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Environmental Health Criteria 18

ARSENIC

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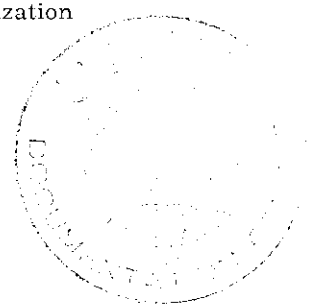

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Division of Environmental Health, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

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Members of the Task Group on Environmental Criteria for Arsenic met in Stockholm from 28 January to 1 February 1980. The meeting was opened on behalf of the Director-General by Mr G. Ozolins, Associate Manager, Environmental Health Criteria and Standards. The Task Group reviewed and revised the draft criteria document and made an evaluation of the health risks from exposure to arsenic and its compounds.

The meeting worked in two subgroups, one on chemical and environmental aspects and metabolism (subgroup 1) and the other on effects (subgroup 2). Comments of the subgroups were discussed in plenary sessions and the conclusions were drawn by the whole group.

The first draft of the biomedical parts of the document was prepared at the WHO Collaborating Centre for Environmental Health Effects, Departments of Environmental Hygiene of the Karolinska Institute and the National Environment Protection Board, Stockholm, Sweden. Dr G. Pershagen and Ms M. Vahter were primarily responsible for its preparation. Discussions were held with a group preparing a report on arsenic for the Health Directorate of the Commission of the European Communities, Luxembourg and the draft was reviewed and revised at a consultation arranged by WHO at the Karolinska Institute in Stockholm from 4 to 6 October, 1978.

The second draft, which was sent out to the national focal points for environmental health criteria documents, included sections on the chemical and environmental aspects of arsenic prepared by Dr. R. S. Braman, Department of Chemistry, University of South Florida, Tampa, FL, USA.

The third draft was prepared by Dr R. S. Braman and Dr G. Pershagen based on comments from the national focal points in Australia, Belgium, Canada, Chile, Finland, Federal Republic of Germany, Greece, Japan, Mexico, New Zealand, Poland, the United Kingdom, and the USA, and from the International Labour Office (ILO) and the American Smelting and Refining Company (ASARCO).

The document, scientifically edited by Dr G. Pershagen and Ms M. Vahter and reviewed by Dr V. B. Vouk, is based primarily on original publications listed in the reference section. However, some comprehensive reviews on the health effects of arsenic including Fowler (1977), NAS (1977), IARC (1973, 1980), and Pershagen & Vahter (1979) have also been used.

The possible role of arsenic as an essential element and the effects of arsine have not been discussed in this document.

Details of the WHO Environmental Health Criteria Programme, including some of the terms frequently used in the documents, may

be found in the introduction to the Environmental Health Criteria Programme published together with the environmental health criteria document on mercury (Environmental Health Criteria 1 — Mercury, World Health Organization, Geneva, 1976), and now available as a reprint.

Mrs M. Dahlquist at the WHO Collaborating Centre for Environmental Health Effects, Stockholm, acted as technical and administrative assistant and her work is greatly appreciated.

* * *

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1. SUMMARY AND RECOMMENDATIONS FOR FURTHER RESEARCH

1.1 Summary

1.1.1 Properties, uses and analytical procedures

1.1.1.1 *Properties and uses*

Arsenic is a ubiquitous element with metalloid properties. Its chemistry is complex and there are many different compounds of both inorganic and organic arsenic. In nature, it is widely distributed in a number of minerals, mainly as the arsenides of copper, nickel, and iron, or as arsenic sulfide or oxide. In water, arsenic is usually found in the form of arsenate or arsenite. Methylated arsenic compounds occur naturally in the environment as the result of biological activity. The most important commercial compound, arsenic(III) oxide, is produced as a by-product in the smelting of copper and lead ores.

Arsenic compounds are mainly used in agriculture and forestry as pesticides, herbicides, and silvicides; smaller amounts are used in the glass and ceramics industries and as feed additives.

1.1.1.2 *Analytical procedures*

If total arsenic has to be determined, the first step usually consists of complete mineralization. The arsenic can then be measured directly by, for example, flame or graphite tube atomic absorption spectrophotometry (AAS). In an ordinary flame, the detection limit is 0.5—1 mg/litre. Using a long-path cell, a detection limit of a few μg/litre can be obtained.

The most commonly used techniques for the determination of arsenic involve its transformation into arsine. Subsequent measurements of arsine can be carried out using, spectrophotometry, flames and electrothermal devices for AAS, atomic fluorescence (AFS), or atomic emission spectroscopy (AES).

Spectrophotometry of the silver diethyldithiocarbamate complex of arsine has been used for several years, and is suitable for determining arsenic levels in the range of 1—100 μg. Passing the arsine, generated, for instance, by sodium borohydride, into a heated tube of an AAS or AES instrument gives an absolute detection limit of about 0.5 ng. If oxidation can be avoided prior to the arsine generation step, it is possible to differentiate between As(III) and As(V) by changing the pH value at this step. Furthermore, cold trapping of the arsines and separation upon heating can be used for the separation and detection of inorganic and methylated arsenic compounds present in natural waters and urine. Other separation methods include ion exchange chromatography, gas chromatography, and liquid chromatography.

Neutron activation analysis using radiochemical separation is a very sensitive method for the determination of arsenic, with detection limits near 1 ng.

1.1.2 Environmental transport and distribution

Arsenic is mainly transported in the environment by water. Sedimentation of arsenic in association with iron and aluminium may sometimes be considerable. In oxygenated water, arsenic usually occurs as arsenate, but under reducing conditions, for instance, in deep well waters, arsenite predominates. Methylation of inorganic arsenic to methyl- and dimethylarsenic acids is associated with biological activity in water. Some marine organisms have been shown to transform inorganic arsenic into more complex organic compounds, such as arsenobetaine, arsenocholine, and arsoniumphospholipids.

In oxygenated soil, inorganic arsenic[a] is present in the pentavalent form. Under reducing conditions, it is in the trivalent form. Leaching of arsenate is slow, because of binding to hydrous oxides of iron and aluminium. There is ample evidence of biomethylation in the soil and of the release of methylarsines into the air and high levels of methylated arsenic compound have been detected in greenhouse air. However, airborne arsenic is mainly inorganic.

1.1.3 Exposure

Because the metabolic fates and toxicities of arsenic compounds differ, it is important to distinguish between them in the environment. The forms of arsenic to which man is actually exposed have

[a] Abbreviations "inorganic arsenic" and "organic arsenic" mean "arsenic and its inorganic compounds" and "organic arsenic compounds", respectively.

not been considered in detail until recently, mainly because of a lack of suitable analytical methods.

Airborne concentrations of arsenic in urban areas may range from a few nanograms to a few tenths of a microgram per cubic metre. Near point emissions of arsenic, such as smelters, airborne arsenic concentrations have exceeded 1 $\mu g/m^3$. Drinking water ordinarily contains a few micrograms of arsenic per litre or less, mainly in the form of inorganic compounds. Levels exceeding 1 mg/litre recorded in some areas, have usually been naturally occurring, but have sometimes been the result of industrial contamination.

Arsenic is present in most foodstuffs in concentrations of less than 1 mg/kg. However, marine fish may contain arsenic concentrations of up to 5 mg/kg wet weight and concentrations in some crustacea and bottom-feeding fish may reach several tens of milligrams per kilogram, predominantly in the form of organic arsenic. Accumulation of arsenic in the tissues of poultry and swine can result from the use of some organic arsenic compounds as feed additives.

Wine and mineral waters can sometimes contain several hundreds of micrograms of arsenic per litre, probably as a result of the use of arsenic-containing pesticides. Inorganic forms of arsenic have been shown to predominate in wine.

The total daily intake of arsenic by man is greatly influenced by the amount of seafood in the diet, but it is usually less than 0.2 mg per day. Normally, the daily intake of inorganic arsenic will not exceed 50 μg. Depending on the content of arsenic in tobacco, an average smoker may inhale between a few micrograms and 20 μg of arsenic daily. Some decades ago, when the arsenic content of tobacco was higher, more than 100 μg might have been inhaled per day. The chemical form of arsenic in tobacco smoke is not known.

Various arsenic compounds have been used in medicine for many years. Inorganic trivalent arsenic, often in the form of sodium arsenite (Fowler's solution) has been used for the treatment of leukaemia, psoriasis, and as a tonic, frequently at a dose of several milligrams daily. Some inorganic as well as organic arsenic compounds are still used in drugs in a number of countries.

Occupational exposure to arsenic mainly occurs through the inhalation of particles containing arsenic, i.e., among smelter workers and workers engaged in the production and use of arsenic-containing pesticides. Concentrations in air ranging from a few micrograms to more than 1 mg/m^3 have been reported.

1.1.4 Metabolism

Studies on animals and man have shown that both trivalent and pentavalent inorganic arsenic compounds in solution are readily

absorbed after ingestion. Inhalation usually involves particles containing inorganic arsenic. Most of the inhaled and deposited arsenic will probably be absorbed from either the respiratory or the gastrointestinal tract.

The biological half-time of arsenic in rats is long (60 days), because of its accumulation in erythrocytes. In other animals and in man, most inorganic arsenic is eliminated at a much higher rate, mainly via the kidneys. As far as exposure to trivalent arsenic in a single dose is concerned, both animal and human data indicate an initial elimination of about 75% in the urine and a few percent in the faeces during the first days or, at the most, the first week. As for pentavalent arsenic, a few animal experiments have indicated that 80—90% of a single dose is eliminated during the first 2 days, while available human data indicate a slower rate of elimination. Animal data show a somewhat higher retention of arsenic in different organs after exposure to trivalent arsenic than after exposure to the pentavalent form. The differences increase with increasing dose levels.

Placental transfer of inorganic arsenic has been demonstrated in both experimental animal (rat and hamster) and human studies. In a study on rats, dimethylarsinic acid was shown to pass through the placental barrier, the blood values in the fetus being comparable with those of the mother.

No data are available which indicate that long-term accumulation of arsenic exists. Some data on mice and rabbits exposed for up to one year to arsenic indicated that levels of arsenic in the body increased during the first 2 weeks and then decreased. There are very few data concerning accumulation in people heavily exposed to inorganic arsenic, such as industrial populations or populations in areas where the drinking water contains high levels of arsenic. However, some data have indicated that arsenic levels in the lungs of smelter workers, several years after exposure, were 6 times those of controls. The concentrations of arsenic in human tissues seem to be log-normally distributed and the highest levels are generally found in hair, skin, and nails.

In vivo methylation of inorganic arsenic has been demonstrated in both animals and man. Following ingestion or inhalation of inorganic arsenic, the major forms of arsenic excreted in human urine are dimethylarsinic acid and methylarsonic acid accounting for about 65% and 20% of excreted arsenic, respectively. In other species, methylarsonic acid has only been observed in minimal amounts.

In both animals and man, organic arsenic compounds ingested via fish and crustacea are readily absorbed from the gastrointestinal tract and 70%—80% is eliminated within a week, mainly in the urine. Some data indicate that these compounds are eliminated without being converted to inorganic arsenic or simple methylated arsenic

compounds. Organic arsenic compounds from other sources show various degrees of absorption, transformation, and retention.

1.1.5 Normal levels in man and biological indicators of exposure

In subjects not known to have been exposed to arsenic, whole blood arsenic levels are in the range of only a few micrograms per litre, while in persons exposed to water containing high levels of arsenic, whole blood levels exceeding 50 μg/litre have been reported. No data are available on the influence of dietary habits on arsenic levels in blood.

Studies on the metabolism of inorganic arsenic show that in most animals and man arsenic is taken up readily by the blood and also rapidly cleared. Arsenic in blood will therefore reflect exposure for only a short period following absorption and will be highly time-dependent. If exposure is continuous, as may be the case with drinking water, it should be possible to find a relationship between arsenic levels in blood and exposure. However, such studies have not been carried out.

Effects of arsenic have been seen in a large number of organs in both animals and man. However, data are not available from which it is possible to correlate such effects with tissue concentrations, or with the concentrations in blood. It has not been possible to define a critical organ for arsenic in the way that the kidney is considered a critical organ for chronic cadmium intoxication and the central nervous system for methylmercury intoxication. The short half-time of arsenic in the blood compared with those in the whole body and individual organs makes it difficult to establish a relationship between concentrations of arsenic in blood and the total body burden. A metabolic model for arsenic has not yet been developed.

Arsenic concentrations in the urine of persons who have not been excessively exposed to arsenic through, for example, occupation or dietary habits, have been estimated to range from 10 to 50 μg/litre. Excretion of up to a few milligrams of arsenic in the urine on the first day following ingestion of fish with a high arsenic content has been reported.

Smelter workers exposed to inorganic arsenic compounds may have urine values of a few hundred micrograms per litre. One study indicated that the major part of the arsenic was excreted as dimethylarsinic acid. Increased urinary levels of arsenic have also been observed in persons living around point sources emitting arsenic.

Urine is a suitable indicator medium for assessment of exposure to inorganic arsenic, since most studies show that the elimination of arsenic, in both animals and man, takes place mainly via the kidneys. A method of assessment must be used that differen-

tiates between the organic arsenic compounds from sea food and the main metabolites of inorganic arsenic.

Arsenic levels in the hair of unexposed human adults are usually below 1 mg/kg. There are no published data to indicate whether exposure to arsenic in sea food results in increased hair values. Levels of up to about 80 mk/kg have been recorded in subjects with chronic arsenic poisoning caused by ingestion of contaminated well water.

The use of arsenic concentrations in hair as an indicator of exposure to airborne arsenic is limited, as no reliable method exists for distinguishing between arsenic from external contamination and arsenic that has been absorbed and metabolized in the body.

1.1.6 Effects and evaluation of health risks

1.1.6.1 *Inorganic arsenic compounds*

Acute and subacute effects of arsenic may involve many organ systems including the respiratory, gastrointestinal, cardiovascular, nervous, and haematopoietic systems. Unfortunately, in most cases of human intoxication, the doses and valence states of arsenic have not been determined. Data from studies on experimental animals indicate that trivalent inorganic arsenic is more toxic than pentavalent. It is also evident that arsenic in solution is more toxic than undissolved arsenic, probably because of better absorption. An ingested dose of 70—180 mg of arsenic (III) oxide has been reported to be fatal in man.

Long-term exposure to inorganic arsenic has been found to give rise to effects in a large number of organs. However, in general, the details of human exposure (e.g., type of arsenic compound), have been inadequate for the establishment of dose-response relationships.

Lesions of the upper respiratory tract including perforation of the nasal septum, laryngitis, pharyngitis, and bronchitis have frequently been encountered in workers in the smelting industry exposed to high levels of arsenic. In general, such lesions have been reported in instances of prolonged exposure to several hundred micrograms of arsenic per cubic metre of air and mostly with arsenic in the trivalent inorganic form. In the case of lower respiratory tract lesions in workers in the smelting industry, the influence of concurrent exposure to high levels of sulfur dioxide should be considered as well as interaction with tobacco smoking.

Inorganic arsenic in the trivalent state can give rise to skin lesions in man, especially palmo-plantar hyperkeratosis which has a characteristic appearance. It has been observed in patients under prolonged medication with Fowler's solution, who have received daily doses of arsenic of up to 10 mg. In one study, the incidence

of hyperkeratosis was reported to be over 50% in a group of patients, each of whom had received a total dose of more than 3 g of arsenic. Palmo-plantar hyperkeratosis has also been reported following ingestion of arsenic in drinking water (oxidation state not determined) in some parts of the world including Argentina, China (Province of Taiwan) and Mexico. Other dermatological symptoms, including hyperpigmentation, have also appeared in inhabitants of these areas.

It should be noted that hyperkeratotic lesions of the palms and soles and hyperpigmentation are very rare among smelter workers exposed to inorganic arsenic, but have been reported in other occupational situations. The reason for this discrepancy is not clear but could be the result of differences in dose.

Disturbances of liver function have been observed in both man and animals after chronic exposure to inorganic arsenic. An association between medication with trivalent inorganic arsenic and the development of portal hypertension in man has been suggested, though this has not been reported in experimental animals. Indications of severe hepatic damage resulting in cirrhosis, have come from both epidemiological and toxicological data. The role of alcohol consumption in situations of arsenic exposure has, unfortunately, not been considered in most of the studies.

Evidence of effects on the heart, including minor ECG changes, has been found in human subjects after exposure to comparatively high doses of arsenic, which produced other symptoms and signs of intoxication. These findings have been supported by animal data. A moderate excess mortality attributed to cardiovascular lesions was detected in 2 independent epidemiological studies on smelter workers exposed to high levels of airborne, inorganic arsenic (exposure levels not given). This finding has not been confirmed in other studies on workers exposed to arsenic.

Peripheral vascular disturbances have been reported in some areas of the world where heavy exposure due to ingestion of inorganic arsenic has occurred, e.g., in Chile, China (Province of Taiwan) and the Federal Republic of Germany. Exposures have been of the order of several hundred micrograms to over one milligram daily; the valence state is not known. Generally, peripheral vascular changes have not been reported in connexion with occupational exposure to inorganic arsenic, and, unfortunately, their possible existence in arsenic-exposed animals has not been considered.

Inorganic arsenic can exert chronic effects on the peripheral nervous system in man. The only information on these effects as far as occupational exposure is concerned comes from case reports, and exposure levels have not been given. It is obviously difficult to draw any conclusions from such reports. Disturbances of CNS function were reported in Japanese youths, 15 years after they had

been exposed as infants to inorganic arsenic in average daily doses of 3.5 mg for about one month. The effects included severe hearing loss and electroencephalographic abnormalities. CNS effects have also been reproduced in animals. Children living near a coal-fired power plant, which emitted large amounts of arsenic, were reported to have moderate hearing losses, but such effects were not confirmed in another instance of exposure to elevated levels of inorganic arsenic in ambient air. Ingestion of moderate amounts of inorganic arsenic at levels of a few hundred micrograms daily in drinking water (length of exposure and valence state of arsenic unknown) has been associated with abnormal electromyographic findings in one study. This effect might serve as a sensitive indicator of arsenic intoxication, but the association must be identified and evaluated elsewhere before any definite conclusions can be drawn.

Because inorganic trivalent arsenic has an effect on the haematopoietic system, it has been used for several decades as a therapeutic agent for various forms of leukaemia, often in doses of several milligrams daily. The impaired resistance to viral infections, associated with arsenic exposure in some animal studies, should be noted, when considering the high frequency of chronic cough, bronchopulmonary disease, and lip herpes observed in persons exposed to arsenic in water in Chile. The lack of evidence of these effects in other studies on human subjects is worth noting. Animal data suggest that arsenic exposure may have chronic effects on the kidneys, but this has not been confirmed for human exposure situations.

There are both *in vivo* and *in vitro* studies indicating effects of inorganic arsenic on human chromosomes. An increased frequency of chromosomal aberrations has been found among persons exposed to arsenic, mainly in the trivalent form, through medication. Similar findings have been reported among workers exposed to arsenic. However, the exposure of these workers to other toxic substances may have been of importance.

Several studies have indicated that inorganic arsenic affects DNA repair mechanisms.

Human data on the teratogenicity of inorganic arsenic are lacking. One epidemiological study on the offspring of women working at a copper smelter, where high levels of airborne arsenic were registered in some workplaces, pointed towards an increased frequency of malformations and spontaneous abortions. Since exposure to several other toxic substances also took place, no conclusions can be drawn as to the specific role of arsenic.

Results of studies on hamsters, rats, and mice have shown that high doses of both trivalent and pentavalent inorganic arsenic induce teratogenic effects. The high doses used in these studies make it difficult to judge how significant such animal data are for man.

There is substantial epidemiological evidence of respiratory carcinogenicity in association with exposure to mainly inorganic arsenic in the manufacture of arsenic-containing insecticides. However, conclusions cannot be drawn on the carcinogenic potential of trivalent versus pentavalent inorganic compounds since exposure to both forms occurred in these workplaces. A possible association between the use of pesticides containing arsenic, often in the form of arsenate, in vineyards and orchards, and in an increased risk of lung cancer has been found, but the data are not conclusive.

The carcinogenic potential of inorganic arsenic in smelter environments is evident from many epidemiological studies. One report revealed a roughly linear relationship between cumulative arsenic exposure and lung cancer risk. Although exposure data are uncertain, it is estimated that exposure to airborne arsenic levels of about 50 $\mu g/m^3$ (probably mostly arsenic (III) oxide) for more than 25 years could result in a nearly 3-fold increase in the mortality rate of cancer in the respiratory tract after the age of 65 years.

Exposure to inorganic arsenic can cause skin cancer, mainly tumours of low malignancy. This has been observed following ingestion of arsenic in drinking water or drugs resulting in a total intake of several grams of arsenic over a number of decades. The form of arsenic in drinking water has yet to be elucidated, but in medication it has most often been inorganic trivalent arsenic.

The association between arsenic and tumours of other organs, most notably the liver and lymphatic and haematopoietic system, needs further confirmation.

