2 and 200 μg/kg. Anthropogenic sources greatly exceed natural emissions into the atmosphere, the principal sources being industrial emissions and organic tin biocides. The latter by leaching from paint films on ships' hulls have been responsible for high pollution levels in harbours, marinas and lakes producing gross disturbance of ecosystems (UNEP, 1981). Toxic effects in the aqueous environment have been observed at levels of tributyl tin at or below 1 ppb (Weis and Kim, 1988). Biomethylation of inorganic tin ($Sn+^4$) has been shown to occur in the marine environment (Brinckman and Olson, 1988). Atmospheric concentrations of tin are of the order of 0.01 $\mu g/m^3$ as a background level, rising to 0.3 $\mu g/m^3$ in some urban areas and to over 4 $\mu g/m^3$ in the vicinity of industrial emissions (WHO, 1980). Much higher levels, of the order of several mg/m^3, have been encountered in smelters and workplaces where concentrates of tin ores are handled.

Tin is present in trace amounts in most foods. It has been used extensively for the coating of cans, for household utensils and as tin foil for the wrapping of some foods and pharmaceuticals. Average daily intake has been variously quoted ranging from 187 μg/day (Hamilton and Minski, 1972/73) in the UK to between 1.5 and 8.8 mg/day in the USA (Tipton et al., 1969). In tinned foods, the tin content increases with low pH, high storage temperature and delay in consumption after opening (WHO 1980). Widely varying levels of tin intake in different populations are likely to reflect differences in consumption of tinned foods and in their packaging, lacquered can surfaces reducing the tin content. In one total diet study performed in five Italian towns daily tin intake ranged from 335 μg to 1 410 μg/day (Byrne and Kosta, 1979).

Table 1: Tin content of Italian freeze-dried total diet samples. (From Byrne and Kosta, 1979).

Town diet sample	Dry weight (g)	Tin concentration (μg/g, mean ±SD)	Daily tin intake (μg)
Aosta	310	4.2±0.4	1 300
L'Aquila	173	8.15±0.5	1 410
Montfalcone	278	1.2±0.2	335
Mount Amiata	377	3.5±0.02	1 320
Rome	285	1.2	340

Effects in humans

While tin is a non-essential element, because of its lack of toxicity it has been used extensively in the food industry. However the ingestion of more than 50–100 mg of tin from acid fruit juices stored in unlacquered tin cans has given rise to outbreaks of diarrhoea and vomiting. Similarly the inhalation of tin oxide dust or fumes is relatively non-toxic, although deposition of inhaled particles in the lung gives rise to minute, dense nodular opacities without significant fibrosis or loss of pulmonary function. The radiological appearance of this benign pneumoconiosis is termed stannosis.

The organic tin compounds contrast sharply with regard to their adverse health effects, certain compounds, in particular trimethyl and triethyl tin being highly toxic. In general the toxicity of the trialkyl organic tin compounds is related to the length of the alkyl radical, the short chain compounds being more toxic than the long chain ones, the latter being less readily absorbed (Barnes and Stoner, 1958). The mono-alkyl tin compounds are less toxic, and the toxicity of the tetra-alkyltin compounds is due to the trialkyl compound resulting from enzymic dealkylation. Extensive animal experimental studies have been performed with a variety of organic tin compounds and these have been reviewed by Magos (1986), by Aldridge and Brown (1988), and by Selwyn (1989).

In humans both local and systemic effects have been observed. Workers handling dibutyl and tributyl tin have developed eye and skin irritation with conjunctivitis and diffuse erythematoid dermatitis. Brief contact has resulted in acute burns with early recovery following rapid removal from exposure, but with a lethal effect following prolonged contact.

The target organ following absorption of trialkyl tin is the central nervous system, but speciation of the compound determines the nature of the damage produced. Thus trimethyl tin causes cell loss due to neuronal necrosis in the central nervous system, while triethyl tin gives rise to oedema of the brain and spinal cord with intramyelinic vacuolation. In France, more than 100 people died and several hundreds were poisoned following the ingestion of Stalinon, a proprietary pharmaceutical used for the treatment of acne, which had been contaminated with up to 10% triethyl tin iodide. Symptoms and signs were those of increased intracranial pressure. The principal findings were oedema of the brain and spinal cord (Alajouanine et al., 1958).

Following occupational exposure, a chemist working with trimethyl tin developed insomnia, absent-mindedness and hyperactivity followed by recovery after removal from exposure (Brown et al., 1979). Two other chemists developed similar symptoms which were ignored and which proceeded to mental confusion with generalized epileptiform convulsions. Again, recovery was complete following removal from exposure, (Fortemps et al., 1978). Two farmers handling triphenyl tin acetate used as a fungicidal spray developed asthenia, vertigo, severe headaches, vomiting and photophobia followed by recovery (Manzo et al., 1987). Tremor, hallucinations and psychotic behaviour have also been reported. Of a group of six workers exposed to trimethyl tin, one died after 12 days with neuronal necrosis involving cerebellar Purkinje cells. Two other workers survived with severe memory and cerebellar deficits (Besser et al., 1987).