At present, no definite evidence exists to show that inorganic arsenic compounds are carcinogenic to animals. This holds true as far as both tumour initiation and promotion are concerned. Results of four studies on rats and mice, however, suggest that arsenic plays a role in the development of tumours of the lung and the haemapoietic system.

An attempt has been made to assess the risk of cancer of the lung and skin from low doses of arsenic by extrapolating data concerning the risks from relatively high doses.

1.1.6.2 *Organic arsenic compounds*

Medication with some organic arsenic compounds such as [4-[2-amino-2 oxoethyl]-amino]-phenyl] arsonic acid (tryparsamide), has induced side-effects, mainly in the central nervous system. These include encephalopathy and optic atrophy. Toxic effects on the nervous system have been reproduced in experimental animals fed high doses of arsanilic acid, which is commonly used as a feed additive for poultry and swine. Limited data indi-

cate that the toxicity of the organic arsenic compounds present in seafood is low.

No conclusive evidence of carcinogenic activity has been reported for any of the organoarsenic compounds tested in experimental animals.

1.2 Recommendations For Further Research

1.2.1 Sampling and analysis

A number of important problems remain to be solved in the following areas:

(*a*) sampling of arsenic in air;
(*b*) pretreatment of samples with special attention to seafood arsenic; and
(*c*) differentiation between the various arsenic species, including the identification of the arsenic compounds in seafood.

The development of reference materials for biological specimens is recommended and interlaboratory calibration exercises should be performed.

1.2.2 Exposure

There are only a few dose-response relationships established for the exposure of man to arsenic, mainly because of a lack of reliable exposure data. More data are therefore needed on the exposure levels of arsenic in both general and occupational environments. Continuous monitoring of arsenic in foodstuffs, especially poultry and pork, is required in view of the use of arsenic compounds as feed additives.

It is important not only to get quantitative measurements of the dose but also to determine the chemical form of arsenic. Such qualitative information is lacking for most foodstuffs as well as for cigarette smoke. In fish and crustacea, most of the arsenic has been reported to be in an organic form. However, data on the chemical form of arsenic in seafood from water polluted with inorganic arsenic are required, as fish probably cannot convert inorganic arsenic to organic arsenic compounds.

More studies are needed to understand the volatilization of arsenic into the air. The effect of naturally occurring oxidants such as ozone and nitrogen oxides on volatilized arsines is of particular interest. The oxidants may demethylate methylarsenic compounds and convert them to inorganic forms. The arsenic forms found over the open oceans and in remote regions also need to be determined to assess the impact of volatilization on global transport.

1.2.3 Metabolism and indicators of exposure

In the evaluation of health effects, arsenic has generally been treated as such without any reference to its chemical form, e.g., trivalent or pentavalent inorganic arsenic. Though it has been shown that both forms are methylated *in vivo*, possible quantitative differences have not been studied. Thus, the rate, extent, and mechanism of biomethylation of different forms of arsenic should be further investigated. Conversion of As(V) to the more toxic As(III) in the body has been indicated in some studies, but data are not conclusive. This needs to be further investigated together with the possibility of *in vivo* oxidation. Data on the biotransformation of arsenic compounds are also needed for the identification of biological indicators of exposure to these compounds.

Further efforts should be made to establish a suitable animal model for arsenic.

More data are required on the concentrations of arsenic in human organs in high-exposure groups, including those heavily exposed to seafood arsenic. It has been shown at autopsies that smelter workers may retain arsenic in their lungs for several years after cessation of exposure. It is important to study the nature of this arsenic.

More data are also needed on possible interactions between arsenic and nutrients in the human diet as well as interactions between arsenic and other pollutants in the human environment.

1.2.4 Effects

Dose-response data on various health effects caused by exposure to arsenic are generally very scanty or nonexistent. Damage to the liver and the cardiovascular and nervous systems, reported in some chronic exposure situations, needs to be validated in future studies. In many instances, animal models would be of use. Sensitive indicators of arsenic exposure have been suggested such as the urinary excretion of uroporphyrin or electromyographic abnormalities, but further confirmation is needed.

It has been demonstrated recently that the two major metabolites formed after exposure to inorganic arsenic compounds are methylarsonic acid and dimethylarsinic acid. It is important to study the toxicity of these compounds. Man is also exposed to large amounts of organic arsenic compounds through consumption of some seafoods. Though the acute toxicity of these compounds must be considered to be low, there are very limited data on possible long-term effects. Studies should be carried out on both human subjects and on animals.

Severe effects of exposure to arsenic have been demonstrated in Japan in the form neurological effects and in Chile and China

(Province of Taiwan) in the form of severe vascular disorders. There is a need to carry out followup studies using modern epidemiological techniques. In order to elucidate the cardiovascular diseases, including peripheral vascular disease in Chile and China (Province of Taiwan), it is recommended that WHO should initiate an internationally coordinated study.

Although there is strong epidemiological evidence that inorganic arsenic is carcinogenic for man, more work is needed to determine if this is true for both valence forms. Conclusive animal data are not available. Further epidemiological investigations concerning the relationship between exposure to arsenic and cancer of the lung and skin should be undertaken in both ambient and occupational exposure situations, because of the considerable uncertainty concerning dose-response relationships.

Health effects of arsenic in industry have generally been seen where exposure to arsenic has been combined with exposure to other metals and irritating substances, such as sulfur dioxide. Possible synergism in relation to the carcinogenic activity of arsenic should be investigated in epidemiological studies as well as in experimental systems.

Some data indicate that arsenic may induce effects in the human reproductive system. More studies in this field are needed.

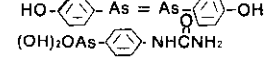
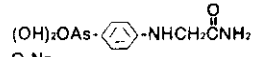
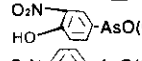
In this document, pulmonary cancer and skin cancer have been regarded as the critical effects in man for long-term exposure to inorganic arsenic through inhalation and oral exposure, respectively. There is still considerable uncertainty regarding the effects of different chemical forms of arsenic and dose-response relationships and it is recommended that these questions should be studied further, both in industry and in the general environment. Studies should comprise both human epidemiological and experimental animal studies. There is also a need for further investigation of the mutagenic activity of different arsenic compounds.

2. PROPERTIES AND ANALYTICAL PROCEDURES

2.1 Chemical and Physical Properties of Arsenic Compounds

There are many different forms of inorganic and organic arsenic. The most important forms for the evaluation of health effects are shown in Table 1.

Table 1. Some common inorganic and organic arsenic compounds

CAS number	Name	Synonyms	Formula
	Inorganic arsenic, trivalent		
1327-53-3	arsenic(III) oxide	arsenic trioxide arsenous oxide white arsenic	As_2O_3 (or As_4O_6)
13464-58-9	arsenous acid		H_3AsO_3
13768-07-05	arsenenous acid arsenites, salts of arsenous acid	arsenious acid	$HAsO_2$ $H_2AsO_3^-$, $HAsO_3^{2-}$ or AsO_3^{3-}
7784-34-1	arsenic(III) chloride	arsenic trichloride arsenous trichloride	$AsCl_3$
1303-33-9	arsenic(III) sulfide	arsenic trisulfide orpiment, auripigment	As_2S_3
	Inorganic arsenic, pentavalent		
1303-28-2	arsenic(V) oxide	arsenic pentoxide	As_2O_5
7778-39-4	arsenic acid	orthoarsenic acid	H_3AsO_4
10102-53-1	arsenenic acid arsenates, salts of arsenic acid (ortho)	metaarsenic acid	$HAsO_3$ $H_2AsO_4^-$, $HAsO_4^{2-}$ or AsO_4^{3-}
	Organic arsenic		
124-58-3	methylarsonic acid	methanearsonic acid	$CH_3AsO(OH)_2$
75-60-5	dimethylarsinic acid	cacodylic acid	$(CH_3)_2AsO(OH)$
4964-14-1	trimethylarsine oxide		$(CH_3)_3AsO$
593-52-2	methylarsine		CH_3AsH_2
593-57-7	dimethylarsine		$(CH_3)_2AsH$
593-88-4	trimethylarsine		$(CH_3)_3As$
98-50-0	arsanilic acid	*p*-aminobenzene-arsonic-acid (4-aminophenyl)-arsonic acid	
139-93-5	arsphenamine	4,4-arsenobis(2-amino-phenol)dihydro-chloride Salvarsan	
121-59-5	carbarsone	[4-[aminocarbonyl-amino]phenyl]-arsonic acid: N-carbamoylarsanilic acid	
554-72-3	tryparsamide	[4-[(2-amino-2-oxoethyl)amino]-phenyl]arsonic acid	
121-19-7	3-nitro-4-hydroxy-phenylarsonic acid		
98-72-6	4-nitrophenylarsonic acid	*p*-nitrophenylarsonic acid	
	arsenobetaine		$(CH_3)_3As^+CH_2COOH$
	arsenocholine		$(CH_3)_3As^+CH_2CH_2OH$
	dialkylchloroarsine alkyldichloroarsine		R_2AsCl $RAsCl_2$

2.1.1 Inorganic arsenic compounds

The most important commercial compound is arsenic (III) oxide, the molecular formula of which is generally accepted to be As_4O_6, at temperatures up to 1073 °C. This compound is recovered from copper smelters as a by-product of copper production. The arsenic

in naturally occurring metal arsenides and arsenic sulfides is volatilized and oxidized during the ore roasting process and condenses as the trioxide in flues. Arsenic-containing coal also produces chiefly arsenic(III) oxide, when it is combusted. Arsenic(III) oxide has a reasonably low boiling point (465 °C) and will sublime at lower temperatures (Durrant & Durrant, 1966; Carapella, 1973). Its vapour pressure at ambient temperatures is significant, a fact which is important in its transport and distribution in the environment (Lao et al., 1974). If data on the vapour pressure of arsenic(III) oxide are extrapolated to 25 °C, the saturating concentration of arsenic(III) oxide is 0.6 $\mu g/m^3$.

The solubility of arsenic(III) oxide in water is fairly low, about 2% at 25 °C and 8.2% at 98 °C (Durrant & Durrant, 1966). The resulting solution is slightly acidic and contains arsenous acid (H_3AsO_3). Arsenic(III) oxide is highly soluble in either hydrochloric acid or in alkali. In aqueous solution, arsenic is usually in the form of the arsenate or arsenite.

Alkali earth metals combine with arsenate anions to form salts that are only slightly soluble; consequently arsenic tends to form a precipitate frequently in association with phosphates.

Reported pKa values for arsenous and arsenic acids are: $HAsO_2$, pKa 9.23; H_3AsO_4, pKa_1 2.20, pKa_2 6.97, pKa_3 11.53 (Flis et al., 1959).

Arsenates and arsenic acid are strong oxidants and may for example, oxidize I^- ion to I_3^-. In air saturated water, arsenic(V) compounds should predominate, but arsenic(III) compounds have been shown to exist under these conditions. Sulfides of arsenic predominate under reducing systems in the presence of reduced forms of sulfur (Ferguson & Gavis, 1972). Reduction by organic matter of arsenic(III) and sulfate ions in the sediments of aquatic systems is likely to be responsible for the formation of both metallic arsenic and arsenic sulfides at the same location. Lead arsenate, copper arsenate, copper(II) acetate meta-arsenate (Paris Green), and calcium arsenate, all of which have been used as insecticides, are only slightly soluble in water.

The halides of arsenic and arsine are not found in the environment but are important in organoarsenic chemistry and in chemical analysis. Arsenic(III) chloride, for example, is formed when arsenic(III) oxide is treated with concentrated hydrochloric acid (Durrant & Durrant, 1966). It is easily hydrolyzed by water. Arsenic halides are rapidly hydrolized and easily alkylated by a number of organic alkylating agents, such as the Grignard reagents.

2.1.2 Organic arsenic compounds

The organic chemistry of arsenic is extensive. Carbon-arsenic bonds are quite stable under a variety of environmental conditions

of pH and oxidation potential. Some methylarsenic compounds, such as di- and trimethylarsines, occur naturally as a consequence of biological activity. In water solutions, these may undergo oxidation to the corresponding methylarsenic acids. These and other higher organic arsenic compounds such as arsenobetaine and arsenocholine, which are found in marine organisms, are very resistant to chemical degradation (Lauwerys et al., 1979).

Methylarsonic acid is a difunctional acid, with pKa_1 4.1, pKa_2 8.7, that forms soluble salts with alkali metals. Dimethylarsinic acid, which acts as a monofunctional weak acid, pKa 6.2, also forms fairly soluble alkali metal salts. The alkylarsenic acids can undergo reduction to the corresponding arsines, a reaction important in analysis. They also react with hydrogen sulfide and alkanethiols to produce sulfur derivatives such as $(CH_3)_2AsS\ SH$ (NAS, 1977). It appears likely that the reduction of dimethylarsinic acid and its subsequent reaction with thiols may be a key to its involvement in biological activity.

The alkylchloroarsines are reasonably stable with respect to hydrolysis but quite reactive with reduced compounds of sulfur. One such compound, 2-chlorovinylarsine dichloride (Lewisite), has been used as a war gas.

An extensive review of the chemical and physical properties of organoarsenic compounds has been made by Doak & Freedman (1970).

2.2 Analytical Procedures

2.2.1 Sampling and sample treatment

Arsenic poses some special problems in sampling not experienced in the determination of other trace elements. Water, urine, and biologically active samples should either be analysed within a few hours or frozen and stored (Andreae, 1977; Feldman 1979). Low concentrations of arsenic compounds found in natural waters slowly decrease with time, unless stabilized in some manner to prevent adsorptive losses. The biomethylation of inorganic arsenic in a biologically active sample can cause a change in its composition.

Since environmental analyses often involve trace concentrations, sample treatment frequently includes some type of preconcentration prior to analysis. Conversion of arsenic to arsine, co-precipitation with iron(III) hydroxide, distillation as arsenic(III) chloride, or extraction are typical examples of the approaches used.

2.2.1.1 *Natural waters*

Sea water and fresh natural waters are generally analysed without oxidative treatment prior to a preconcentration step, when the

molecular forms of arsenic are to be analysed. If the preconcentration step or the final steps in the analytical method require the conversion of organoarsenic compound to an inorganic form, oxidation procedures may be necessary. An acid-potassium persulfate preoxidation method (Pierce et al., 1976) and a method involving ultraviolet (UV) have both been automated (Fishman & Spencer, 1977). Acid-permanganate oxidation was found to be effective in the conversion of dimethylarsinic acid to inorganic arsenic (Sandhu & Nelson, 1978).

Arsine generation followed by cold trapping in liquid nitrogen is a technique that can be used with or without prior oxidation (Braman et al., 1977; Siemer & Koteel, 1977). Arsine generation has long been used as a first step in the determination of arsenic in water samples, prior to spectrophotometric analysis of the complex formed with silverdiethyldithiocarbamate (SDDC) (Skonieczny & Hahn, 1978). A recent adaptation of this method is the analysis for the SDDC complex by graphite tube furnace AAS which gives an improved detection limit of about 10 ng (Shaikh & Tallman, 1977). Arsenic has been separated from samples by volatilization as the trichloride or tribromide. A recent application combines distillation as the chloride with anodic stripping voltametry (Davis et al., 1978).

A number of coprecipitation methods have been reported for the preconcentration of arsenic from water followed by different methods of analysis. Iron(III) hydroxide (Portmann & Riley, 1964) and hydroxides of zirconium and cerium (Plotnikov & Usatova, 1964) are among the many coprecipitants that have been studied. Thionalide has also been used in the coprecipitation of arsenic from sea water (Portmann & Riley, 1964) with 95% efficiency, but the procedure is slow, requiring much sample handling, a problem with all of the precipitation methods.

2.2.1.2 *Air*

Air sampling for trace amounts of arsenic in the environment has mainly been confined to sampling the particulate phase. It is likely that many different types of particulate filters are satisfactory for this type of sampling, though arsenic is usually associated with small size particles.

As the estimated saturated concentration of arsenic(III) oxide in air at 25 °C is about 600 ng/m^3, it is possible that, when air concentrations are below this level, arsenic(III) oxide collected on a filter may evaporate or may not be collected completely. Results of laboratory work using filters and pure arsenic(III) oxide in air support this theory (Lao et al., 1974; Walsh et al., 1977b). Nevertheless, in studies using a filter impregnated with ethyleneimine in

glycerol which is 65% efficient in trapping arsenic(III) oxide vapour, it was shown that the major portion of arsenic in air (78—99%) could be collected on untreated, 0.4 micrometer pore size, polycarbonate type filters (Nuclepore Co.). Millipore membrane filters have also given satisfactory results (Walsh et al., 1977b). This was found to be the case for both ambient air samples containing low levels of arsenic and near-smelter air samples containing high levels. Approximately 15% of the arsenic in the air collected was found to be in a vapour form that was not collected on untreated filters. These results agree with those of Johnson & Braman (1975a) who also found that approximately 15% of the collected arsenic was volatile.

Vapour forms of arsenic in air, particularly the arsines, can be preconcentrated from air onto silver-coated glass beads (Johnson & Braman, 1975a). Even if oxidized after adsorption, the identity of the compound is not lost. For example, dimethylarsine, if present, can only be oxidized to dimethylarsinic acid. Adsorbed compounds can be desorbed using dilute sodium hydroxide (Braman et al., 1977).

2.2.1.3 *Biological materials*

Samples of biological materials to be analysed for total arsenic are generally completely oxidized prior to analysis. A number of oxidation methods have been studied, the majority of which involved the use of oxidizing acids or persulfates. The completeness of the oxidation has however seldom been checked. Perhaps the best oxidizing procedure involves the use of a mixture of sulfuric and nitric acids (Chu et al., 1972), a mixture of sulfuric, nitric, and perchloric acids (Christian & Feldman, 1970) or hydrogen peroxide (Samsahl, 1967). Dry ashing with magnesium oxide or magnesium nitrate has been succesfully applied in the analyses of a variety of biological samples (Snell & Snell, 1945; Evans & Bandermer, 1954). Other methods with fewer contamination problems or losses of arsenic are the Parr bomb (Beamish & Collins, 1934) and the Carius oxidation (Day, 1964) techniques. Schoeninger flask oxidation has been used in the oxidation of dried tissue samples (Schwedt & Russel, 1972). The proper preanalytical treatment for samples of certain marine organisms containing compounds such as arsenobetaine has yet to be established (Edmonds, et al., 1977).

There has been some success in analysing homogenized samples without oxidation by treating them with hydrochloric acid (Kingsley & Schaffert, 1951) or sodium hydroxide (Johnson & Braman, 1975b) prior to analysis. This approach is particularly necessary if the molecular forms of arsenic present are to be identified. In no case has the accuracy of the analyses been unequivocally determined.

Various methylarsenic compounds have been determined in human urine samples without pretreatment (Braman, et al., 1977; Crecelius, 1977b).

2.2.2 Analytical methods

2.2.2.1 *Methods for total arsenic*

One early very common method for the determination of total arsenic was the Gutzeit method (Vogel, 1955).

Spectrophotometry using the silver diethyldithiocarbamate (SDDC) complex of arsine is the classical method for determining arsenic in the 1—100 microgram range (Vasak & Sedivec, 1952). Arsenic is reduced to arsine by either granular zinc in hydrochloric acid or by sodium borohydride. Arsine reacts with SDDC in pyridine and the absorption of the red coloured complex is read at 533 nm. Methylarsine and dimethylarsine, but not trimethylarsine, form SDDC complexes which absorb at 533 nm, but their complexes have lower molar absorptivities.

A large number of studies can be found in the literature concerning the use of the SDDC method as it is often designated a standard method of analysis (Stratton & Whitehead, 1962). Some more recent papers include one in which the somewhat disagreeable pyridine solvent was replaced by L-erythro-2-(methylamine)-1-phenylpropan-1-ol (L-ephedrine) in chloroform (Hundley & Underwood, 1970; Gastiner, 1972; Kopp, 1973). Ionic interference in the SDDC procedure has been studied by Sandhu & Nelson (1978).

The arsenate ion reacts with ammonium molybdate to form a complex which, when reduced, gives a blue colour (Portmann & Riley, 1964). Under favourable conditions, the limit of detection is near 0.1 μg. An adaptation of the method has been used to determine the amounts of phosphate, arsenate, and arsenite in sea water (Johnson & Pilson, 1972). The method is applicable to sea water samples with arsenic concentrations below 3×10^{-6} mol/litre. Precision is of the order of $\pm 0.015 \times 10^{-6}$ mol/litre.

Atomic absorption spectrophotometry (AAS) is gaining in popularity as a method for the determination of total arsenic. Sensitivity of the ordinary flame type AAS for arsenic in solution is comparatively poor, detection limits are in the 0.5—1 mg/litre range (Holak, 1969; Kirkbright & Ranson, 1971). When an electrodeless discharge lamp and an argon-air-hydrogen flame are used, the detection limit is reduced to 0.1 mg/litre (Menis & Rains, 1969). With a long-path cell, the detection limit is about 6 μg/litre (Ando et al. 1969). Arsine can also be passed into a heated graphite or quartz furnace mounted in an AAS instrument. The arsine can be continuously passed through the atomizer (Smith, 1975; Siemer et al., 1976) or collected

in a cold trap and passed through rapidly when the cold trap in heated (Griffin et al., 1975; McDaniel et al., 1976). This second technique provides the best detection limits which are in the fraction of a ng range (Siemer & Koteel, 1977).

Neutron activation analysis is one of the more sensitive analytical methods. The arsenic-75 isotope is converted to arsenic-76 by thermal neutron absorption. Detection limits are near 1 ng, but the method is susceptible to interference, particularly from sodium. There have been many applications of this method in the analyses of biological samples (Takeo & Shibuya, 1972; Heydorn & Damsgaard, 1973; Maruyama & Komiya, 1973; Orvini, et al., 1974), water (Ray & Johnson, 1972) and particulate matter in air (Walsh et al., 1977b). Activated sample solutions are frequently subjected to separation to eliminate interfering radioisotopes (Gallorini, et al., 1978).

The determination of trace amounts of arsenic has also been performed using differential pulse polarography and anodic stripping voltametry (Arnold & Johnson, 1969; Myers & Osteryoung, 1973; Davis, et al., 1978). The second of these methods was applied to biological samples that were wet ashed with nitric, sulfuric, and perchloric acids before distillation of arsenic as arsenic(III) chloride. The detection limit was in the ng range. Some of the organoarsenic compounds are also electroactive (Elton & Gieger, 1978) but no pratical methods for environmental analyses have appeared since mg/kg concentrations are required to observe responses.

A variety of other analytical methods have been successfully used for the determination of trace amounts of arsenic. Among these are: atomic emission spectroscopy (Kirkbright et al., 1973; Braman et al., 1977; Robbins et al., 1979), X-ray fluorescence (Thomson, 1975), and isotope dilution mass spectrometry (Zeman et al., 1964).

Recently an electron spectroscopic method (ESCA) has been reported in which arsine collected on filter surfaces was analysed (Carvalho & Hercules, 1978). Detection limits were in the ng range so that preconcentration resulted in further reduction of detection limits to sub μg/kg.

A recent enzyme method gave reasonable results in the 0.02–2.0 mg/kg range (Goode & Matthews, 1978).

Very recently, a small interlaboratory comparison study on the determination of total urinary arsenic was performed with the participation of 4 laboratories using different analytical procedures (NAA and AAS). Ten samples containing arsenic concentrations of between 0.001 and 1 mg/litre were examined (Buchet et al., in press).

2.2.2.2 *Analyses for specific arsenic compounds*

Low concentrations of inorganic arsenic(III) and arsenic(V) in sea water can be determined using the molybdenum blue method

(Johnson & Pilson, 1972). Inorganic arsenic(III) and (V) can be separated by direct extraction with toluene of acidified aqueous solutions containing, for example, cysteine (Lauwerys et al., 1979). Differentiation between arsenic(III) and arsenic(V) is also possible using pH sensitive, selective reduction with sodium borohydride followed by atomic emission spectroscopy or AAS detection. Inorganic and methylarsenic compounds are reduced according to the reactions shown in Table 2. By buffering at pH 4, reduction of

Table 2. Reduction reactions of inorganic and methylarsenic compounds

Compound	pKa_1	pH	Product	B.P.
arsenous acid (meta) ($HAsO_2$)	9.23	< 7	AsH_3	—55 °C
arsenic acid (ortho) (H_3AsO_4)	2.20	> 4.0	no reaction	
		1.5	AsH_3	—55 °C
methylarsonic acid ($CH_3AsO(OH)_2$)	4.1	> 5.0	little reaction	
		1.5	CH_3AsH_2	2 °C
dimethylarsinic acid ($(CH_3)_2AsO(OH)$)	6.2	1.5	$(CH_3)_2AsH$	36 °C
trimethylarsine oxide $(CH_3)_3AsO$	—	1.5	$(CH_3)_3As$	70 °C
phenylarsonic acid ($C_6H_5AsO(OH)_2$)		1.5	$C_6H_5AsH_2$	148 °C
p-aminophenyl arsinic acid (arsanilic acid) *p*-H_2N-$C_6H_4AsO(OH)_2$	—	1.5	$H_3^+N\ C_6H_4\ AsH_2$	—

arsenic(V) is avoided. At pH 1.5, all compounds are reduced. The methylarsine compounds produced may be cold trapped, separated, and detected individually. Cold trapping and separation on heating, with detection by d.c. discharge in helium, has been used in the determination of arsenic in natural water, human urine (Braman et al., 1977; Crecelius, 1977b) and sea water (Johnson & Braman, 1975b; Andreae, 1977) at μg/kg and sub μg/kg concentrations. The detector cell has recently been studied and improved (Feldman & Batistoni, 1977) as has the analysis train (Crecelius, 1978).

Gas chromatographic detection of arsines trapped in cold toluene solvent using a microwave stimulated plasma detector has been developed by Talmi & Norvell (1975). The detection limits of this method are excellent (about 20 pg).

The electrochemical reactions of dimethylarsinic acid and trimethylarsine were studied by Elton & Geiger (1978). Dimethylarsinic acid may be converted to its iodide and determined by gas chromatography (Söderquist, et al., 1974) but the method is not applicable to the same wide range of arsenic compounds as the hydride-generating procedures.

Arsenic has been determined in marine organisms (Portmann & Riley, 1964). Substantial efforts have been made to identify the different organic arsenic compounds and, only recently, arseno-

betaine was identified in rock lobsters (Edmonds et al., 1977) and arsenophospholipids in algae (Cooney et al., 1978). Analytical methods for the determination of these compounds are not well developed. Thin layer chromatography was used in studies by Lunde (1977), the results of which indicated the possible presence of several as yet unidentified organic arsenic compounds.

Analytical methods for the determination of total arsenic and different forms of arsenic in human biological materials have recently been reviewed by Lauwerys et al. (1979).

3. SOURCES AND OCCURRENCE OF ARSENIC IN THE ENVIRONMENT

3.1 Natural Occurrence

3.1.1 Rocks, soils, and sediments

Arsenic is widely distributed in a large number of minerals. The highest mineral concentrations generally occur as arsenides of copper, lead, silver, or gold or as the sulfide. Major arsenic-containing minerals are arsenopyrite (FeAsS), realgar (As_4S_4), and orpiment (As_2S_3). The arsenic content of the earth's crust is 1.5—2 mg/kg; it ranks 20th in abundance in relation to other elements (NAS, 1977). Oxidized forms of arsenic are usually found in sedimentary deposits. The elemental oxidation state, though stable in reducing environments, is rarely found. Table 3 gives some ranges

Table 3. Arsenic in crustal materials[a]

Type	Range
	As (mg/kg)
Igneous rocks	
ultrabasic	0.3 — 16
basalts	0.06—113
andesites	0.5 — 5.8
granitic	0.2 — 13.8
silicic, volcanic	0.2 — 12.2
Sedimentary rocks	
limestones	0.1 — 20
sandstones	0.6 —120
shales and clay	0.3 —490
phosphorites	0.4 —188

[a] From: NAS (1977).

of the arsenic contents of crustal materials. Although the values shown are generally low, mineralized zones of sulfidic ores may contain much higher concentrations of arsenic.

High levels of arsenic may also occur in some coals. The average arsenic content of coal in the USA was estimated at 1—10 mg/kg (Davis & Associates, 1971). In some coal mined in Czechoslovakia, the concentration of arsenic has been shown to be as high as 1500 mg/kg (Cmarko, 1963).

Uncontaminated soils were found to contain arsenic levels between 0.2 and 40 mg/kg, while arsenic-treated soils contained up to 550 mg/kg (Walsh & Keeney, 1975). The soil in the city of Antofagasta, Chile, contains natural levels of arsenic of about 3.2 mg/kg (Borgono & Greiber, 1972). In the Comarca Lagunera, Mexico, values between 3 and 9 mg/kg were found at the soil surface and more than 20 mg/kg, deep down (Gonzalez, 1977).

Peat may contain considerable quantities of arsenic. Minkkinen & Yliruokanen (1978) found maximum arsenic concentrations in various Finnish peat bogs of between 16 and 340 mg/kg dry peat.

The natural level of arsenic in sediments is usually below 10 mg/kg dry weight (Crecelius, 1974). Bottom sediments can become substantially contaminated by arsenic from man-made sources. Levels of up to 10 000 mg/kg dry weight were found in bottom sediments near a copper smelter in Washington, USA (Crecelius, 1974).

3.1.2 Air

Airborne particulate matter has been shown to contain both inorganic and organic arsenic compounds (Johnson & Braman, 1975a; Attrep & Anirudahn, 1977). Crecelius (1974) showed that only 35% of the inorganic arsenic in rain from an urban area was present as arsenite; however, some post-sampling oxidation could not be excluded. In studies by Johnson & Braman (1975a), methylarsines made up approximately 20% of the total arsenic in ambient air from rural and urban areas.

In unpolluted areas, airborne arsenic concentrations ranging from less than one to a few nanograms per cubic metre have been reported (Peirson, et al., 1974; Johnson & Braman, 1975a; Walsh, et al., 1977b; Beavington & Cawse, 1978; Brimblecombe, 1979).

3.1.3 Water

Arsenic occurs in both inorganic and organic forms in water (Braman & Foreback, 1973; Crecelius, 1974). The main organic arsenic species, methylarsonic acid and dimethylarsinic acid, are

generally present in smaller amounts than the inorganic forms, arsenite and arsenate. The chemistry of arsenic in the aqueous environment has been reviewed by Ferguson & Gavis (1972).

The arsenic contents of surface waters in unpolluted areas vary but typical values seem to be a few micrograms per litre or less. In a study of river waters in the USA, about 80% of the samples contained levels of less than 0.01 mg/litre (Durum et al., 1971). Quentin & Winkler (1974) found an average value of 0.003 mg/litre in river water and 0.004 mg/litre in lake water in the Federal Republic of Germany. A mean arsenic concentration of 0.0025 mg/litre was reported in some Norwegian rivers (Lenvik et al., 1978). Much higher values have been reported from some areas including Antofagasta, Chile, where the average arsenic level in a river water supply of drinking water between 1958 and 1970 was 0.8 mg/litre (Borgono et al., 1977).

The oxidation state of arsenic in surface waters in various parts of the world remains largely unknown. Braman & Foreback (1973) found that the ratio of trivalent to pentavalent inorganic arsenic ranged from < 0.06 to 6.7 in a few uncontaminated surface water samples containing between 0.0025 and 0.0030 mg As/litre. About 8% of the total arsenic in 2 samples of well-aerated stream water (0.014 and 0.06 mg/litre, respectively) was reported by Clement & Faust (1973) to be in the trivalent form. In anaerobic reservoirs, all of the arsenic present (0.14—1.3 mgAs/litre) seemed to be in this form.

Penrose et al. (1977) reported that sea-water ordinarily contains arsenic concentrations ranging from 0.001—0.008 mg/litre. Levels of about 0.002 mg/litre have been reported by Onishi (1969) and Johnson & Braman (1975b). The major chemical form of arsenic appears to be the thermodynamically stable arsenate ion; even so, arsenite often accounts for one third of the total arsenic (Johnson, 1972; Andreae, 1978).

Clement & Faust (1973) analysed water from 2 groundwater supplies with very high levels of arsenic (224 and 280 mg/litre) and found that about 50% was present as arsenic(III). In a groundwater-fed stream, 26% of the total arsenic (0.08 mg/litre) was in the form of trivalent arsenic. Arsenic speciation has also been performed on well water samples from an area in Alaska containing high levels of arsenic (Harrington et al., 1978). In 5 samples containing arsenic concentrations ranging from 0.52 to 3.6 mg/litre, between 3% and 39 % of the arsenic present was trivalent, the rest being pentavalent. No methylated arsenic compounds could be detected.

High levels of arsenic have been found in waters from areas of thermal activity. Thermal waters in New Zealand have been shown to contain up to 8.5 mg/litre (Ritchie, 1961). Geothermal water in Japan contained arsenic levels of 1.8—6.4 mg/litre and neighbouring streams contained about 0.002 mg/litre (Nakahara et al., 1978).

The chemical forms of arsenic in thermal water from New Zealand were investigated by Aggelt & Aspell (1978). In the geothermal bores, more than 90% of the arsenic was present in the trivalent form. However, in a river flowing through the area, the pentavalent form was predominant but some seasonal variation in the ratio between the two valence states was indicated.

3.1.4 Biota

The sorption of arsenate ions in the soil by iron and aluminum components, greatly restricts the availability of arsenic to plants (Walsh et al., 1977a). The arsenic content of plants grown on soils that had never been treated with arsenic-containing pesticides varied from 0.01 to about 5 mg/kg dry weight (NAS, 1977). Plants grown on arsenic-contaminated soils may, however, contain considerably higher levels, especially in the roots (Walsh & Keeney, 1975; Grant & Dobbs, 1977; Wauchope & McWhorter, 1977). Some grasses growing on soils containing high levels of arsenic have been found to have elevated arsenic contents (Porter & Peterson, 1975). Andersson & Nilsson (1972) reported that arsenic in soils treated with sewage sludge was highly available to plants, but only a few samples were analysed. In contrast, Furr et al. (1976) claimed that soil arsenic is not readily available to plants.

Marine algae and seaweed usually contain considerable amounts of arsenic. Lunde (1970) showed values of 10—100 mg/kg dry weight in marine algae from the Norwegian coast. The degree of enrichment was found to be between 1500 and 5000 compared with the level of arsenic in the growth medium (Lunde, 1973a). Similar and even higher enrichment ratios were reported for fresh water plants in the Waikato River, New Zealand (Reay, 1972). The elevated arsenic concentrations in the water (0.03—0.07 mg/litre) gave rise to concentrations of up to 971 mg As/kg dry weight in aquatic plants.

3.2 Industrial Production and Uses of Arsenic

3.2.1 Industrial production

Based on the limited data available (US Bureau of Mines, 1975; Nelson, 1977), it can be estimated that the total world production in 1975 was around 60 000 tonnes. This production seems to be stable. The main producers are: China, France, Federal Republic of Germany, Mexico, Namibia, Peru, Sweden, USA, and USSR. These countries account for about 90% of the production. For a more detailed discussion of production of arsenic and its compounds, see IARC (1980).

Arsenic(III) oxide, the major basic chemical of the arsenic industry, is emitted as a by-product in smelting, mainly of copper and lead ores. It is recovered from the flue dust in a reasonably pure form.

3.2.2 Uses of arsenic compounds

Arsenic compounds are mainly used in agriculture and forestry (NAS, 1977). Much smaller amounts are used in the glass and ceramics industry and as feed additives and drugs. The use pattern for arsenic(III) oxide in 1975–78 has been reported as follows: manufacture of agricultural chemicals (pesticides), 82%; glass and glassware, 8%; industrial chemicals, copper and lead alloys, and pharmaceuticals, 10% (US Bureau of Mines, 1979).

In agriculture, compounds such as lead arsenate, copper acetoarsenite, sodium arsenite, calcium arsenate, and organic arsenic compounds are used as pesticides. Substantial amount of methylarsonic acid and dimethylarsinic acid are used as selective herbicides. These herbicides are particularly necessary for the control of Johnson grass *(Sorghum halepense)* in cotton fields. They are also used to treat other weeds such as sandbur *(Cenchrus* sp.), cocklebur (*Xanthium* sp.) and crabgrass in lawns (Weed Science Society of America, 1974). Dimethylarsinic acid is used as a silvicide in forest control and workers may be exposed to the compound and its volatile reaction products in the soil (Wagner & Weswig, 1974). Dimethylarsinic acid was the Agent Blue used in Viet Nam as a defoliant for military purposes.

Chromated copper arsenate, sodium arsenate, and zinc arsenate are used as wood preservatives (Lansche, 1965). When these compounds are applied under pressure they react with the wood to create water insoluble compounds. The preserved timber is resistant to both fungal and insect attack (Dobbs et al., 1976). The use of arsenic in wood preservatives is increasing.

Some phenylarsenic compounds such as arsanilic acid are used as feed additives for poultry and swine and to combat certain diseases in chickens.

Small amounts of arsenic compounds continue to be used as drugs in some countries. Other applications of arsenic are found in metallurgy, where it is used to dope germanium and silicon or in the production of gallium arsenide or indium arsenide.

3.2.3 Sources of environmental pollution

The burning of coal and smelting of metals are major sources of arsenic in air. A British study showed yearly average concentrations

in suspended matter in town air of 0.04–0.14 $\mu g/m^3$ (Goulden et al., 1952). In Prague, Vondracek (1963) found a winter mean concentration in air of 0.56 $\mu g/m^3$ and a summer mean of 0.07 $\mu g/m^3$. In urban areas in the USA, air concentrations of arsenic ranged from below the detection limit (0.01 $\mu g/m^3$) to 0.36 $\mu g/m^3$ on a quarterly average basis in 1964 (Sullivan, 1969). In 1974, about 200 of the 280 US National Air Surveillance Network sites recorded quarterly average concentrations below 0.001 $\mu g/m^3$ (Thompson, 1977). Only 13 sites, mainly highly urbanized areas and smelter locations, showed levels exceeding 0.02 $\mu g/m^3$.

In the vicinity of smelters, levels of arsenic in air exceeding 1 $\mu g/m^3$ have been recorded. Rozenshtein (1970) found levels of airborne arsenic, given as arsenic(III) oxide, of 0.7–2.5 $\mu g/m^3$ (i.e., 0.5–1.9 μg As/m^3) within 4 km of a copper smelter in the USSR. Data were not given on the duration of sampling. In the USA, quarterly average levels of up to 1.4 $\mu g/m^3$ were reported in El Paso, Texas, at the site of a large copper smelter (Sullivan, 1969). Near a copper smelter in Tacoma, Washington, monthly averages of arsenic in air of up to 1.46 $\mu g/m^3$ were recorded (Nelson, 1977) and a maximum 24-h concentration of 7.9 $\mu g/m^3$ was reported by Roberts, et al. (1977). Daily mean concentrations of up to 1.6 $\mu g/m^3$ were found in the air near a smelter in Romania (Gabor & Coldea, 1977). Auermann et al. (1977) reported airborne arsenic concentrations in a polluted region of the German Democratic Republic ranging from 0.9–1.5 $\mu g/m^3$ (average 0.9 μg As/m^3; duration of sampling not stated). In the vicinity of a Canadian gold mine, where ore was roasted, annual mean arsenic concentrations in ambient air ranged from 0.06 to 0.09 $\mu g/m^3$ between 1973 and 1975 (Hazra & Prokupok, 1977). Individual 24-h arsenic concentrations varied from less than 0.01 to 3.91 $\mu g/m^3$. The concentrations of arsenic in flue dust from a coal-fired power plant in Czechoslovakia ranged from 43 to 110 mg/kg (Zdrazil & Picha, 1966). In fly ash from 24 US coal-fired power plants, the arsenic concentrations ranged between 2.3 and 312 mg/kg (Kaakinen et al., 1975; Furr et al., 1977).

In the stack dust from nonferrous smelting operations, arsenic is predominantly in the trivalent inorganic form (Crecelius, 1974, Rosehart & Chu, 1975). No conclusive data on the extent of oxidation of airborne trivalent arsenic are available at present.

A thorough study has been made of arsenic in the environs of a copper smelter near Tacoma, WA, USA (Crecelius, 1974). Dated segments of sediment cores showed that the arsenic buildup started with the operation of the smelter. Less than 30% of the arsenic entering neighbouring waterways accumulated in the sediments. The remaining 70% presumably left the location in solution. Elevated concentrations of arsenic were found in water

in locations within 2—4 km of the smelter. Analyses of air, rain water, and snow all indicated elevated arsenic levels in the Tacoma, Washington area, attributable to the smelter effluent. Levels of up to 380 mg/kg (dry weight) were found in top soil in the vicinity of the plant.

A similar pattern, was observed in a study of the distribution of arsenic from a copper smelter in Sweden (Lindau, 1977). The arsenic concentrations in air a few kilometres from the smelter were higher than normal, as were arsenic levels in the soil, moss, and nearby natural water bodies.

Suzuki et al. (1974) reported concentrations of arsenic of up to 2470 mg/kg in soil near a smelter in Japan.

Attrep & Anirudhan (1977) found a quarterly average total arsenic concentration in air of 0.08 $\mu g/m^3$ in an area polluted by arsenic from defoliants. About half of the airborne arsenic was in the form of organic arsenic compounds. Four years later, during a season of low arsenic use, a monthly average of 0.009 $\mu g/m^3$ was detected in the same area. At this time, only about 15% of total airborne arsenic was in the form of organoarsenic compounds.

Burning of wood treated with arsenic-containing preservatives, mainly inorganic pentavalent compounds, can result in the release of arsenic into the atmosphere. The concentration of arsenic in the combustion fumes is closely related to the temperature. Smouldering of wood, treated with inorganic arsenic salts, at a temperature of 415 °C resulted in volatilization of 8.6% of the total arsenic in the wood (Watson, 1958). When wood treated with a preservative containing inorganic pentavalent arsenic salts was burned at temperatures of 700—800 °C, about 50% of the arsenic was present in the ashes (the rest was mainly in the smoke), while at 1000 °C only about 15% remained in the ashes (Öhman, 1960).