Bile duct proliferation and liver damage have been observed in animal experimental studies in particular with dibutyl and triphenyl tin compounds. Reports of liver damage following human exposure have been uncommon (Mijatovic, 1972). Dose-related kidney damage has been reported in rats and monkeys with trimethyl tin, ranging from slight vacuolation to extensive degeneration of proximal tubular cells after three days (Opacka and Sparrow, 1985).

Extensive studies have also been performed on animals on the immunosuppressive effects of organic tin compounds. A series of di- and tri-substituted organic tin compounds induce thymus atrophy associated with a reduction in spleen and lymph node

weights and reduction in circulating lymphocytes. Function studies have shown evidence of diminished T-cell mediated immunity and depression of non-specific resistance (Penninks et al., 1990). Observations on immunomodulatory effects in humans are lacking. However inhibition of proliferation of human thymocytes has been demonstrated *in vitro* with dibutyl tin (Penninks and Seinen, 1980).

The high toxicity of the organotin compounds is reflected in the ACGIH threshold limit value (TLV) of 0.1 mg Sn/m^3 compared with 2.0 mg Sn/m^3 for tin, tin oxide and other inorganic compounds with the exception of tin tetrahydride.

Metabolism

Absorption

Following ingestion, inorganic tin is poorly absorbed from the gastrointestinal tract. Two male and two female volunteer subjects with undetectable tin levels in blood (< 2 ng/ml) each consumed 60 mg tin in fruit juice from an unlacquered can. Blood samples taken after two, five and 24 hours showed, in the females, detectable tin at 3 ng/ml only in the five-hour samples. One male showed a peak of 4.7 ng/ml after two hours, the other of 3.9 ng/ml after 24 hours, the remaining samples having undetectable amounts (Byrne and Kosta, 1979). Another study in humans in which 50 mg tin was added to the diet estimated absorption to be of the order of 3% (Johnson and Gregor, 1982). However, when intake was reduced to about 0.1 mg/day, the proportion absorbed increased to about 50% of the total. Following inhalation, tin oxide dust is deposited in the lungs but there are no reliable data on absorption from this site.

The organic tin compounds are more readily absorbed from the gastrointestinal tract. In general, gastrointestinal absorption increases with the number of organic radicals and decreases with their size. In studies in the rat, trimethyl tin has been shown to be almost totally absorbed (Brown et al., 1979) while the absorption of monoethyl tin has been estimated to be of the order of 8%. (Bridges et al., 1967) Similar large differences in absorption have been shown with other organic tin compounds. Absorption of the short chain alkyl tin compounds and of triphenyl tin also occurs through the skin.

Distribution

All human tissues contain tin, in variable amounts. Following absorption inorganic tin accumulates and is stored mainly in bone with lower concentrations in liver and kidneys. The inhalation of tin oxide leads to a progressive accumulation in the lung with age. Following occupational exposure, high levels of tin oxide are found in the lungs.

Following absorption, certain organic tin compounds are followed by enzymic dealkylation. Thus, tetramethyl tin is rapidly dealkylated to trimethyl tin and tetraethyl tin is metabolized to triethyl tin, mainly by the mixed function oxidase system in the liver (Cremer, 1959).

While there are extensive data on the distribution of a number of organic tin compounds in experimental animals, data in humans are lacking. In general, tissue distribution differs both with speciation of the organic tin compound and with animal species. Examples are given to illustrate these points: in the rat, retention of injected tin in the brain was found to increase in the following order: tricyclohexyl tin, triphenyl tin, tributyl tin, tripropyl tin, trimethyl tin and triethyl tin (Mushak et al., 1982). Thus, the neurotoxic effects of trimethyl and triethyl tin could in part be attributed to their increased availability to the central nervous system. In the blood of the rat, both trimethyl and triethyl tin are located mainly in the red blood cells, but this is not so in other experimental animals. As a result of this high affinity of rat haemoglobin for these two alkyl tin compounds, four hours following the intravenous injection of 10 μg/kg triethyl tin chloride the blood concentration of tin was found to be 26.6 μg/ml in rats and just below 1.0 μg/ml in hamsters and guinea-pigs (Rose and Aldridge, 1968) The tissue concentrations 24 hours following injection were, in decreasing order, blood, liver, kidney and brain. In the rat, following oral administration, dimethyl tin has been shown to cross the placental barrier and to accumulate in foetal brain (Noland et al., 1983). Further data on tissue distribution of organic tin compounds in animal species are given by Magos (1986).