The use of geothermal energy can result in severe arsenic contamination. Crecelius, et al. (1976) found that the natural arsenic level 0.002 mg/litre had increased 1000 times in a water reservoir in which some of the discharge from a Mexican geothermal power plant was emitted. Between 6% and 51% of the total arsenic in this reservoir was present as trivalent inorganic arsenic and the rest as pentavalent. The emissions of arsenic into the environment from the plant totalled about 60 kg/day. In El Salvador, water from a reservoir near a geothermal power plant contained an arsenic level of 8.9 mg/litre (Jernelöv et at., 1976).

Arsenic is also present in trace amounts in fertilizers. In a recent study, it was reported that concentrations of up to several hundred mg/kg were present in some instances (Senesi et al., 1979).

4. ENVIRONMENTAL TRANSPORT AND DISTRIBUTION

4.1 General

Most environmental transformations of arsenic appear to occur in the soil, in sediments, in plants and animals, and in zones of biological activity in the oceans. Biomethylation and bioreduction are probably the most important environmental transformations of the element, since they can produce organometallic species that are sufficiently stable to be mobile in air and water. However, the biomethylated forms of arsenic produced are subject to oxidation and bacterial demethylation back to inorganic forms.

The biomethylation of arsenic was first recognized long ago when arsines were produced from cultures of a fungus *Scopulariopsis brevicaulis* (Challenger, 1945). This work was done in an investigation of poisoning incidents attributed to arsenic-containing wall paper — thought to contain Paris Green colouring pigment. It was eventually ascertained that methylarsines were the toxic agents. More recently, the methylation of arsenic by methanogenic bacteria (McBride & Wolfe, 1971) and by reaction with methylcobalamine (Schrauzer et al., 1972) or L-methionine-methyl-d_3 (Cullen et al., 1977) has been demonstrated in laboratory work. McBride et al. (1978) reported that dimethylarsine was mainly produced by anaerobic organisms, while trimethylarsine resulted from aerobic methylation. The following mechanism for the methylation of arsenate has been proposed by Challenger (1945) and McBride et al. (1978).

$$As^{V}O_4^{3-} \xrightarrow[-O^{2-}]{2e} \ddot{A}s^{III}O_3^{3-} \xrightarrow{CH_3^+} CH_3As^{V}O_3^{2-} \xrightarrow[-O^{2-}]{2e} CH_3\ddot{A}s^{III}O_2^{2-} \xrightarrow{CH_3^+}$$

$$(CH_3)_2As^{V}O_2^{-} \xrightarrow[-O^{2-}]{2e} (CH_3)_2\ddot{A}s^{III}O^{-} \xrightarrow{CH_3^+} (CH_3)_3As^{V}O \xrightarrow[-O^{2-}]{2e} (CH_3)_3\ddot{A}s^{III}$$

The proposed mechanism indicates that As(V) has to be reduced to As(III) before being methylated.

4.2 Aquatic Systems

Studies on the molecular forms of arsenic compounds in sea water have been reported. The concentration ratio As(III)/As(V) was found to be 0.18 in some Sargasso sea water (Johnson & Braman, 1975b). Fluctuations in the As(III)/As(V) ratio from 0.02 to 0.09 in the saline water of Naragansett Bay appeared to be

associated with phytoplankton activity (Johnson & Burke, 1978). Sea water samples off southern California also exhibited a variable As(III)/As(V) ratio, again associated with biological activity (Andreae, 1977). In some instances, the arsenic(III) concentrations exceeded those of arsenic(V). The same type of biological activity was observed in natural fresh waters (Braman & Foreback, 1973; Clement & Faust, 1973). It is evident that the presence of arsenic(III) compounds is the result of some reductive activity, which could be either biological or a non-biological effect of dissolved organic matter on arsenic(V).

The oxidation rate of arsenic(III) in Sargasso seawater was studied under carefully controlled laboratory conditions by Johnson & Pilson (1975). Temperature, pH, salinity, and the presence of light all influenced the rate of arsenite oxidation.

The finding of methylarsenic acids in seawater and fresh natural water is evidence that arsenic goes through reactions other than simple oxidation or reduction. In both sea and fresh water, the occurrence of methylarsenic compounds is associated with phytoplankton activity. In fresh water, the levels of methylarsenic compounds were especially high in locations where nutrients from fertilizers (presumably, also containing arsenic) had built up in lakes and ponds. There is little evidence that sediments play a substantial role in the methylation of arsenic (Braman, 1975). Sediment samples from two natural water environments did not contain unusually large amounts of methylarsenic compounds.

The analysis of biota associated with Sargassum weed indicated that substantial amounts of arsenic were present in forms other than the inorganic or methylarsenic forms (Johnson & Braman, 1975b). Only small amounts of methylarsenic acid type compounds were present in the organisms.

The involvement of arsenic in the biochemistry of marine organisms through production of arsenobetaine, arsenocholine, and arsenophospholipids is a new and only partially explored aspect of the local cycle. Much work has been done in an effort to identify arsenic compounds in marine organisms (Edmonds et al., 1977; Irgolic et al., 1977; Lunde, 1977; Penrose et al., 1977; Cooney et al., 1978).

4.3 Air-soil Systems

It has already been mentioned (section 3) that large quantities of arsenic compounds are used in agriculture and are initially distributed in the soil. This is an important aspect of arsenic distribution in the environment. The occurrence and distribution of arsenic in soils and plants have been reviewed by Walsh et al. (1977a). Arsenic is converted to arsenates except under highly

reducing conditions. Arsenate ions are readily sorbed by hydrous oxides of iron and aluminum and thus leaching of arsenate is slow. Absorption appears to be a major factor in the retention of arsenic in soils.

Slow removal of arsenic from the soil is of concern, when old orchards previously treated with arsenic are used for crop growing (Bishop & Chisholm, 1962). High arsenic levels can cause a depression in plant growth but the amounts required to produce this effect depend on the plant species. Bioaccumulation of arsenic in food crops is not particularly high.

Methylarsines are released into the air from soil treated with various arsenic compounds. Dimethylarsine and trimethylarsine were detected over grass areas treated with the methylarsenic compounds, soon after application. Methylarsines evolved much more slowly from grass treated with sodium arsenite (Braman, 1975). Despite these observations in locations where arsenic was obviously volatilized into the air following biomethylation, the amounts of methylarsenic compounds actually found in unpolluted air appear to be small. In one study, approximately 15% of the total arsenic in outdoor air was in a methylated form (Johnson & Braman, 1975a). The total arsenic was much greater in greenhouse air than in ambient air outside and the methylarsenic forms were much in excess of inorganic forms.

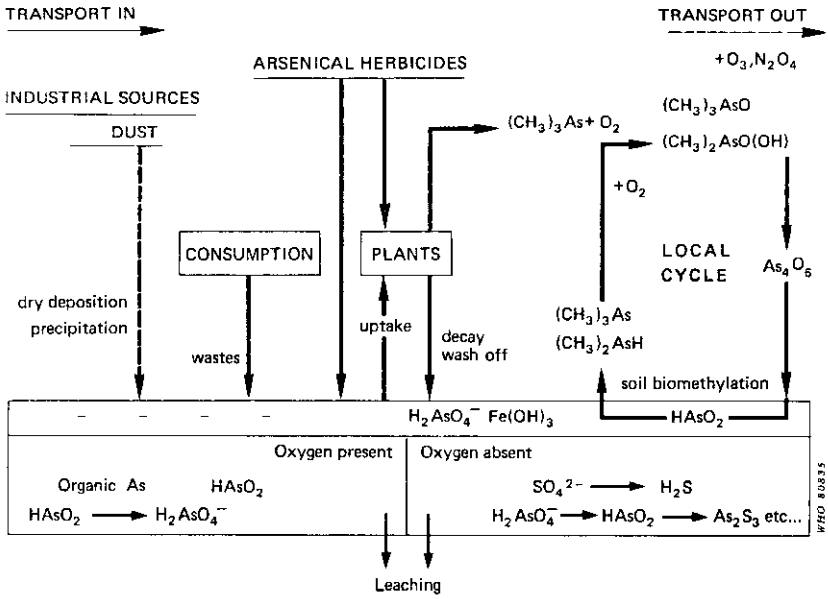


Fig. 1. Local soil-air cycle for arsenic.

A proposed model of an air-soil arsenic system is shown in Fig. 1. The system has little chance of being in apparent equilibrium, since air transport of transpired volatile arsenic is rapid, compared with evolution rates. Because of lack of data concerning arsenic compounds in air, especially in locations with arsenic-rich soils, the rates of evolution and buildup of arsenic in air are not known. A pseudo-equilibrium can be approached if the air transported into a site is equivalent to the air transported away from a site. This cycle is similar to one developed for an agronomic ecosystem, in which arsenic pesticides were the input (Sandberg & Allen, 1975). The most important translocation factors were absorption by soil and oxidation, uptake by vegetation, and volatilization after biomethylation.

5. LEVELS OF EXPOSURE TO ARSENIC AND ITS COMPOUNDS

Identification of the form in which arsenic occurs has only recently become part of the determination of arsenic in various environmental media. Generally, only total arsenic concentrations have been measured. In several reports however, the concentration of arsenic has been expressed as arsenic(III) oxide, even though the exact nature of the compound has not been determined. An attempt has been made in this section to distinguish between the various forms of arsenic, where sufficient knowledge exists. Unless specifically noted, the concentrations given in this section refer to elemental arsenic. The levels should be considered tentative as, in most instances, the accuracy of the analytical methods has not been assured.

5.1 General Population Exposure through Air, Drinking-Water, Food, and Beverages

5.1.1 Air

From data on air concentrations of arsenic in unpolluted areas (section 3.1.2), it can be calculated that the amount of arsenic inhaled per day is about 0.05 μg or less (assuming that about 20 m^3 of air is inhaled per day). However, in areas where coal with

a high arsenic content is used in power plants, or in the vicinity of smelters, the intake of arsenic may be considerably higher. Airborne arsenic levels of about 1 $\mu g/m^3$, have been detected in such areas (section 3.2.3), which would result in the inhalation of approximately 20 μg of arsenic per day.

The amount of arsenic absorbed from the lungs depends on particle size and the chemical form of the arsenic. Analysis of arsenic in airborne fly ash from coal-fired power plants indicated that the highest concentration was associated with respirable particles. On a mass basis, 76% of the arsenic present was recovered from particles with a diameter of less than 7.3 μm (Natusch et al. 1974).

5.1.2 Drinking-water

The natural concentration of total arsenic in drinking-water varies in different parts of the world. McCabe et al. (1970) investigated more than 18 000 community water supplies in the USA and found that less than 1% had arsenic levels exceeding 0.01 mg/litre. In a report by Grantham & Jones (1977) on arsenic concentrations in water from more than 800 wells in Nova Scotia Canada, 13% had arsenic levels exceeding 0.05 mg/litre. Apparently some of these wells had been contaminated by gold-mining activities in previous years. In some areas where chronic arsenic poisoning has occurred, levels exceeding 1 mg/litre have been recorded in well water. In the region of Cordoba, Argentina Arguello et al. (1938) reported maximum levels of arsenic of between 0.9 and 3.4 mg/litre. Artesian well water in the Tainan county of the Province of Taiwan contained up to 1.8 mg/litre (Kuo 1968). Well waters in Oregon also contained elevated levels of arsenic (0.07—1.7 mg/litre) (Goldblatt, et al., 1963).

Drinking-water can be severely contaminated through industrial operations. In the city of Torreon, Mexico, Espinosa González (1963) reported that levels of arsenic in drinking-water from a deep well ranged from 4 to 6 mg/litre. In Niigata, Japan, waste water from a factory producing arsenic sulfide contaminated nearby well water, and arsenic levels up to 3 mg/litre were recorded (Terada 1960). Leaching of arsenic from coal preparation wastes and fly ash from coal-fired power plants may also result in the contamination of water (Williams, et al., 1977; Chu, et al., 1978).

When considering exposure through drinking water, it is important to ensure that exposures are assessed for water delivered from the consumer's tap. Conventional flocculation treatment using either aluminum or ferric salts removes a high proportion, at least, of arsenic(V) (Gulledge & O'Connor, 1973).

5.1.3 Food and beverages

Arsenic levels in food, with the exception of some seafoods, are generally well below 1 mg/kg wet weight (Westöö & Rydälv, 1974). Marine fish on an average contain below 5 mg/kg wet weight (LeBlanc & Jackson, 1973; Lunde, 1973b; Leatherland & Burton, 1974; Kennedy, 1976; Stoeppler & Mohl, 1980). Certain bottom feeding fish, crustacea and shellfish may contain arsenic concentrations of several tens of milligrams per kilo (Westöö & Rydälv, 1972; Crecelius, 1974; Munro et al., 1974). Arsenic concentrations of between 0.6 and 58 mg/kg dry weight, have been found in some food supplements prepared from kelp (Walkiw & Douglas, 1975). Edible seaweed, a common product in Japan, has been reported to contain arsenic levels ranging from 19 to 172 mg/kg dry weight with a mean concentration of 112 mg/kg (Watanabe et al., 1979). The use of some organic arsenic compounds as feed additives for poultry and swine may lead to accumulation of arsenic in certain organs (Ledet et al., 1973; Calvert, 1975) (section 6.2.2.2) and limits of tolerance have been established in the USA for edible by-products from chickens, turkeys, and swine (Jelinek & Corneliussen, 1977).

Most of the arsenic in marine organisms occurs in the form of either fat-soluble or water-soluble organoarsenic compounds (Lunde, 1975. The water-soluble compounds are characterized by high chemical stability. Lunde (1973b) separated inorganic and organic arsenic in some fish and crustacea from the Norwegian Atlantic coast. The concentrations of inorganic arsenic (including organic-bound arsenic degradable by 6.6 M hydrochloric acid) ranged from 1.0 to 2.5 mg/kg and those of organoarsenic compounds from 3 to 37 mg/kg. Seafood arsenic, i.e., the major organic arsenic compounds found in seafood, is not degradable by this treatment. Crecelius (1977b) did not find any increase in human urinary excretion of inorganic or of simple methylated arsenic compounds, i.e., methylarsenic acid and dimethylarsenic acid, following the ingestion of 2 mg of arsenic in crab meat. This indicated that the inorganic arsenic content of the crab meat was very low ($< 1\%$ of the arsenic).

Wine may contain appreciable amounts of arsenic. Noble et al. (1976) found concentrations between 0.02 and 0.11 mg/litre in 9 US wines produced between 1949 and 1974. Crecelius (1977a) also investigated the levels and forms of arsenic in some US table wines. In over half of the samples, levels greatly exceeded 0.05 mg/litre (tentative limit in the international drinking water standards published by WHO). Most of the arsenic present was in the trivalent form. Arsenate was also found, but no methylated species were detected. This study indicated that considerable reduction from arsenate to arsenite occurred during the fermentation of grape juice by wine yeast. It is probable that the arsenic in the

wines originated mainly from the arsenic-containing insecticides used on the grapes.

Elevated arsenic levels have been found in some bottled mineral waters. Zoeteman & Brinkmann (1976) reported a mean arsenic concentration of 0.021 mg/litre (range < 0.001–0.19 mg/litre) in bottled mineral waters sold in countries within the European Community. In an investigation on lager beers from various countries, none of the samples contained more than 0.02 mg/litre (Binns et al., 1978).

5.1.4 Tobacco

The content of arsenic in tobacco grown on soils not treated with arsenic compounds is usually below 3 mg/kg[a] a (Satterlee, 1956; Bailey et al., 1957; Hjern, 1961; Griffin et al., 1975). During the first part of this century, the use of arsenic insecticides, mainly in the USA, brought about a steady increase in the content of arsenic in tobacco products. In the 1950s, levels of up to 52 mg/kg, given as As(III) oxide (40 mgAs/kg) were found in American cigarettes (Holland & Acevedo, 1966). However, during the last 20 years the concentrations of arsenic have decreased to below 8 mg/kg, because of a great reduction in the use of inorganic arsenic compounds in agriculture. Of the total arsenic originally present in cigarettes 10–15% was recovered in the main stream smoke, the remainder mainly being distributed in the ash and butt (Thomas & Collier, 1945). Cigarettes in Japan have been reported to contain arsenic levels of less than 1 mg/kg (Maruyama et al., 1970). The chemical form of arsenic in the smoke has yet to be elucidated.

5.1.5 Drugs

Both inorganic and organic arsenic compounds have been widely used in medicine. Arsenical Solution, also called Liquor Arsenicalis, Solutio Kalii Arsenitis or Fowler's Solution, contained arsenic(III) oxide dissolved in potassium hydroxide, neutralized with hydrochloric acid and diluted with chloroform water (Martindale, 1977). The arsenic administered was thus in the form of arsenite. The drug ordinarily contained an arsenic concentration of 7.6 g/litre and the daily dose of arsenic was sometimes as high as 10 mg (Pearson & Ponds, 1971). It was used for the treatment of leukaemia, psoriasis, chronic bronchial asthma, and as a tonic. Other preparations described in the Extra Pharmacopoeia by Martindale (1977) include various pastes containing inorganic arsenic in combination

[a] The weight of a cigarette is approximately 1 g.

with other drugs, such as cocaine or procaine. Sodium arsenate was formerly used in the treatment of chronic skin diseases, some parasitic diseases, and anaemia (Martindale, 1977). Pearson's Arsenical Solution, which contained about 0.5% arsenic in the form of arsenate, has been included in several pharmacopoeias. The recommended dose was 1—10 mg of the arsenate (0.2—2.4 mg As) with a maximum of 20 mg in 24 h. Drugs containing inorganic arsenic compounds are being phased out and replaced by more effective and less toxic drugs.

Salvarsan (arsphenamine), an organic arsenic compound containing 32% arsenic, was formerly used in the treatment of syphilis (Martindale, 1977). Because of the difficulties in preparing it for injection and because of its high toxicity, it was replaced by neoarsphenamine. The recommended dose used to be 100—600 mg (32—192 mg As) administered intravenously. Antibiotics have finally replaced these drugs. Some organic arsenic compounds including carbarsone, melarsoprol, and tryparsamide, are still in use in human medicine, mainly as antiparasitic drugs.

5.1.6 Total daily intake in the general population

Daily intake of arsenic from ambient air and water will ordinarily be of the order of a few micrograms, predominantly in the inorganic form (section 5.1.1 and 5.1.2).

As mentioned previously, the total daily dietary intake of arsenic depends, to a great extent, on the amount of seafood in the diet. A seafood meal may lead to the ingestion of several milligrams of arsenic, predominantly in organic forms. The daily intake of total arsenic in Japan has been reported to be between 0.07 and 0.17 mg (Nakao, 1960). The US Food and Drug Administration has monitored arsenic in foodstuffs since 1967 (Jelinek & Corneliussen, 1977). Data from this programme indicate that the total daily intake of arsenic has decreased from about 0.05—0.1 mg per day in the late sixties to 0.01—0.02 mg per day in 1972—74. Most of the arsenic was found in the group "meat, fish, and poultry". From analysis of composites of food representing the Canadian diet during 1970—73, it was estimated that the total intake of arsenic was 0.025-0.035 mg daily (Smith et al., 1972, 1973, 1975). Hamilton & Minski (1973) estimated the total intake of arsenic in the United Kingdom to be about 0.1 mg/day, based on analysis of diets containing fish. The considerable variations in the estimated dietary arsenic intake can be expected because of differences in the amounts of seafood in the diets investigated. Moreover, in neither of the reports was a distinction made between the amount of inorganic and organic arsenic consumed. Because of differences in metabolism and toxicity (sec-

tions 6, 7, and 8), it is important to distinguish between inorganic and organic forms of arsenic.

During the 1950s, the smoking of some tobacco, especially from the US, may have led to inhalation of more than 0.1 mg of arsenic daily. At present, the arsenic content of most tobacco is much lower and it can be estimated that less than 0.02 mg may be inhaled by an average smoker.

Data on the urinary excretion of various arsenic compounds in individuals not excessively exposed to arsenic can be helpful for deducing daily intake figures. Inorganic arsenic will be excreted mainly as inorganic and simple methylated arsenic compounds (Crecelius, 1977b). Smith et al. (1977) found an average urinary concentration of these forms of arsenic of 17.5 μg/litre in 41 male workers in the USA without known occupational exposure to arsenic. This would correspond to an intake of 0.025—0.040 mg of inorganic arsenic per day.

5.2 Occupational Exposure

Occupational exposure to arsenic compounds takes place mainly among workers, especially those involved in the processing of copper, gold, and lead ores. Occupational exposure may also occur among workers using or producing arsenic-containing pesticides. Unfortunately, very few data exist on the actual air levels of arsenic to which persons in such occupations have been exposed. This is also the case for wood treatment plant workers and carpenters, who may become exposed to inorganic arsenic compounds (mainly pentavalent) through their use as wood preservatives (section 3.2.2).

In a plant where sodium arsenite was being manufactured, Perry et al. (1948) found mean air arsenic concentrations of between 0.078 and 1.034 mg/m^3 around various workstations during sampling times of "10 minutes or more". The respirable fraction (< 5 μm) of the airborne arsenic ranged from 20% to 38% by mass. Ott et al. (1974) reported airborne arsenic levels in 1943 of 0.18 to 18 mg/m^3 in the packaging department of a plant where lead arsenate and calcium arsenate insecticides were produced. In 1952, airborne arsenic levels ranged between 0.26 and 40.8 mg/m^3 in another workplace at the plant. In the workroom air of a factory producing lead arsenate, Horiguchi et al. (1976) found levels ranging from 0.01 to 0.9 mg/m^3 during the years 1959—70.

When the airborne arsenic in a Swedish copper smelter was measured, the average concentrations near the roasters, reverberatory furnaces, and in the converter hall ranged between 0.06 and 2 mg/m^3 during sampling times of "several hours" (Lundgren, 1954). No data were given on the size distribution of the airborne arsenic-containing particles. At the same Swedish copper smelter Carlsson

(1976) found weighted 8-h average concentrations at different workplaces of between 0.002 mg and 0.23 mg/m^3 in the air inhaled by the workers (i.e., after filtration in a respirator). The highest exposures were found among the roasterworkers. Kodama et al. (1976) measured airborne arsenic concentrations in a copper refinery, where arsenic(III) oxide was being manufactured. They found levels of between 0.006 and 0.012 mg/m^3 when the ventilation was normal, and up to 0.2 mg/m^3 when the ventilation was shut off. Around the furnaces in the copper smelter, average concentrations of between 0.001 and 0.012 mg/m^3 were reported, and around the furnaces in a ferronickel smelter, the corresponding concentrations were between 0.002 and 0.005 mg/m^3. Smith et al. (1977) described a study at a US copper smelter where airborne particulate matter was collected in personal exposure samplers. The concentrations were found to be log-normally distributed, with a geometric mean of 0.053 mg/m^3 in a high exposure group (i.e., workers in the baghouse, flue, cotterell, stack, and reverberatory furnace areas). Workers in the concerter area were exposed to 0.046 mg/m^3 (geometric mean). In the high exposure area, only 32% of the airborne arsenic was respirable (< 5 μm), compared with over 80% in the converter area. Pinto et al. (1976) reported an overall mean airborne arsenic concentration of 0.05 mg/m^3 (range 0.003—0.3 mg/m^3) in the working environment of 24 smelter workers wearing personal air samplers on 5 consecutive days.

Airborne arsenic particulate matter in smelters is generally assumed to consist primarily of arsenic(III) oxide. However, it is probable that some of the arsenic is firmly bound to other metals, especially in the reverberatory furnace. There is also evidence of the presence of arsenic sulfides (Smith et al., 1976). The form in which arsenic is present clearly depends, to a great extent, on the characteristics of the industrial process involved, such as the temperature, humidity, and other elements present. More work is urgently needed to characterize the arsenic compounds by form and size distribution.

Workers may be exposed to airborne arsenic in cutting and sawing operations on wood treated with arsenic-containing preservatives. Arsenault (1977) found concentrations of arsenic in air of 0.043—0.36 mg/m^3 originating from the sawing of wood treated with copper, chromium, and arsenic salts. The duration of measurement was 100 min. Only about 5% of the dust particles (on a mass basis) were less than 10 μm.

6. METABOLISM OF ARSENIC

The metabolism of arsenic in man is very complex since the fate of arsenic compounds in the human body varies with the type of compound. The metabolism of a compound also varies with animal species, for example, the metabolism of arsenic in the rat is unique and quite different from that in man or other mammals. The rat is therefore not a suitable model for most metabolic pathways in man and the emphasis in this document has been placed, as much as possible, on data concerning other experimental animals.

6.1 Inorganic Arsenic

The metabolism of inorganic arsenic depends on its chemical form. Possible changes in the different forms of inorganic arsenic before the time of exposure should be considered. Even commercially available isotopes of pentavalent arsenic have been shown to contain up to 98% of trivalent arsenic (Lunde, 1973a; Reay & Asher, 1977). In many studies on the metabolism of arsenic, the valence of the compound used has not been under complete control. Throughout the following description, an attempt has been made to assess the validity of information concerning valence. In cases where the valence has been checked before exposure, this has been stated. If no such statements are made, it must be appreciated that substantial uncertainty exists.

6.1.1 Absorption

6.1.1.1 Respiratory deposition and absorption

Human exposure to inorganic arsenic through inhalation usually occurs occupationally or during cigarette smoking. Information on the respiratory deposition and clearance of different inorganic arsenic compounds is very limited. Inhaled arsenic is mainly in the form of an aerosol and it can be assumed that its deposition is the same as that of other particulate matter. In many workplaces, the particles containing arsenic are of relatively large size (Perry et al., 1948; Pinto & McGill, 1953), resulting in deposition primarily in the upper respiratory passages (i.e., nasal cavity, nasopharynx, larynx, trachea, and bronchus). Subsequent absorption can then take place either directly from the respiratory tract or gastrointestinally after mucociliary clearance in the airways. Retention, deposition, and absorption from the respiratory tract depend, furthermore, on the solubility of the inhaled material.

6.1.1.1.1 *Animals*

Hairless mice exposed for several weeks to a solid aerosol of fly ash (particle size less than 10 μm) containing arsenic at a concentration of 0.18 mg/m^3 showed increased tissue levels of arsenic (Bencko & Symon, 1970). Hairless mice were used to minimize oral intake of arsenic deposited on the fur. Despite this, it was not possible to differentiate between the amount of arsenic absorbed after inhalation and that absorbed after ingestion. A similar study has also been performed on rats exposed to arsenic(III) oxide in the form of condensation aerosols (arsenic concentrations of 0.001, 0.0037 and 0.046 mg/m^3) for 3 months (Rozenshtein, 1970). Increased tissue levels were found in the groups exposed to the 2 highest concentrations. It was not possible to differentiate between inhaled and ingested arsenic.

Rapid absorption of arsenic in rats following intratracheal administration of a solution of sodium arsenate (0.1—4 mg As per kg body weight) labelled with ^{74}As has been reported by Dutkiewicz (1977). The rapidity of the absorption was indicated by the relatively high tissue levels (2.5 and 0.7% of the dose per gram tissue in liver and spleen, respectively) found one hour after the administration.

6.1.1.1.2 *Man*

Holland et al. (1959) studied the uptake of inorganic arsenic in 8 terminal lung cancer patients who volunteered to smoke cigarettes impregnated with ^{74}As-labelled arsenic, reported to be in the form of sodium arsenite. Between 5% and 8% of the arsenic originally present in the cigarettes was deposited in the thoracic region. In 2 other lung cancer patients inhaling a nebulized solution of ^{74}As-arsenite, the fractions of radioactive arsenic deposited were 32% and 62%, respectively. Clearance from the lungs seemed to be fast. Four days after exposure, only about 20% of the dose could be detected by external scanning of the thoracic region. Since the study was performed on terminal lung cancer patients, great care must be exercised in extrapolating these data to healthy human subjects.

Some information on the absorption of arsenic following inhalation is given in reports on urinary excretion among persons exposed to arsenic occupationally. Pinto et al. (1976) studied the excretion of arsenic in 24 workers exposed regularly to airborne arsenic in a copper smelter (section 7.2). The workers wore personal air samplers for 5 consecutive working days and the overall average concentration of airborne arsenic was 0.053 mg/m^3. Urine was collected for 2 days prior to the working week, each day during the working week, and for 3 days afterwards. A correlation was found between urinary arsenic levels and average airborne arsenic concentrations

over the ranges studied. This investigation seems to indicate a fair absorption of inhaled arsenic, although no precise estimations can be made.

Arsenic-containing dust which enters the body orally may be present in the gastrointestinal tract together with the arsenic transported by mucociliary clearance from the respiratory tract. In workers exposed to dust (cadmium and nickel dust) in a battery factory, Adamsson et al. (1979) recently showed that, in some cases, the amount of cadmium in the faeces was more than 10 times the amount that could have been inhaled.

6.1.1.2 *Gastrointestinal absorption*

Absorption of inorganic arsenic from the gastrointestinal tract can occur following the ingestion of food, water, beverages, or drugs, containing arsenic or as a result of inhalation and subsequent mucociliary clearance. The absorption of ingested arsenic will depend on the solubility of the compound in question. Gastrointestinal absorption will also depend on whether the arsenic compound is given in solution or as undissolved particles.

6.1.1.2.1 *Animals*

Trivalent arsenic in the form of arsenic(III) oxide, suspended in a gum solution was administered to rabbits and rats in single doses of 22 mg of arsenic per kg body weight. The recovery of arsenic in the faeces in the 4 days following dosing was 59% for the rabbits and 69% for the rats (Ariyoshi & Ikeda, 1974). Arsenic(III) oxide dissolved in water and mixed in the food was administered to rats by Coulson et al. (1935). Of the calculated average intake of arsenic (0.37 mg), only about 14% was eliminated with faeces during the first 3 days. The results of these 2 studies indicate that dissolved arsenic(III) oxide is more rapidly absorbed than undissolved arsenic(III) oxide. However, the differences in dose might have contributed to the differences in absorption.

Pigs given 0.3 mg of arsenic per kg body weight as arsenic(III) oxide with pig chow eliminated about 10% of this single dose with the faeces during 10 days (Munro et al., 1974). Adult female Cynomolgus monkeys given a single dose of arsenic(III) oxide (1 mg As/kg body weight) by stomach tube eliminated only about 2% of the dose with the faeces during 14 days indicating that essentially all the administered dose had been absorbed from the gastrointestinal tract (Charbonneau et al., 1978a).

Absorption of a water solution of arsenic(III) oxide infused into a ligated loop of the ileocaecal part of the intestine of rabbits was

studied by Tsutsumi & Nozaki (1975). They found that about 30% of the infused arsenic (total 15 mg As) was absorbed into the blood over 1 h.

Otani (1957) studied the absorption of arsenic(III) oxide solutions from different parts of the digestive tract in cats and rats. The concentration of arsenic in blood and tissues was measured after administration of the arsenic solution (15 mg As/kg body weight) directly into the mouth, stomach, small intestine, or colon. The highest absorption took place in the small intestine; absorption from the mouth and stomach was relatively low.

Dogs given a single dose of pentavalent arsenic in the form of ^{71}As-arsenate (about 0.02 μg As/kg body weight) orally in a gelatin capsule eliminated less than 5% of the dose with the faeces during the first week, indicating almost complete absorption from the gastrointestinal tract (Hollins et al., 1979). In Golden Syrian hamsters given ^{74}As-arsenic acid orally (0.01 μg As/hamster), as much as 70% of the dose was recovered in the faeces (Charbonneau et al., 1980).

The absorption of orally administered ^{74}As-labelled trivalent and pentavalent arsenic (checked as to valence state at the time of exposure) has been studied in mice (Vahter & Norin, 1980). The elimination of arsenic with faeces during the first 48 h was 6—9% of the dose (0.4 or 4 mg/kg body weight) for both valence forms. As about the same faecal elimination of arsenic was seen after subcutaneous administration, the results indicate almost complete initial absorption from the gastrointestinal tract following oral administration.

The nature of the daily diet may effect the enteric absorption of arsenic. Arsenic(III) oxide added to a milk diet (80% whole milk powder and 20% dextrin) was eliminated with the faeces of rats in greater amounts, after several weeks of feeding, than the same substance added to a cereal diet (Tamura et al., 1972). When the cereal diet of rats was supplemented with casein (20%), in addition to As(III) oxide, the faeces contents of arsenic were higher than after supplementation with cheese, butter, or whey powder (Nozaki, 1972). No differences in the faecal elimination of arsenic were noted in rats fed arsenic together with cereal and cereal supplemented with 20% egg albumin, lactalbumin, polypeptone, or polyamine, or with 1% methionine, taurine, or cysteine (Tamura et al., 1974a,b,c). The doses in these experiments were very high (500 mg As per kg diet) and may have injured the gastrointestinal mucosa. In a more recent study by Tamura et al. (1977), rats were exposed to arsenic(III) oxide in both milk and cereal diets (75 mg As per kg diet) for 6 months, but no significant differences in the faecal elimination of arsenic were observed. It is of interest to note that milk increases enteric absorption of other metals, such as lead and cadmium (Kello & Kostial, 1973, 1977; Engström & Nordberg, 1978).

Enteric absorption of arsenic(III) oxide from the rabbit intestine, ligated in the ileocaecal portion, was inhibited by casein and a polypeptide from hydrolyzed casein with a relative mass of more than 14 000 (Nozaki et al., 1975). When the 2 substances were examined by dialyses or gel filtration, binding to arsenic was not detected. The enteric absorption of arsenic(III) oxide was also inhibited by phosphoric acid and potassium dihydrogen phosphate.

6.1.1.2.2 *Man*

As in animals, dissolved trivalent inorganic arsenic is readily absorbed from the gastrointestinal tract in man. Bettley & O'Shea (1975) gave 8.5 mg of arsenic as Liquor Arsenicalis (B.P. 1963; arsenite solution; see section 5.1.5) to 7 patients in a skin ward. The total amount of arsenic recovered in the faeces over a 10-day period was, at the most, 3.5% of the total dose implying that by far the major part of the dose was absorbed. A high absorption of trivalent arsenic in solution, in man, is also evident from data on high urinary levels of arsenic (section 6.1.3.2).

In an experiment on himself, Mappes (1977) took a single oral dose of 12 mg of finely powdered arsenic selenide (equal to 4.8 mg As). The urinary arsenic level did not increase, indicating that this compound, which is almost insoluble in water or 0.1 mol/litre hydrochloric acid, was poorly absorbed from the gastrointestinal tract. A low uptake of arsenic would also be expected if the relatively poorly soluble arsenic(III) oxide were ingested in the form of undissolved particles.

The fate of pentavalent arsenic, in the form of ^{74}As-arsenate, following ingestion by healthy human volunteers was studied by Tam et al. (1979a). At the end of the 7th day, cumulative elimination with the faeces equalled 6.1% of the dose.

6.1.1.3 *Skin absorption*

6.1.1.3.1 *Animals*

Results of studies by Dutkiewicz (1977) in which rat tails were immersed in solutions containing different concentrations of sodium arsenate (As levels of 750, 7500, and 15 000 mg/litre) labelled with ^{74}As, showed that arsenic is absorbed through the intact skin of rats.

6.1.1.3.2 *Man*

Human data concerning the uptake of arsenic through the skin are extremely limited. Robinson (1975) reported a case of systemic

poisoning in a patient whose cheek had been treated with arsenical paste.

6.1.1.4 Placental transfer

6.1.1.4.1 *Animals*

Arsenic was detected (no quantitative data given) in newborn rats of dams given a diet containing 27 or 215 mg of arsenic/kg diet as arsenic(III) oxide (Morris et al., 1938). Placental transfer of arsenic has been shown in hamsters intravenously injected with high doses (20 mg/kg body weight) of sodium arsenate labelled with ^{74}As (Ferm, 1977) or 4.5 mg of arsenic/kg body weight labelled with ^{74}As (Hanlon & Ferm, 1977). Examination of tissues, 24 or 96 h after injection, showed that ^{74}As crossed the placenta during the critical stage of embryogenesis and entered the embryonic tissues. The arsenic level in the embryo 24 h after dosing was comparable with that in the maternal blood, i.e., about 0.05 mg As/kg tissue.

6.1.1.4.2 *Man*

In studies on tissue levels of arsenic in fetuses and newborn babies in Japan (Kadowaki, 1960), the total amount of arsenic in the fetus tended to increase with age (from 4 to 7 months). The origin of the arsenic in the tissues was not known. It may have been organoarsenic compounds present in the mother's food as well as exposure to inorganic arsenic.

Further evidence of placental transfer of arsenic was presented in a case of arsenic(III) oxide ingestion during the third trimester of pregnancy (Lugo et al., 1969). A total of about 400 mg (as As) was taken in a liquid preparation causing the death of the child. On the fourth day after ingestion, concentrations in the infant of between 0.2 mg As/kg wet weight (brain) and 5.6 mg As/kg wet weight (liver) were reported. In this case, destruction of normal placental function by arsenic must also be considered.

In studies on 101 women in 2 southern cities in the USA (Kagey et al., 1977), cord blood levels of arsenic were about as high as maternal blood levels.

6.1.2 Distribution in organisms

6.1.2.1 *Fate of arsenic in blood*

6.1.2.1.1 *Animals*

It has long been recognized that rats accumulate arsenic in the blood. The blood levels of arsenic in rats after oral or parenteral

administration of single doses of trivalent or pentavalent inorganic arsenic have been measured in a considerable number of studies (Hunter et al., 1942; Ducoff et al., 1948; Lanz et al., 1950; Ariyoshi & Ikeda, 1974; Cikrt & Bencko, 1974; Klaassen, 1974; Tsutsumi & Kato, 1975; Dutkiewicz, 1977). From some of these studies, it can be estimated that about half of the dose is accumulated in the blood, mainly in the red blood cells. The half-life of arsenic, administered as trivalent or pentavalent inorganic arsenic, in the blood of rats varied from 60 to 90 days (Lanz et al., 1950; Ariyoshi & Ikeda, 1974).

Accumulation of arsenic in the blood does not occur in other animals. In mice, guineapigs, rabbits, and monkeys, less than 1% of the administered dose of trivalent inorganic arsenic (0.1—22 mg As/kg body weight) was found in the blood, 1—2 days after dosing (Hunter et al., 1942; Ducoff et al., 1948; Crema, 1955; Ariyoshi & Ikeda, 1974). The work of Crema (1955) indicated a multi-phase clearance of trivalent arsenic from the blood in mice 1—48 h after intravenous injection of ^{76}As-arsenic(III) oxide (0.1—0.2 mg As/kg body weight). It appears that in monkeys, dogs, and rabbits given trivalent arsenic in the form of arsenite or arsenic(III) chloride, only part of the blood arsenic is localized in the erythrocytes (Hunter et al., 1942; Klaassen, 1974), the whole blood arsenic levels being 2—7 times higher than the plasma levels.

When intramuscular injections of pentavalent arsenic (carrier-free ^{74}As-arsenate oxidized with nitric acid to the pentavalent state) were given to dogs, rabbits, guineapigs, chicks, and mice, less than 0.3% of the dose was found in the blood 48 h after dosing (Lanz et al., 1950). The corresponding value for cats was 5.6%. Lambs poisoned with arsenic acid also showed very low arsenic levels in the blood (Nelson et al., 1971).

Vahter & Norin (1980) examined the distribution of arsenic in the blood of mice 0.5—24 h after a single oral administration of ^{74}As-labelled arsenic(III) or arsenic(V) in doses of 0.4 mg and 4 mg/kg body weight. The oxidation states were checked at the time of dosing. At the high dose level, the ratio between the arsenic concentrations in the erythrocytes and plasma was about 2—3 after exposure to arsenic(III) but close to 1 for arsenic(V). A similar tendency was also evident in the low exposure groups. A higher retention of arsenic in the blood of the arsenic(III)-treated animals was observed, but because of the rapid elimination of arsenic from the blood in all groups, this was of minor importance after 24 h.

Radioactive arsenic followed a 3-phase kinetic pattern in its disappearance from the blood of chickens exposed to ^{74}As-arsenate (Overby & Frederickson, 1963). The half-times for the first 2 phases were rapid (3 and 12 h, respectively), while the remaining ^{74}As (less than 0.1% of the dose) had a biological half-time in blood of 60 h. The disappearance of ^{74}As from the blood of dogs intravenously administered carrier-free ^{74}As-arsenic acid has been shown to fit a

3-phase model similar to that for man (Charbonneau et al., 1978b). Most of the injected ^{74}As left the blood at a very high rate (half-times of the first 2 phases of 1 and 5 h, respectively), while the remaining, minor amount was cleared with a half-time of about 35 h. The small amount of arsenic still present in the blood 3 h after the injection was known to be equally distributed between plasma and erythrocytes.