Excretion

Inorganic tin is excreted mainly into urine and to a lesser extent in faeces via the bile. In humans, an increased dietary intake of inorganic tin is reflected by an increased excretion in the urine (Johnson and Gregor, 1982). Mono- di- and trimethyl tin have been identified in human urine samples (Braman and Tompkins, 1979).

Organic tin compounds are also excreted mainly into urine and to a lesser extent into faeces via the bile, but with certain exceptions. Thus, due to high biliary excretion, the faecal excretion of diethyl tin in the rat was found to be twice as high as the urinary excretion (Bridges et al., 1967).

After occupational exposure to triphenyl tin, the urinary excretion of tin has been shown to be increased (Manzo et al., 1981).

Biological indicators

Indicators of internal dose

Widely varying values have been reported by different investigators for levels of tin in blood and in urine in the general population, in part due to analytical problems at low levels and to the lack of inter-laboratory comparison. Normal values for tin in blood have ranged from non-detectable to 290 μg/litre and in urine between 1.0 and 65 μg/litre in different studies. More recent studies have shown lower values, probably to be related to improved analytical procedures. Thus, the mean concentration of tin in blood has been given as 5 μg/litre (Hamilton et al., 1972/73), and in a series of 14 unexposed subjects, below a detection unit of 2 ng/ml (Byrne and Kosta, 1979). Total tin concentration in plasma was found to be 3.3±2.92 μg/100 g in a group of eight workers engaged in soldering processes, compared with 1.76±0.35 μg/100 g in a group of controls. (Ogihara et al., 1981)

In urine, in a series of 11 unexposed male subjects the average tin concentration was 1.0 μg/litre, of which 18% of the total excreted was present in methylated forms (Braman and Tompkins, 1979). The individual values are shown in Table 2. Possible mechanisms for the biomethylation of tin on the basis of oxidation-reduction chemistry and the environmental conditions under which this may occur are considered by Ridley et al. (1977).

Table 2: Analysis of human urine samples for total and methylated forms of tin. (From Braman and Tompkins, 1979).

Subject	Tin	(IV)<	Methyltin		Dimethyltin		Trimethyltin		Total tin
(Age)	μg/litre	(%)	μg/litre	(%)	μg/litre	(%)	μg/litre	(%)	μg/litre
26	0.36	64	ND	–	0.067	12	0.13	23	0.56
47	1.0	83	0.041	3.4	0.11	9.2	0.017	1.4	1.2
28	0.72	87	0.028	3.4	0.074	8.9	0.007	0.82	0.83
28	0.92	77	0.089	7.4	0.11	9.2	0.041	3.4	1.2
28	0.27	40	0.32	48	0.003	9.4	0.016	2.4	0.67
26	0.93	90	ND	–	0.074	7.2	0.029	2.3	1.0
30	1.1	85	0.15	12	0.049	3.8	ND	–	1.3
25	1.1	69	0.27	17	0.17	11	0.074	4.6	1.6
26	0.88	95	ND	–	0.035	3.8	0.012	1.3	0.93
25	0.06	85	0.043	5.5	0.054	6.9	0.0023	2.9	0.78
30	1.1	92	0.054	4.5	ND	–	0.055	4.6	1.2
Average	0.82	82	0.09	9.0	0.073	7.3	0.042	4.2	1.0

(ND < 0.02 μg/litre)

Data on blood and urine levels following occupational exposure to organotin compounds are lacking. Because of analytical difficulties regarding speciation, total tin concentration in blood and urine are likely to be the better indicators of exposure. In one case of clinical poisoning by triphenyl tin acetate followed by recovery, samples taken on the day of exposure, showed by neutron activation analysis mean values of 48±29 ng tin/ml for blood and 113±20.6 ng tin/ml urine on six determinations (Manzo et al., 1981).

Indicators of effect

There are no validated, specific indicators of effect for tin or its compounds. Inhalational exposure to inorganic tin, as occurs in the occupational environment, is best monitored by means of routine chest X-ray, early evidence of stannosis, a benign pneumoconiosis, being an increase in bronchovascular markings and hilar thickening. (Schuler et al., 1958)

As with inorganic lead, inorganic tin has been shown experimentally to inhibit delta-aminolaevulinic acid dehydratase with increased coproporphyrin levels in blood and urine (Chiba et al., 1980). In this study rabbits injected with tin chloride at 5 μmol/kg body weight sustained a decrease in erythrocyte delta ALAD to almost zero levels, which remained low for two days before increasing to normal. Tin has been shown to increase haemo-oxygenase activity in liver and kidney and to decrease the mitochondrial concentration of respiratory cytochromes (Kappas and Maines, 1976).