6.1.2.1.2 *Man*

Radioactive arsenic has been used for locating tumours in man. Mealey et al. (1959) measured the plasma and erythrocyte levels of radioactive arsenic following intravenous injections of labelled arsenite. The rate of decline of arsenic in the erythrocytes was comparable with that in plasma but the red cells contained about 3 times more arsenic than the plasma, 10 h after the injection. The plasma curve, shown in Fig. 2, fits a 3-compartment model. The first half-time seems to be very short and the bulk of the arsenic was removed from the plasma at this high rate. Twenty-four hours after dosing, less than 0.1% of the dose remained per litre of

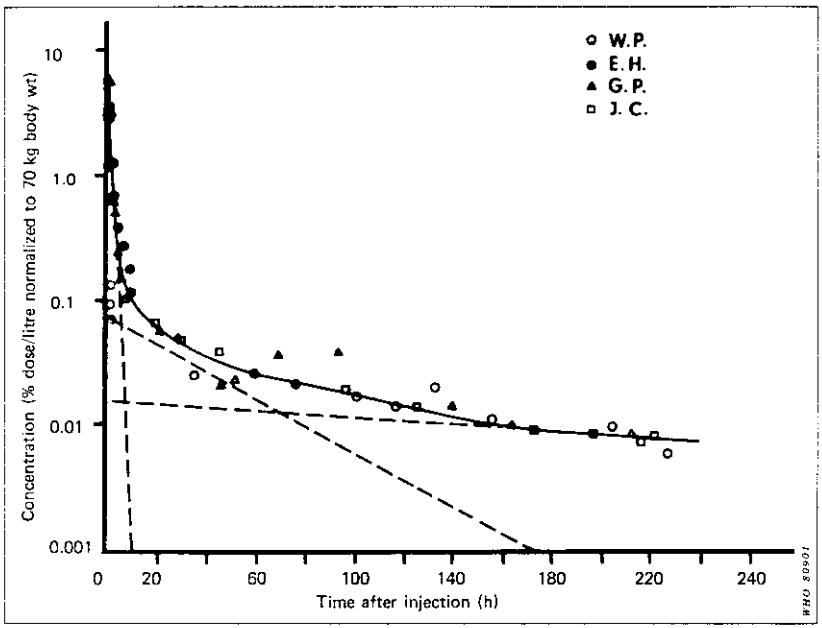


Fig. 2. Concentration of radioactive arsenic in the plasma of four subjects given intravenous doses ^{74}As-arsenite of 85 MBq (2.3 mCi)/70 kg body weight (From: Mealey et al., 1959).

plasma. The second phase of the curve shows a half-time of about 30 h, which is comparable with that calculated from the data of Hunter et al. (1942). The third phase of the curve, beginning about one week after the injection, shows a very low rate of disappearance. The half-time can be estimated to be over 200 h.

Among three healthy subjects, Bergström & Wester (1966) found a mean arsenic level in serum of 0.0008 mg/litre. The corresponding value for uraemic patients was 0.023 mg/litre. The arsenic concentration in these patients decreased considerably following dialysis, indicating that arsenic is not firmly bound to the high relative molecular mass serum proteins. A much smaller decrease was found in whole blood, indicating that arsenic is only slowly released from the cells.

6.1.2.2 *Tissue distribution*

6.1.2.2.1 *Animals*

Mice, rabbits, guineapigs, hamsters, chickens, and monkeys given radiolabelled arsenic in the trivalent form in parenteral doses of 0.1—4 mg of arsenic/kg body weight displayed highest levels of arsenic in the liver, kidney, skin, lung, and spleen (Hunter et al., 1942; Ducoff et al., 1948; Crema, 1955; Cikrt et al., 1980). The tissue distribution of radioactive arsenic 10 min, and 1 h, 6 h, and 48 h after intravenous administration of ^{76}As-arsenic(III) oxide (0.1—0.2 mg As/kg body weight) is shown in Table 4. As can be seen, the highest activity of ^{76}As per gram of tissue was found in the liver and kidney of the mice. In most organs, the arsenic levels fell fairly rapidly with time. In some organs, such as skin, brain, and skeleton, arsenic levels decreased more slowly. The rate of decrease of arsenic

Table 4. The distribution of arsenic in mice after intravenous administration of ^{76}As-arsenic(III) oxide (0.1—0.2 mg As/kg body weight). [a]

	activity per gram tissue/injected activity per gram body weight			
Organ	10 min	1 h	6 h	48 h
liver	6.1	2.47	0.64	0.10
kidney	3.55	3.90	1.40	0.12
spleen	1.37	1.14	0.48	0.08
blood	0.85	0.48	0.15	0.01
skin	0.56	0.91	0.72	0.30
muscle	0.50	0.62	0.40	0.08
small intestine	2.05	2.50	0.60	0.08
large intestine	0.76	0.68	0.26	0.13
skeleton	0.06	0.09	0.11	0.05
brain	0.002	0.02	0.08	0.01
lung	1.73	1.90	0.45	0.02

[a] From: Cremă (1955).

levels in the skin appeared to be especially slow as high arsenic levels were still present 48 h after exposure.

Marked species differences in the biliary excretion of arsenic were observed after intravenous administration of 1 mg of arsenic/kg body weight as ^{74}As-arsenic(III) chloride to rats, rabbits, and dogs (Klaassen, 1974). The rate of excretion of arsenic into the bile in rats was 40 times that in rabbits and 800 times that in dogs. Rats as well as mice and hamsters given trivalent arsenic excreted arsenic into the bile at a higher rate than when given pentavalent arsenic (Cikrt & Bencko, 1974; Cikrt et al., 1980; Vahter & Norin, 1980).

Arsenic administered as arsenite or arsenic(III) oxide passes the blood-brain barrier in mice, guineapigs, rabbits, hamsters, and monkeys, although the levels found in the brain are low compared with those in other tissues (Hunter et al., 1942; Ducoff et al., 1948; Crema, 1955, Peoples, 1964; Vahter & Norin, 1980).

When arsenite was given to guineapigs, chimpanzees, and baboons, the bulk of the tissue arsenic was shown to be in the protein fraction and minor amounts in the acid-soluble and lipid fractions (Lowry et al., 1942). Spontaneous tumours in mice (mammary carcinoma) did not show any specific affinity for arsenic (Crema, 1955).

Du Pont et al. (1941) administered pentavalent arsenic in the form of ^{76}As-labelled sodium arsenate intravenously to rabbits (2 mg As/rabbit, oxidation of As_2S_5 with hydrogen peroxide and addition of sodium hydroxide to form arsenate prior to the dosing) and measured the distribution at various times after the dosing. The percentage of the dose per whole organ 1 h after dosing was 16.5% in muscle, 12.2% in skin-fur, 9.5% in bone, 8.5% in blood serum, 5.9% in kidney, and 5.6% in liver. Intramuscular injections of pentavalent arsenic as carrier-free ^{74}As-arsenate (0.30–0.44 MBq/kg body weight, 8–12 μCi/kg body weight) in cats, rabbits, guineapigs, chicks, and mice resulted in a tissue content of radioactive arsenic of less than 0.2% of the dose per gram wet weight, 48 h after dosing (Lanz et al., 1950).

Autoradiography of mice given carrier-free ^{74}As-arsenic acid intravenously showed a high affinity of arsenic for the intestinal mucosa as well as for the kidney cortex, bone, and hair follicles (Deak et al., 1976).

From the work of Vahter & Norin (1980), it is possible to compare the tissue distribution of arsenic following administration of the trivalent and pentavalent forms in the same animal species. ^{74}As-labelled arsenite and arsenate were both administered to mice in single oral doses of 0.4 or 4 mg of arsenic/kg body weight. Concentrations of ^{74}As-labelled arsenic in various organs 0.5–24 h after dosing are given in Table 5 for both valence forms and dose levels. Higher levels are seen in most tissues of animals receiving arsenic(III), es-

Table 5. Arsenic in organs (μg As/g) of mice 0.5—24 h after single oral administration of 10 μg As/mouse (0.4 mg/kg body weight) or 100 μg As/mouse (4 mg/kg body weight) of ^{74}As-labelled arsenate As(V), or arsenite, As(III). The figures represent the mean for 6 animals [a]

Organ	Dose level (mg/kg body weight)	0.5 h		2 h		6 h		24 h	
		As(V)	As(III)	As(V)	As(III)	As(V)	As(III)	As(V)	As(III)
kidney	0.4	1.17	0.74	0.97	1.01	0.72	0.61	0.03	0.05
	4	7.24	7.41	8.73	7.44	4.33	4.37	0.06	0.78 [b]
liver	0.4	0.93	2.02 [b]	0.57	0.92 [b]	0.26	0.31	0.02	0.04 [b]
	4	2.71	6.43 [b]	3.52	6.72 [b]	0.92	3.19 [b]	0.04	0.39 [b]
bile	0.4	1.86	3.31	0.51	5.30 [b]	0.34	0.94 [b]	—	—
	4	4.01	12.3 [c b]	7.18	23.8 [b]	2.16 [b]	15.1 [c b]	<0.1	<0.1
brain	0.4	0.01	0.01	0.03	0.04 [b]	0.05	0.06	<0.01	<0.01
	4	0.09	0.06	0.54	0.17 [b]	0.39	0.28 [b]	<0.01	0.05
skeleton	0.4	0.08	0.07	0.12	0.16	0.18	0.18	0.02	0.01
	4	0.62	0.72	1.00	0.97	0.58	0.87	<0.01	0.03
skin	0.4	0.07	0.06	0.10	0.15 [b]	0.11	0.13	0.02	0.06 [b]
	4	0.44	0.64 [b]	0.94	1.10	0.37	1.10 [b]	0.04	0.76 [b]

[a] From: Vahter & Norin (1980).
[b] $p < 0.05$.
[c] Based on 3 animals.
[d] Based on 2 animals.

pecially in the liver and bile and the differences are more pronounced at the higher dose level. The high retention of arsenic in the skin seen in the animals receiving arsenic(III) may be explained by reaction of trivalent arsenic with sulfhydryl groups of proteins, which are abundant in the skin (section 7.6).

Using considerably lower doses, Sabbioni et al. (1979) did not find any major differences in tissue distribution, 16 h after intraperitoneal injection of radiolabelled trivalent and pentavalent inorganic arsenic in rabbits. Both oxidation states were administered in doses of 0.5—1 μg or 50 μg of arsenic per animal. Intracellular distribution was similar after exposure to either form of arsenic in lung, liver, and kidney, where over 80% of the arsenic was found in the nuclei and cytosol.

Several attempts have been made to demonstrate adaptation or tolerance towards arsenic in experimental animals. In 2 studies, where mice were given drinking water containing arsenic(III) oxide (32 days at 250 mg As/litre and 256 days at 50 mg As/litre), the maximum arsenic concentrations in skin and liver were reached on the 16th day with a marked drop in concentrations (about 15-fold) during the rest of the long-term experiment (Bencko & Symon, 1969a). Similar results were obtained in a later experiment where mice were exposed to fly ash with a mean concentration of arsenic of 180 μg/m^3 for 6 h daily, 5 days a week, for up to 6 weeks (Bencko & Symon, 1970). Arsenic levels in the liver and kidney reached a peak after 2 weeks' exposure, but, by the 6th week, they were only slightly higher than those in the unexposed controls.

Similar dynamics in arsenic accumulation have been found in rabbits exposed for up to one year to air near a power plant emitting arsenic (Bencko et al., 1968) and in dogs given daily oral doses of arsenious acid (0.2–0.4 mg As/kg body weight) for several months (Katsura, 1958). The work by Bencko & Symon (1969b) and Bencko et al. (1973) indicated increased tolerance towards parenterally administered arsenic (5–18 mg As/kg body weight) in mice pretreated with arsenite in the drinking water (50 mg As/litre).

6.1.2.2.2 *Man*

Following injection of radiolabelled arsenite in patients terminally ill with malignant diseases, the isotope was found to be widely distributed in the body, just as is the case in experimental animals (Hunter et al., 1942; Ducoff et al., 1948; Mealey et al., 1959). The highest concentrations were in the liver and kidney.

Twenty-four hours after subcutaneous injections of radiolabelled arsenite (0.73–1.65 mg As) in patients who were to undergo pneumoencephalography, no arsenic could be detected in the spinal fluid (Hunter et al., 1942). Measurements of radioactive arsenic in biopsy samples of the normal brain tissue of brain-tumour patients intravenously injected with ^{74}As-arsenite 85 MBq (2.3 mCi/70 kg body weight) showed an arsenic concentration of about 0.30% of the dose per kg tissue during the first hour after injection (Mealey et al., 1959). The arsenic levels decreased to about 0.25% during the second hour and were down to about 0.16% by the seventh day. Intracranial tumours were shown to contain much higher (2–30 times) arsenic concentrations than normal brain tissue.

The concentrations of arsenic in different areas of the brains of 5 persons (15–81 years of age) were determined at autopsy using neutron activation analysis (Larsen et al., 1979). Cerebral white matter contained, on average, 2.7 times more arsenic than the grey matter of the cerebral cortex which contained about 2 mg/kg wet weight. A similar ratio was found between cerebellar white matter and cerebellar cortex.

No data seem to be available on the biliary excretion of arsenic in man. Data are also lacking concerning the distribution of pentavalent inorganic arsenic in man.

6.1.3 Elimination

6.1.3.1 *Animals*

The elimination of arsenic in rats is very slow because of the accumulation in red blood cells (section 6.1.2.1.1). In animals other

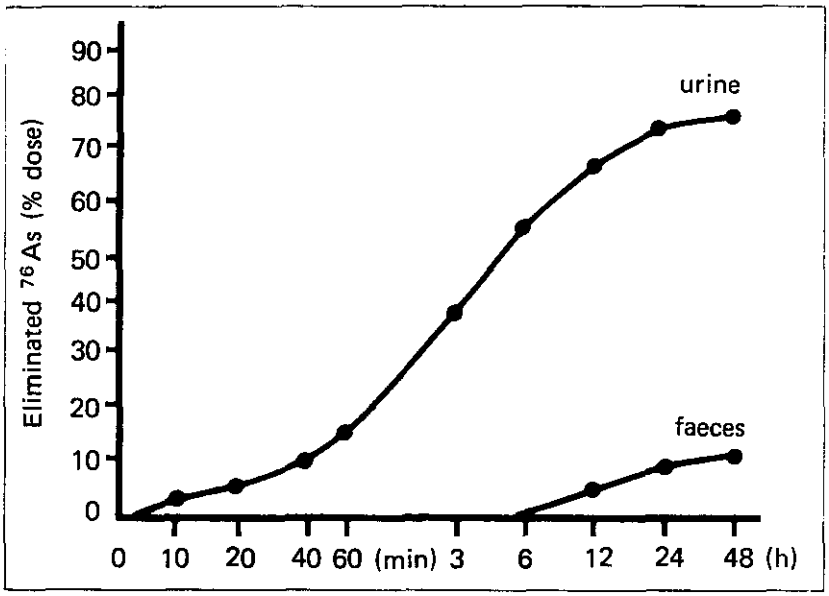


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Fig. 3. The cumulative elimination of arsenic in mice after intravenous administration of ^{76}As-arsenic(III) oxide (0.1–0.2 mg As/kg body weight). Each value represents the mean of 4–8 animals (From: Crema, 1955).

than the rat, absorbed arsenic is excreted from the body at a much higher rate, mainly via the kidneys. Mice and rabbits excreted about 70% of injected trivalent inorganic arsenic via the kidneys in the first 24 h following exposure (Ducoff et al., 1948; Crema, 1955). The elimination of arsenic 10 min — 48 h after intravenous injections of ^{76}As-arsenic(III) oxide (0.1–0.2 mg As/kg body weight) in mice is shown in Fig. 3 (Crema, 1955). As can be seen, almost 10% of the dose was eliminated in the faeces during 2 days. It can also be seen that the arsenic remaining in the body after the first day was eliminated at a very low rate. About the same elimination pattern was shown in pigs given a single test meal containing 0.3 mg As/kg body weight in the form of arsenic(III) oxide; 75% of the absorbed dose was found in urine collected over a 10-day period (Munro et al., 1974). Following administration of arsenic(III) oxide (1 mg As/kg body weight) by stomach intubation, the average urinary excretion in 3 adult female Cynomologus monkeys was 57% of the absorbed dose during the first day and a total of 73% over 14 days (Charbonneau et al., 1978a).

Whole body retention and elimination in dogs following intravenous or oral administration of ^{74}As-arsenic acid (0.02 μg As/kg body

weight) were studied by Hollins et al. (1979). It was concluded that 85% of the dose was cleared very rapidly with a half-time of about 6 h. The second phase of elimination, representing 14% of the dose, has a half-time of 2.4 days. No significant differences were found between intravenous and oral administration.

Whole body retention and elimination were studied in mice following administration of ^{74}As-labelled As(III) and As(V), with strict control of valence state at the time of exposure (Vahter & Norin, 1980). In mice given a single oral dose of 4 mg As/kg body weight, whole body retention was 2–3 times higher after exposure to As(III) than after exposure to As(V). A similar difference was seen after subcutaneous injection of 0.4 mg/kg body weight but differences in retention were not seen when this dose was given orally.

Daily doses of 0.03–0.66 mg As/kg body weight given to cows in the form of arsenic acid for up to 8 weeks did not cause the arsenic levels in milk to rise (Peoples, 1964). Following an outbreak of arsenic poisoning in cattle in Mexico caused by the ingestion of feed containing up to 0.28% arsenic, there was a very drastic reduction in milk production. Levels of up to 0.5 mg As/litre were found in the milk of cows still producing it (de Navarro, 1976; Gonzales, 1977). In view of the high exposure, these levels of arsenic in milk indicate that arsenic ingested in the form of inorganic arsenic does not readily pass the blood-mammary barrier.

Two studies in rats on the elimination of arsenic via the lungs have been reported (Lanz et al., 1950; Dutkiewicz, 1977). Both seem to indicate that little, if any, is eliminated by this route. A study by Overby & Fredrickson (1963) using chickens also indicated a very low elimination of ^{74}As-arsenic through the lungs, following exposure to ^{74}As-arsenate.

6.1.3.2 *Man*

Mappes (1977) described a series of experiments in which he, himself, ingested 2 mg of arsenic as arsenic(III) oxide in an aqueous solution. About 30% of the ingested arsenic had been recovered in urine (molybdenum blue method) 24 h after exposure. Mappes also took daily doses of 0.8 mg of arsenic as arsenic(III) oxide in an aqueous solution. The excretion rate of arsenic reached equilibrium after 5 days, by which time about 70% of the daily dose was being excreted in the urine daily.

Crecelius (1977b) studied the excretion of arsenic in the urine of a person who had ingested arsenic-rich wine (50 μg As(III) and 13 μg As(V)) and water containing 0.2 mg of arsenic mainly in the pentavalent form. About 80% of the arsenic ingested with the wine was excreted within 61 h. The biotransformation of the ingested arsenic

was also studied (section 6.1.4.2) and the apparent biological half-time for the *in vivo* methylated arsenic, which was the major species of arsenic excreted, was found to be of the order of 30 h, compared with 10 h for arsenic eliminated in the inorganic form. Only 50% of the pentavalent arsenic ingested with the water was recovered in the urine during the first 70 h following ingestion.

A single oral dose of carrier-free ^{74}As was administered in a gelatine capsule to each of 6 adult male volunteers (about 0.01 μg As/man; over 90% As(V)) (Tam et al., 1979a; Pomroy et al., 1980). During the first 24 h after dosing, 22.4% of the ^{74}As dose was excreted via the urine. After 5 days, a total of 58% had been recovered in the urine. No data were presented on faecal elimination. Data from whole body measurements were best represented by a 3-compartment exponential model. 65.9% of the dose was eliminated with a half-time of 2.1 days, 30.4% with a half-time of 9.4 days, and 3.7% with a half-time of 38.4 days.

Though absorbed arsenic is excreted mainly via the kidneys, a small amount is removed by other routes. Studies on the constituents of profuse sweat induced in a hot and humid environment have been reported by Vellar (1969). The mean concentration of arsenic in the sweat of 2 subjects was 1.5 μg As/litre (neutron activation analysis) and the calculated hourly loss of arsenic was 2 μg. Data concerning sweat levels under normal conditions were not reported. Desquamation of skin will also result in the removal of arsenic, since arsenic has a high affinity for skin (section 6.1.2.2). Molin & Wester (1976) calculated the daily loss of arsenic through desquamation of normal skin (10 male patients, apparently unexposed to arsenic) to be 0.1—0.2 μg, based on their finding of a mean arsenic concentration in skin of 0.18 mg/kg dry weight (neutron activation analysis). There are some data on the role of the hair as a route of elimination of arsenic. Several authors (section 7.3) have reported hair levels of arsenic exceeding 100 mg/kg among occupationally exposed subjects. Some of this arsenic may result from external exposure, however. Hair arsenic levels in Japanese subjects poisoned by contaminated soy sauce (3 mg of arsenic daily for 2 or 3 weeks) were between 1.8 and 13 mg/kg, 2 weeks after ingestion (Mitzuta et al., 1956). If a hair weight of 20 g is assumed (Task Group on Reference Man, 1975), this would account for 0.6% of the ingested arsenic, at the most.

Grimanis et al. (1979) determined the concentrations of arsenic and some other trace metals in human milk using neutron activation analysis. There were no differences between levels in human colostrum, transitional, and mature milk, all of which were about 3 μg/litre (range 0.6—6.3 μg/litre). Colostrum and transitional milk were obtained from 15 healthy mothers living in the Athens area with a mean age of 26 years. Mature milk was obtained from 5 of the 15 mothers.

6.1.4 Biotransformation

The form of arsenic present in most tissues is largely unknown because of the analytical difficulties involved. However, differentiation between the various forms of arsenic is more reliable in plasma and urine, where arsenic can be measured without previous digestion.