Triethyl tin accumulates in brain mitochondria, inhibits oxidative phosphorylation and glucose oxidation and the incorporation of phosphate into brain phospholipids (Rose and Aldridge, 1968; Aldridge and Street, 1971; and Cremer, 1970). A number of other enzymes are inhibited by triethyl and trimethyl tin (See Aldridge and Brown, 1988). These include adenosine triphosphatases, cytochrome oxidase, NADP transhydrogenase, hexokinase, pyruvate kinase, glutatione-s-transferase and cytochrome P-450 in liver and adenylate cyclase in brain.

There is at present no evidence that any of the above possible mechanisms of action could provide indicators of early effect following human exposure. Similarly, there are no studies in humans exposed to the di- and tri-substituted organic tin compounds to show whether the immunosuppressive effects demonstrated in experimental animals produce effects in humans which could be of value as early indicators of effect.

Conclusions

Inorganic tin and its more commonly encountered compounds in the general and the occupational environment are of a low order of toxicity. Numerous animal experimental studies with a range of mono-, di-, tri- and tetra-substituted organic tin compounds have shown a wide range of toxic effects involving, in particular, the nervous system, the liver and biliary system, the kidney, the immune system, the skin and mucous membranes. Complex interactions with cellular proteins and enzymes have been demonstrated. The speciation of the organic tin compound is critical with regard to the effect produced, there is also evidence for species specificity. Of the large number of organic tin compounds synthesized, triethyl tin has exhibited the greatest hazard to humans followed by trimethyltin and tripropyltin. Tributyl tin, because of its use as an anti-fouling agent, has been responsible for gross disturbance of marine ecosystems but has been less toxic to mammals.

While, following exposure, tin both in inorganic and organic forms is present in blood and is excreted in urine, analytical methods have been insufficiently precise and speciation of organic tin compounds has been inadequate to enable blood and urine levels to be used for biological monitoring as indicators of absorption. There are no quantitative data on the relationship between occupational exposure to organic tins at different levels, the corresponding concentrations in blood and urine and their relationship to adverse health effects.

There are currently no early indicators of effect applicable to either inorganic or organic tin compounds.

Biological monitoring of workers exposed to inorganic or organic tin compounds is not currently feasible because of inadequate data on indicators of internal dose and of early effect.

Research needs

(i) The validation of reference values for inorganic tin in blood and urine and the speciation of organic tin compounds in biological samples.

(ii) Studies on the relationship between concentrations of tin in blood and urine and exposure levels, both in the occupational and the general environment.

(iii) To ascertain whether the effects of tin on haemosynthesis and on porphyrin metabolism observed in experimental animals also occur in humans and if so to assess whether these might be used as early indicators of effect (Alessio and Dell'Orto, 1988).

(iv) To ascertain whether abnormalities of liver function or of renal function, in particular renal tubular dysfunction, may occur following low-level exposure to organic tin compounds.

(v) To ascertain whether the immunosuppressive effects of the organic tins demonstrated in experimental animals also occur in humans and to ascertain whether surveillance of the immune response in workers exposed to organic tin compounds may provide an early indicator of an adverse effect.

Analytical methods

A variety of analytical techniques have been used for estimating tin in biological and environmental samples. These include spark source spectrometry, emission spectroscopy, neutron activation analysis, total reflecting X-ray fluorescence, isotope dilution mass spectrometry and atomic absorption spectrometry with flame, furnace and hydride/cold vapour techniques. Platform furnace techniques with correction systems based on the Zeeman effect have increased detection power and reliability for estimation of tin in biological samples at low levels (Stoeppler, 1988). The wide range of normal values for blood and urine quoted, with lower levels in more recent publications could in part be due to lower levels of tin intake in food in more recent years but in larger part to improved analytical methodology. The lack of inter-laboratory comparison procedures makes it difficult to evaluate their precision and accuracy. Weber (1985) considered that tin concentrations in blood, plasma and urine cannot at the present time be regarded as reliable.

With regard to the organic tin compounds, because of the analytical problems involved in their speciation in blood and urine, total tin concentration is perhaps the most useful indicator. The gas chromatographic speciation of hydrated tin compounds followed by atomic absorption spectrophotometric estimation is one promising approach to the problem (Jackson et al., 1982).

With regard to the environment, the analysis of organic tin compounds in water and in marine and other sediments is one of the most actively researched areas in environmental organometallic chemistry. A summary of 27 reported methods over the period 1978 to 1988 of quantitative analysis of alkyl tin compounds from environmental matrices is given by Ashby et al., (1988).

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