6.1.4.1 *Animals*

After intramuscular administration of arsenate (arsenic(V)) to rats, about 10—15% of the total urinary arsenic was reported to be in the form of arsenic(III) (Lanz et al., 1950). The different forms were separated by precipitation of magnesium-ammonia-arsenate. In dogs, given an intravenous infusion of ^{74}As-arsenate, arsenic(III) was reported to be present in the urine (about 14% of the total arsenic) as well as in the plasma (about 5.5% of the total plasma arsenic) (Ginsburg & Lotspeich, 1963). The method used for the separation of the different forms of arsenic was that described by Crawford & Storey (1944) in which arsenic(III) was extracted with ethyl xanthate. In further work, Ginsburg (1965) reported that injection of arsenate in dogs caused arsenic(III) to appear in the glomerular filtrate and, to a still greater extent, in the urine.

When trivalent arsenic (arsenite) was intravenously infused, both arsenate and arsenite were detected in the plasma, glomerulus filtrate, and urine of dogs indicating an *in vivo* oxidation of trivalent to pentavalent arsenic (Ginsburg, 1965). Bencko et al. (1976) reported that *in vivo* oxidation of arsenite can occur in mice. About one half of the intramuscularly administered arsenic (^{74}As-labelled sodium arsenite, 1.3 mg As/kg body weight) was recovered as pentavalent arsenic in urine taken directly from the bladder (analysed by paper chromatography). When the mice were exposed to arsenite in drinking water before the injection, an even greater part of the excreted arsenic was pentavalent.

The studies, just referred to, did not take into consideration that *in vivo* methylation of arsenic occurs. It was therefore not possible for the Task Group to evaluate to what extent such methylated forms of arsenic may have interfered in the separation of the two inorganic forms. In the absence of more detailed studies, no firm conclusions can be drawn about the *in vivo* reduction or oxidation of inorganic arsenic.

Methylated arsenic has been detected in the urine of cows and dogs fed arsenate or arsenite (Lakso & Peoples, 1975). When the dogs were fed doses of about 1.0 mg As/kg body weight of either valence form for 5 days, approximately equal amounts of inorganic and methylated arsenic were excreted in the urine. The cows pro-

duced about 3 times as much methylated arsenic as inorganic arsenic in their urine.

Following intravenous administration of carrier-free ^{74}As-arsenic acid to an adult male beagle (14.8 MBq, 0.4 mCi), ^{74}As was present in plasma or urine predominantly as inorganic arsenic and dimethylarsinic acid, as revealed by separation on a cation-exchange column (Tam et al., 1978, 1979b). When plasma, red blood cells, or urine from a beagle were incubated *in vitro* with ^{74}As-arsenic acid, no methylated arsenic was found in the plasma or urine samples but a small amount (0.2%) of dimethylarsinic acid did appear in the erythrocyte samples (Tam et al., 1979c).

Ten minutes after intravenous administration of ^{74}As-arsenic acid to beagles (0.5 μg As/dog), about 8% of the total amount of ^{74}As present in the erythrocytes was in the form of dimethylarsinic acid whereas no methylated arsenic could be found in the plasma (Charbonneau et al., 1978b). Six hours after dosing, the small amount of ^{74}As still present in the erythrocytes and plasma was predominantly in the form of dimethylarsinic acid as was 5—25% of the total ^{74}As present in urine 1 h after dosing and 90%, 6 h after. When a single oral dose of 0.2—0.6 μg As was administered to beagles as ^{74}As-arsenic acid, a similar metabolic pattern was revealed (Charbonneau et al., 1979).

6.1.4.2 *Man*

Braman & Foreback (1973) reported the presence of methylated forms of arsenic in the urine of 4 subjects. Dimethylarsinic acid constituted on average 66% of the total urinary arsenic, while methylarsonic acid, pentavalent arsenic, and trivalent arsenic accounted for 8.0, 17.0, and 8.4%, respectively. Actual *in vivo* methylation of inorganic arsenic was later indicated by the work of Crecelius (1977b), who measured the different forms of arsenic in the urine of a subject who had ingested wine containing 50 μg of arsenic(III) and 13 μg of arsenic(V). Urinary dimethylarsinic acid accounted for 50% of the ingested arsenic, methylarsonic acid for 14% and inorganic arsenic for 8%. Dimethylarsinic acid was also the major form of arsenic found in the urine of smelter workers occupationally exposed to arsenic, chiefly in the form of arsenic(III) oxide (Smith et al., 1977).

In a person who had ingested well water containing 0.2 mg of pentavalet arsenic, the inorganic arsenic(V) concentration in urine showed a marked increase (5-fold) the first 10 h after exposure, indicating that some of the ingested arsenic was rapidly excreted unchanged in the urine (Crecelius, 1977b). The urinary levels of dimethylarsinic acid increased 5 to 10-fold between 10 and 70 h after exposure. Only 50% of the arsenic ingested was excreted in

the urine within 70 h. Following oral ingestion of ^{74}As (> 90% As(V)) by 6 adult males (about 0.01 μg As/man), 58% of the dose was excreted in the urine during the first 5 days (Tam et al., 1979a). Of the excreted arsenic, 51% was in the form of dimethylarsinic acid, 21% monomethylarsenic compounds, and 27%, inorganic arsenic.

No methylation of ^{74}As was found in human plasma or urine incubated *in vitro* with ^{74}As-arsenic acid (Tam et al., 1979c).

Further studies are required in other species to determine whether the monomethylarsenic compound is a metabolite unique to man.

6.2 Organic Arsenic Compounds

6.2.1 Absorption

6.2.1.1 *Respiratory absorption*

6.2.1.1.1 *Animals*

One organic arsenic compound of interest is dimethylarsinic acid (cacodylic acid), since it may be inhaled when it is used as a herbicide. Absorption of this compound following intratracheal administration was studied in rats by Stevens et al. (1977). He found that a solution of ^{14}C-dimethylarsinic acid was rapidly absorbed from the lung. Less than 5% remained unabsorbed after 15 min and the absorption half-time was calculated to be 2.2 min.

6.2.1.1.2 *Man*

No data are available concerning the respiratory absorption of organic arsenic in man.

6.2.1.2 *Gastrointestinal absorption*

6.2.1.2.1 *Animals*

Absorption of seafood arsenic from the gastrointestinal tract was investigated in rats by Coulson et al. (1935). When rats were given a shrimp diet, only about 4% of the ingested organic arsenic (approximately 0.5 mg As) was recovered in the faeces during the first 2 days following exposure, indicating almost complete absorption from the gastrointestinal tract.

When fish containing arsenic was given to pigs in a single meal in amounts corresponding to 0.3 mg As/kg body weight, 23% of the ingested arsenic was recovered in the faeces collected over a period of 10 days following exposure (Munro, 1976). About the same high absorption (80% or more) was observed by Munro (1976) in adolescent monkeys fed arsenic-containing fish corresponding to a dose of 1 mg As/kg body weight and by Charbonneau et al. (1978a) in adult female cynomolgus monkeys given a single test meal (via a stomach tube) of homogenized fish containing arsenic (1 mg As/kg body weight).

Thirty-one percent of an oral dose of 0.5 ml of an aqueous solution containing 40 μg of radiolabelled dimethylarsinic acid (approximately 20 μg As/rat) was eliminated in the faeces of rats during 24 h (Stevens et al., 1977).

From reports on the effects and distribution of other organic arsenic compounds (pesticides, feed additives for poultry and swine, chemotherapeutic agents), it is evident that uptake of these compounds occurs, when they are given orally to laboratory animals. The amount of the administered dose absorbed from the gastrointestinal tract differs over a wide range, depending on the chemical properties of the compound. A chemotherapeutic agent of low lipid solubility, *p*-*N*-glycol-arsanilate, was shown to be poorly absorbed from the gastrointestinal tract (McChesney et al., 1962). Other chemotherapeutic agents, such as carbarsone (*p*-ureidophenylarsonic acid) and tryparsamide (*N*-(carbamoylmethyl) arsanilic acid), and pesticides such as sodium methane arsenate and dimethylarsinic acid, were readily absorbed, when fed to rats and rabbits (Hwang & Schanker, 1973; Exon et al., 1974; Stevens et al., 1977). The absorption half-times of carbarsone, tryparsamide, and dimethylarsinic acid from the small intestine of the rat were 87, 184, and 201 min, respectively (Hwang & Schanker, 1973). The absorption process did not show any evidence of saturation when the concentrations of the compounds were increased up to 100-fold. The absorption rates were ranked in the same order as the chloroform-to-water partition coefficients indicating, according to the author, that absorption takes place mainly by diffusion.

Liver, from pigs fed arsanilic acid, which contained about 6 mg As/kg, was administered to rats at a level of 30% of the diet. The daily faecal elimination of the rats contained 70–85% of the intake of arsenic, indicating that this form of arsenic is not as readily absorbed as inorganic arsenic or "seafood arsenic" (Overby & Frost, 1962).

The same type of experiment was reported by Calvert (1975) who fed wethers dried broiler manure containing 3-nitro-4-hydroxyphenylarsonic acid in concentrations of 3.4–5 mg As/kg of diet. He collected urine and faeces during the last 5 days of a 15-day feeding period and found 60–73% of the ingested arsenic in the faeces.

6.2.1.2.2 *Man*

A single meal of fish or crustacea containing high levels of mainly organic arsenic may result in the ingestion of several milligrams of arsenic, most of which is apparently absorbed from the gastrointestinal tract. Coulson et al. (1935) reported an experiment in which each of 2 human subjects ate boiled shrimps containing about 1 mg of arsenic. By the fourth day, approximately 5% had been recovered in the faeces indicating that absorption from the gastrointestinal tract was almost complete. Four persons who ate plaice and cod with high arsenic levels excreted an average of 83% of the ingested arsenic (0.5—2.2 mg/person) in the urine during the 2.5 days following exposure indicating that the fish arsenic was readily absorbed (Westöö & Rydälv, 1972).

Arsanilic acid, used as a feed additive for poultry and swine, may be ingested in trace amounts, when meat from these animals is eaten. The availability to man of arsanilic acid or of arsenic in the tissues of chicks fed arsanilic acid was studied by Calesnick et al. (1966). Four adult male volunteers ingested single doses of 1.3—3.0 mg of arsenic as ^{74}As-arsanilic acid. The average faecal elimination within 6 days of exposure was 74% of the dose. Following ingestion of pâté made from chicks fed ^{74}As-arsanilic acid, approximately 64% of the arsenic ingested was recovered in the faeces. Apparently, arsenic from the flesh of animals fed with additives containing arsenic is not absorbed from the gastrointestinal tract as readily as arsenic from fish or crustacea.

6.2.1.3 *Skin absorption*

No data are available on the absorption of various organic arsenic compounds through the skin of animals or man.

6.2.1.4 *Placental transfer*

6.2.1.4.1 *Animals*

There are no data on the placental transfer of organic arsenic compounds present in seafood. Dimethylarsinic acid has been shown to pass the placental barrier of rats, when administered intravenously just prior to parturition (Stevens et al., 1977). The dose given to the pregnant rats was 40 μg of radiolabelled dimethylarsinic acid per rat (20 μg As/rat). Fetal whole blood levels were comparable with those in the maternal blood.

Transfer of organic arsenic from hens to eggs has been reported. Increased concentrations of arsenic were found in eggs of hens fed

50 or 100 mg As/kg diet as 3-nitro-4-hydroxyphenylarsonic acid (Daghir & Hariri, 1977). The highest levels of arsenic (about 0.24 mg/kg) were found after 4–6 weeks of feeding, after which the levels gradually decreased, indicating that the hens developed a tolerance to organic arsenic similar to that found towards inorganic arsenic (section 6.1.2.2.1).

6.2.1.4.2 *Man*

There are no human data available concerning the placental transfer of organic arsenic compounds.

6.2.2 Distribution in organisms

6.2.2.1 *Fate of organic arsenic in blood*

6.2.2.1.1 *Animals*

Data are not available on blood arsenic levels following ingestion of seafood arsenic.

Stevens et al. (1977) investigated the kinetics of dimethylarsinic acid in the plasma of rats after intravenous administration of 200 mg ^{14}C-dimethylarsinic acid/kg body weight (108 mg As/kg body weight). After a single injection, the plasma concentration followed a three-exponential equation with half-times of 0.014, 0.217, and 3.42 h. The retention of ^{14}C-dimethylarsinic acid in whole blood was high, about 10% of the dose 3 months after the administration indicating that the rat differs from other animals with regard to metabolism of this arsenic compound. As dimethylarsinic acid is a major metabolite of inorganic arsenic, it might be expected to be cleared from the blood fairly rapidly.

The clearance of the major part of the arsenic from the blood of chickens given a single oral dose of arsanilic acid showed 2 rapid phases, with half-times of about 90 min and 6 h, respectively (Overby & Fredrickson, 1963). About 99.9% of the dose was cleared at these rates. The remaining 0.1% was cleared with a half-time of 36 h.

Less than 6% of doses of 4 different organo-arsenic drugs, given intravenously to rabbits, remained in the blood 2 h after the administration (Hogan & Eagle, 1944). The 4 arsenic compounds were unsubstituted phenylarsenoxide, 2 substituted phenylarsenoxides, and tryparsamide. Red blood cells and plasma showed marked differences in clearance rate and distribution. In the case of the most toxic compound, the unsubstituted phenylarsenoxide (trivalent arsenic), almost all the injected arsenic was still in the

blood 0.75—1.5 min after the injection. More than 95% of the dose was found in the red blood cells. More than 50% of the dose of the less toxic tryparsamide (pentavalent arsenic) had left the blood within the same span of time, and more than 95% of the remaining arsenic was in the plasma. The same distribution among blood cells and plasma was obtained in *in vitro* studies of the binding of arsenic compounds to red blood cells. The amounts of the various phenylarsenoxides (acid-substituted compounds excepted) bound to red blood cells corresponded very well to their acute toxicities in white mice. The arsonic acids were bound only to a minor degree to the red blood cells *in vitro*. They were also relatively nontoxic *in vivo*, but the toxicity varied from one compound to another.

6.2.2.1.2 *Man*

No human data are available concerning the fate of organoarsenic compounds in the blood.

6.2.2.2 *Tissue distribution of organic arsenic*

6.2.2.2.1 *Animals*

Data on the tissue distribution of seafood arsenic in experimental animals and man are lacking. The only available report is that of Lunde (1972), who studied the distribution of organic arsenic in fish (rainbow trout) fed a marine diet containing about 15 mg As/kg in the form of organoarsenic compounds to which inorganic ^{74}As had been added. The content of radioactive inorganic arsenic in the fish was negligible, 6—10 days after the addition of radioactive arsenic was stopped, but a small fraction of the inorganic arsenic was converted to organoarsenic compounds. Autoradiography revealed that the ^{74}As was especially concentrated in the eyes, throat, gills, and pylorus organ. The liver and kidney also contained much radioactivity, but arsenic disappeared faster in these than in other organs, when the feeding of radioactive arsenic was discontinued.

Administration of a diet containing 50 mg/kg of monosodium methane arsonate (MSMA) (27.5 mg As/kg) for 52 weeks caused a rapid increase in the arsenic contents in the liver and kidney of rabbits during the first 2 weeks (Exon et al., 1974). Accumulation of arsenic in hair was observed in cattle exposed to dietary MSMA or dimethylarsinic acid (Dickinson, 1972). The animals were fed daily doses of dimethylarsinic acid at 10 mg/kg body weight (5.4 mg As/kg body weight) and had arsenic levels in hair of 2.0—4.3 mg/kg (three animals) after 10 days and 13—33 mg/kg after 48 days.

Calvert (1975) fed wethers various amounts of arsanilic acid and measured the arsenic levels in the liver, kidney, and muscle. The results, shown in Table 6, suggest that arsenic given as arsanilic acid is concentrated in the liver and kidney. When the animals were placed on an arsenic-free diet, the tissue levels decreased rapidly, as shown in Table 7, and had dropped to about 15% of the original value by the sixth day.

Table 6. Arsenic levels in tissues of wethers, fed arsanilic acid for 28 days[a]

Arsenic fed	Whole blood	Liver	Kidney	Muscle
(mg/kg of diet)		mg/kg dry tissue		
0.0	< 0.01	< 0.01	< 0.01	< 0.01
26.8	0.063	3.1	3.2	0.2
144.4	0.270	26.8	12.2	1.1
273.3	0.536	29.2	23.6	1.2

[a] From: Calvert (1975).

Table 7. Depletion of arsenic in the liver of wethers fed arsanilic acid for 28 days[a]

Arsenic fed	Withdrawal time (days)			
	0	2	4	6
(mg/kg of diet)		mg/kg dry tissue		
0.0	< 0.01	< 0.01	< 0.01	< 0.01
26.8	3.1	4.9	2.9	1.9
144.4	26.8	15.4	8.4	3.5
273.3	29.2	27.0	11.4	5.0

[a] From: Calvert (1975).

When pigs were fed arsanilic acid (1000 mg/kg diet, approximately 340 As mg/kg diet), the maximum arsenic level in most tissues was reached on the 13th day (Ledet et al., 1973). However, maximum levels in the nervous tissues (CNS and peripheral nerves) were not reached until the 20th day. Clearance of arsenic was slower in these than in the other tissues. Highest levels were found in liver and kidney.

Injections of the trivalent organoarsenic drug phenylarsenoxide in rabbits resulted in 50—100 times higher liver arsenic levels than injections of the relatively nontoxic 3-NH_2-4-OH derivative of the pentavalent compound tryparsamide (substituted phenylarsonic acid) (Hogan & Eagle, 1944). After injections of these compounds at the LD_{50}-level, comparable amounts of arsenic were found in the tissues despite the 500-fold difference in dose. The highly toxic acid-substituted 4-COOH-phenylarsenoxide caused extraordinarily high

kidney levels in the first hours after injection (10–20% of the dose) and levels comparable with the other substituated phenylarsonic acids after 24–48 h.

6.2.2.2.2 *Man*

No data are available on the distribution of organic arsenic compounds in man.

6.2.3 Elimination

6.2.3.1 *Animals*

A substantial fraction of seafood arsenic administered to animals is rapidly eliminated from the body. About 75% of a dose of shrimp arsenic (approximately 0.5 mg As) given to rats in food was eliminated within the first day, and an additional 20% was eliminated during the second day, predominantly in the urine (Coulson et al., 1935). Pigs given a fish diet providing a dose of 0.3 mg As/kg body weight eliminated 90% of the ingested arsenic within 3 days (Munro, 1976). About 70% of the dose was recovered in the urine. When the same type of diet was given to adolescent monkeys *(Macaca irus)* corresponding to doses of 1 mg As/kg body weight, only 63% of the dietary arsenic was recovered in the excreta within 10 days (18% in the faeces and 45% in the urine). When a single oral dose of fish arsenic providing about 1 mg fish arsenic/kg body weight to adult female cynomolgus monkeys, 57–84% of the ingested arsenic was excreted in the urine within 3 days. The total recovery in the excreta was 66–85% during 14 days (Charbonneau, et al., 1978a).

The feeding of organic arsenic in the form of arsanilic acid to poultry and swine as a feed additive, may result in tissue residues. Rats fed protein from swine liver containing 24.4 mg arsenic/kg protein as arsanilic acid, at a level of 300 g/kg diet for 14 days, eliminated almost all of the arsenic within 7 days of the end of the feeding period (Overby & Frost, 1962). The amount of arsenic excreted in the urine was one third of the amount of arsenic eliminated in the faeces during this period. Experiments with pigs given a diet containing 0.01% arsanilic acid for 31 days showed a rapid decrease in the tissue levels of arsenic during the first days after the feeding of arsanilic acid was discontinued (Ferslew & Edds, 1979). The livers contained arsenic concentrations of 1.5–2 mg/kg on the 31st day of feeding and about 0.2 mg/kg on the 7th day after the removal of arsanilic acid from the diet.

When pentavalent arsenic compounds in the form of dimethylarsinic acid, *p*-*N*-glycolylarsanilate, arsanilic acid, 4-nitrophenylarsonic acid, and 3-nitro-4-hydroxyphenylarsonic acid were administered parenterally to rats, some 50%—80% of the injected dose was excreted in the urine within the first 48 h (McChesney, et al., 1962; Schreiber & Brouwer, 1964; Stevens, et al., 1977). Only minor amounts were found in the bile and faeces. Seventy percent of a dose of *p*-*N*-glycolylarsanilate (used in veterinary medicine), intravenously injected into cats, was excreted in the urine and 0.8% excreted in the bile during the first 160 min following exposure (McChesney, et al., 1962). Rabbits injected intravenously with another drug, tryparsamide, excreted 68% of the dose in 24 h and 81% of the dose in 48 h (Hogan & Eagle, 1944). Derivatives of phenylarsenoxide, a trivalent organoarsenic compound, were excreted in the urine of rabbits at much slower rates than the pentavalent arsenic compound, tryparsamide. The elimination rates depended on the functional groups on the benzene ring and varied from 5% in 24 h for unsubstituted phenylarsenoxide to 60% for the 3-NH_2-4-OH-derivative.

Cristau et al. (1972, 1975) investigated the influence of the molecular structure of some arsenic-containing drugs on the elimination kinetics of rats and guineapigs. Acetarsol, tyrparsamide, diphetarsone, and melarsonyl, all of which possess hydrophilic functional groups that facilitate elimination without biotransformation, were rapidly eliminated (65%—90% of the dose in 24 h). Acetarsol and tryparsamide were mainly excreted in the urine and to a much lesser extent in the bile. Melarsonyl, which has a higher relative molecular mass (532.5) than the other drugs tested, was excreted to a greater extent in the bile in both species. About 10 times more diphetarsone, which has a relative molecular mass of 460, was excreted in the bile of rats than in the bile of guineapigs. This was reported to agree with previous observations that rats excrete more of some drugs in the bile than guineapigs. Melarsoprol and arsthinol are both hydrophobic, which indicates that they must undergo biotransformation prior to elimination. Both drugs were excreted slowly (20%—50% of the dose in 24 h), predominantly via the bile.

There are only a few reports on the excretion of arsenic in the milk of animals. The arsenic level in cow's milk did not increase with the blood concentration when the cows were fed methylarsonic acid or dimethylarsinic acid (Peoples, 1975). However, the milk arsenic levels did increase when cows were fed arsanilic acid or 3-nitro-4-hydroxyphenylarsonic acid (1.6—3.2 mg As/kg body weight) (Calvert, 1973).

No radioactive arsenic was detected in air exhaled by chickens given an ^{74}As-labelled arsanilic acid orally, indicating that this arsenic compound was not eliminated via the lungs or metabolized to form expirable products (Overby & Fredrickson, 1963).

6.2.3.2 *Man*

Only a few studies are available on the elimination of organic arsenic compounds in man. As early as 1919, Bang stated that organic arsenic in fish and other marine foods was readily excreted, mainly in human urine. Chapman (1926) reported that a person, who had ingested lobster containing 33 mg of arsenic, excreted 74% of the arsenic in the urine within 48 h. In studies by Coulson, et al. (1935), 2 subjects were given sea food arsenic almost all of which (> 90% of approximately 1 mg As) was recovered in the urine within 4 days of ingestion. When the urinary excretion of arsenic was measured in 4 subjects after they had ingested plaice and cod containing high arsenic levels, about 70% of the ingested arsenic (0.5, 2.0, 2.1 and 2.2 mg As, respectively) was excreted in the urine during the first 24 h after ingestion and 83% in 2.5 days (Westöö & Rydälv, 1972). Freeman, et al. (1979) gave 6 men flounder containing high levels of arsenic, corresponding to a total ingested quantity of 5 mg of arsenic per man. During the first day, the urinary excretion of arsenic corresponded to more than half of the ingested amount of arsenic and the mean total arsenic excreted during 9 days was 77%.

Calesnick, et al. (1966) studied the recovery of ^{74}As in the urine and faeces of human subjects who had ingested radiolabelled arsanilic acid or pâté made from chickens fed ^{74}As-labelled arsanilic acid. After 6 days, only 20% of the ingested dose was recovered in the urine and between 64% and 74% was recovered in the faeces regardless of whether the arsenic had been given as pure arsanilic acid or in the form of pâté from arsenic-exposed chickens.

6.2.4 Biotransformation

6.2.4.1 *Animals*

Stevens, et al. (1977) investigated the *in vivo* biotransformation of dimethylarsinic acid. They injected ^{14}C-dimethylarsinic acid (18 µg As) and ^{74}As-dimethylarsinic acid (1.9 µg As) simultaneously into rats and measured the distribution in different organs. Since the tissue distributions of ^{74}As and ^{14}C were the same, dimethylarsinic acid was thought not to be converted to inorganic arsenic in rats. In another experiment by Stevens, et al. (1977), doses of 200 mg/kg body weight of ^{14}C-dimethylarsinic acid (108 mg As/kg body weight) were administered intravenously, intratracheally, or orally to rats. Radioactive carbon dioxide was measured in the air emitted from the animal chambers. Approximately 0.008%—0.13% of the dose was detected as $^{14}CO_2$ during a 24-h period. This result was interpreted as indicating that only a small fraction of the

dimethylarsinic acid was demethylated by the rats. The lowest fraction (0.008%) of the dose was exhaled by the rats that had received intravenous injections, while the highest fraction (0.13%) was exhaled by the peroraly exposed rats. The *in vivo* transformation of dimethylarsinic acid in other species is unclear.

Orally administered dimethylarsinic acid was found to be mainly unchanged in the liver of rats (Winkler, 1962) and in the excreta of chickens (Overby & Fredrickson, 1963; Moody & Williams, 1964a,b,c). Dimethylarsinate was detected in the blood, urine, and faeces of rats given oral doses of ferric methane arsonate (approximately 40 mg As/kg body weight). This would point towards *in vivo* methylation of the compound (Odanaka, et al., 1978). The major components in the urine were dimethylarsinate and unchanged methane arsonate.

Investigations on the biotransformation of some of the organic arsenic compounds used as feed additives and drugs indicate that they are converted to more easily excretable and, in some cases, more toxic substances (Hogan & Eagle, 1944; Cristau, et al., 1972, 1975; Calvert, 1975). These changes in the molecular structure of the arsenic compound seldom affect its valence state; nor do they result in the formation of inorganic arsenic compounds. Hogan & Eagle (1944) cited considerable evidence of the reduction of arsonic acids *in vivo* to the corresponding arsenoxides.

6.2.4.2 *Man*

Elevated levels of inorganic arsenic, methylarsonic acid, or dimethylarsinic acid were not found in human urine following ingestion of crab meat containing 2 mg of arsenic (Crecelius, 1977b). Digestion of the urine with hot 2 *N* sodium hydroxide solution was reported to convert the unknown organic arsenic compound to dimethylarsinic acid. The author interpreted his results as indicating that organoarsenic compounds originating from seafood are excreted without being biotransformed in the body. Canon et al. (1979) demonstrated the presence of arsenobetaine in the urine of 2 human subjects after ingestion of rock lobster tails. This indicates that this compound is not biotransformed in the body.

7. NORMAL LEVELS IN MAN AND BIOLOGICAL INDICATORS OF EXPOSURE

This section will deal with concentrations of arsenic in "unexposed" persons as well as in persons excessively exposed to arsenic

through food, drinking-water, drugs, or occupation. It will also deal with concentrations of arsenic in biological indicator media and the extent to which they reflect exposure, e.g., concentrations in ambient or industrial air, drinking-water, or food. It would have been desirable to discuss the extent to which concentrations in biological indicator media reflect concentrations of arsenic in critical organs, i.e., organs where the earliest toxic symptoms are manifested. However, since no organ is generally accepted as the critical organ for arsenic toxicity, such data are lacking. Some comments will be made based on human and animal metabolic data. The arsenic levels in biological media will be discussed separately.

7.1 Blood

The reported figures on arsenic levels in the blood vary. Using neutron activation, Brune et al. (1966) found a mean arsenic concentration of 0.004 mg/kg in the whole blood of 8 normal subjects. Bergström & Wester (1966), also using neutron activation, noted a mean level of 0.002 mg/kg in whole blood (3 samples), of which 0.0011 mg/kg was present in the serum. A mean concentration of 0.0011 mg/litre was also found in 11 samples of normal human serum by Damsgaard, et al. (1973) using neutron activation analysis. Mean arsenic values (7—16 samples) of 0.0024 mg/litre in plasma, 0.0027 mg/litre in red cells and 0.025 mg/litre in whole blood have been reported for healthy Danish individuals (Heydorn, 1969) whereas corresponding values for normal subjects (6—17 samples) from China (Province of Taiwan) were 0.0154 mg, 0.0327 mg, and 0.0216 mg/litre, respectively. All measurements were performed using neutron activation analysis. Blackfoot disease patients and members of their families living in the endemic area of China (Province of Taiwan) (section 8.3.4) showed mean values of about 0.03 mg/litre in plasma (Astrup, 1968; Heydorn, 1969), 0.093 mg/litre in red cells, and 0.060 mg/litre in whole blood (Heydorn, 1969). The mean concentrations of arsenic in well water in the endemic area ranged from 0.054 mg to 0.743 mg/litre (Kuo, 1968).

Kagey, et al. (1977) reported a mean blood arsenic level of 0.0023 mg/litre among 50 female smokers and a mean of 0.0015 mg/litre among 49 nonsmokers in the USA (atomic absorption spectrophotometry).

A mean blood level of arsenic of 0.00145 mg/kg (range 0.0005—0.032 mg/kg, neutron activation analysis) has been reported for 10-year-old children living in a country town in Czechoslovakia (Bencko & Symon, 1977). A mean blood-arsenic level of 0.00188 mg/kg (range 0.0005—0.0038 mg/kg) was found among children of the same age in a metropolitan city and a mean of 0.00453 mg/kg (range

0.0025—0.0082 mg/kg) among children living near a coal-fired power plant.

In a study by Wagner & Weswig (1974), levels of arsenic in the blood ranging from 0.01 to 0.27 mg/kg were found in forestry workers exposed to dimethylarsinic acid (SDDC method). Unexposed workers were reported to have levels in the range of 0.01—0.13 mg/litre, which seem to be high compared with normal values reported by others using neutron activation analysis. An average arsenic level in whole blood of 0.033 mg/kg (range 0.012—0.055 mg/kg; atomic absorption spectrophotometry) was found among 23 workers in a workshop producing wood preservatives (arsenic acid) from arsenic(III) oxide which probably was the cause of most of the airborne arsenic (Yamamura & Yamauchi, 1976). The average value for the controls was reported to be 0.007 mg/kg.

The major part of both inorganic and organic arsenic in blood is cleared fairly rapidly in man. Blood arsenic will therefore reflect exposure for only a short period following absorption and will be very timedependent. Only if exposure is continuous and steady, as is sometimes the case with exposure through drinking-water, will arsenic reach a steady-state in the blood and, thus, make it possible to arrive at a relationship between blood arsenic levels and exposure. Even so, data are not available that indicate any quantitative relationship relevant to man between arsenic exposure and concentrations of arsenic in the blood.

The short half-time of arsenic in the blood compared with the biological half-time in the whole body makes it difficult to establish a relationship between the blood level of arsenic and total body burden or concentrations in different organs. A metabolic model for the different forms of arsenic has yet to be established.

7.2 Urine

Values given in the literature for normal background levels of arsenic in urine cover quite a wide range, probably because of the influence of dietary sources and differences in analytical methods. When a person has ingested a seafood meal, the urinary arsenic concentration can often rise to over 1 mg/litre during the subsequent 24 h (Schrenk & Schreibeis, 1958; Pinto et al., 1976). Westöö & Rydälv (1972) found that up to 1.5 mg of arsenic was excreted in the urine during the first day following ingestion of fish containing about 2 mg of arsenic. Studies by Crecelius (1977b) and Cannon et al. (1979) indicated that the organic arsenic compounds present in marine organisms are probably not metabolized in the human body, but are excreted in the urine in the form in which they are ingested (section 6.2.4). Determination of inorganic arsenic and methylated arsenic acids in urine (the main metabolites of inorganic

arsenic), using a method described by Braman & Foreback (1973) and Crecelius (1977), is not influenced by the presence of organic arsenic compounds in seafood (Crecelius, 1977). Thus, it is possible to differentiate between arsenic taken in the form of inorganic arsenic and that ingested in the form of seafood organoarsenic compounds.

A mean urinary value of about 0.011 mg/litre (SDDC method) was reported by Bencko & Symon (1977) for a group of 10-year-old boys with no known exposure to arsenic. Seafood was probably only a minor ingredient in the diet. The mean urinary arsenic values in groups of children living within 7.5 km of o coal-fired power plant were 0.0189—0.0253 mg/litre (range $<$ 0.001—0.105 mg/litre).

In preemployment examinations of over 200 men, Pinto et al. (1976), using the arsine generation/spectrophotometric method, found a background arsenic value in urine of 0.053 mg/litre. Samples were collected without regard to prior seafood consumption. Using arsine generation/plasma excitation emission spectrophotometry Smith et al. (1977) reported a geometric mean of 0.021 mg/litre among 41 unexposed workers. The total urinary arsenic concentrations as well as various forms of arsenic (inorganic arsenic, dimethylarsinic acid, methylarsonic acid) were log-normally distributed among the 41 male workers. Braman & Foreback (1973) reported total arsenic levels (arsine generation and atomic emission spectrophotometry) in the urine of 4 subjects of between 0.010 and 0.030 mg/litre. They found that the predominant form of arsenic was dimethylarsinic acid, which accounted for between 40% and 87% of the total arsenic. Other forms of arsenic in the urine were methylarsonic acid and inorganic trivalent and pentavalent arsenic.

Increased urinary levels of arsenic have been detected among people living in the vicinity of smelters. Holmqvist (1975) measured arsenic in the urine of smelter workers with low exposure to arsenic and women living in 2 villages, 1 within 3 km of the smelter and the other approximately 5 km from it. The highest values, mean 0.05 mg/litre (analytical method not given), were found in women living in the village 5 km from the plant. Women living over 70 km from the plant showed a mean value of 0.03 mg/litre.

In a survey among children in 11 copper smelter towns in the USA, a geometric mean of 0.019 mg As/litre of urine (atomic absorption spectroscopy) was found and 0.006 mg/litre in 3 control towns without a smelter (Baker et al., 1977). The children in the town most heavily contaminated with arsenic had a geometric mean of 0.018 mg As/litre of urine.

Total arsenic in urine has been used traditionally to assess occupational exposure to inorganic arsenic. It is obvious that detailed records of dietary habits should accompany all studies in which total urinary arsenic is used as an indicator of industrial or other environmental exposure. Generally, this has not been the

case. There are many reports concerning total urinary arsenic excretion following industrial exposure, some examples of which will be given here. Lundgren (1954) found an average arsenic concentration of 0.54 mg/litre in the urine of smelter employees, as opposed to only 0.04 mg/litre in workers without arsenic exposure (analytical method not given). An average urinary concentration of 0.82 mg/litre (median 0.58 mg/litre; titrimetric method) was reported by Pinto & McGill (1953) in men exposed to arsenic in a smelter in the USA. In the same smelter, more than 20 years later, Pinto, et al. (1976) found an average urinary level of arsenic of 0.174 mg/litre (range 0.038—0.539 mg/litre). Kodama, et al. (1976) reported an average urinary arsenic concentration of 0.056 mg/litre (standard deviation 0.045) among 42 workers in a copper smelter in Japan (molybdenum blue method).

Using the silver diethyldithiocarbamate method, Tarrant & Allard (1972) studied the urinary excretion of forest workers in thinning operations whereby they were exposed mainly to dimethylarsinic acid (cacodylic acid) and monosodium methane arsonate. The average urinary arsenic value at the beginning of a working week (Monday morning) was 0.08 mg/litre compared with 0.32 mg/litre at the end of the week (Friday afternoon).

Concentrations of arsenic in both air and urine have been reported in only a few studies. Pinto et al. (1976) found a correlation between urinary arsenic levels in smelter workers and concentrations of arsenic in the air in the smelter (Fig. 4). Arsenic was determined by an arsine generation/spectrophotometric method. The workers wore personal monitors for 5 consecutive workdays to measure the levels of arsenic in the air. The correlation was reported to be significant at arsenic concentrations in air below 0.3 mg/m^3 and urinary arsenic levels below 0.5 mg/litre. However, as can be seen in Fig. 4, there is considerable scatter in the values and this correlation is not evident at air levels below 0.05 mg/m^3.

Carlsson (1976) studied urinary arsenic excretion in workers at a Swedish smelter. Where it was established that subjects had eaten seafood on the days immediately prior to the collection of urine samples, they were excluded from the study. The men used gas masks and personal air samplers in such a way that only the arsenic present in the inhaled air was measured. The 8-h mean arsenic concentration in air was 0.057 mg/m^3 (range 0.002—0.227 mg/m^3: X-ray spectrometric method) and the mean arsenic concentration in the morning urine, collected the day following that of the exposure was 0.2 mg/litre (Gutzeit method). No clear linear relationship emerged between airborne arsenic exposure and the total urinary arsenic.

Only one report has been published on the different forms of arsenic in the urine of exposed smelter workers. Smith et al. (1977) measured the concentration of respirable (< 5 μ) and nonrespirable

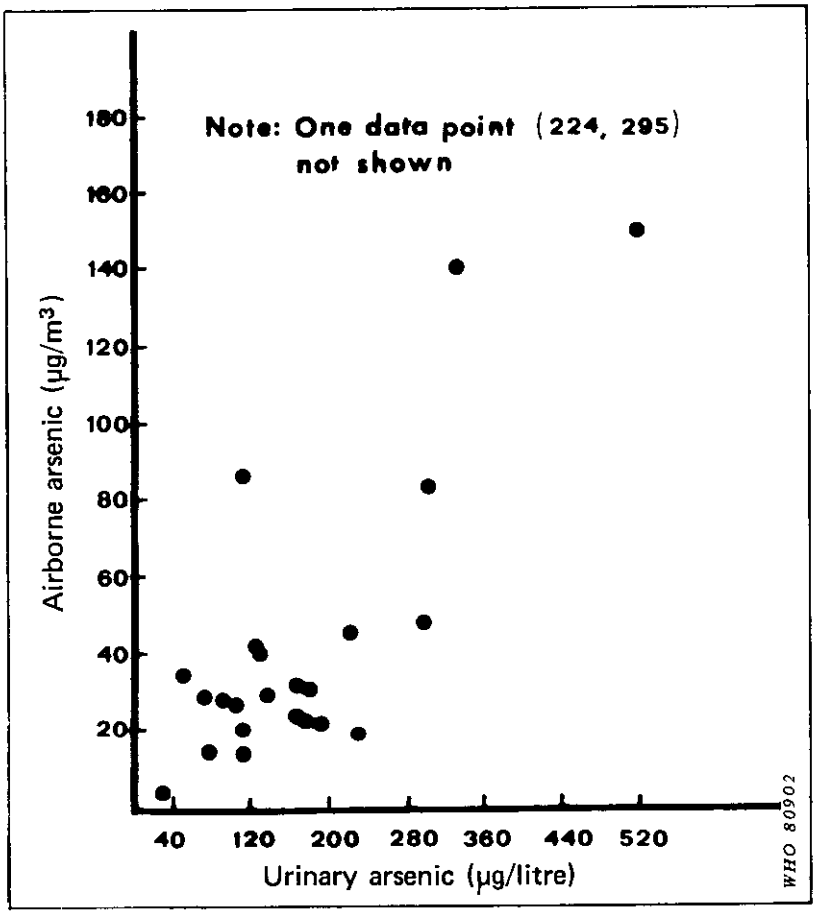

Fig. 4. Relationship between urinary arsenic excretion and concentration of inhaled arsenic (From: Pinto et al., 1976).

arsenic in the air during one working day as well as the concentrations in urine. Arsenic was mainly excreted as dimethylarsinic acid and the proportion of the different forms of arsenic in the urine was, according to the authors, independent of exposure levels (arsine generation/plasma excitation emission spectrophotometry). The correlation between total airborne arsenic and total urinary arsenic and the correlation between airborne arsenic and the different forms of urinary arsenic were reported to be significant. However, the values showed substantial scatter and furthermore, the data could not be used to arrive at a correlation between airborne

arsenic and urinary excretion, since the workers used chemical cartridge respirators, and it was not stated how much of the arsenic was captured on the filters.

Urinary arsenic levels have also been shown to be correlated with intake of arsenic in drinking-water. A survey was conducted by Harrington, et al. (1978) among a population in an area with elevated arsenic levels in the well water. Drinkers of well water with an arsenic content exceeding 0.1 mg/litre (mean 0.401 mg/litre and an estimated total daily intake of 0.324 mg of arsenic) had an average urinary concentration of 0.178 mg/litre (atomic absorption spectroscopy). Drinkers of well water containing an average arsenic concentration of 0.031 mg/litre (estimated daily intake of 0.046 mg of arsenic) had a mean urinary arsenic concentration of 0.041 mg/litre. Ingestion of arsenic in water was also found to be reflected in urinary excretion in a smelter town in the USA (Morse et al., 1979). Children drinking tap water containing arsenic at 0.09 mg/litre excreted an average of 0.059 mg As/litre of urine, while children in a control town, where the arsenic level in the water was 0.01 mg/litre, excreted a mean concentration of 0.018 mg As/litre of urine. Children in both towns, who drank bottled water (with undertectable arsenic contents), excreted average urinary arsenic levels of 0.03 mg/litre and 0.01 mg/litre, respectively.

7.3 Hair

Arsenic is normally found in higher concentrations in human hair and nails than in other parts of the body. This has been explained by the high content of keratin in these tissues (Shapiro, 1967). The SH-groups of keratin may bind trivalent arsenic.

The level of arsenic in hair was found to be less than 1 mg/kg in more than 80% of 1000 persons examined in a study using neutron activation analysis (Smith, 1964). The average level was 0.81 mg/kg and the median 0.51 mg/kg. Liebscher & Smith (1968) found a log-normal distribution of arsenic concentrations in over 1200 hair samples from residents of the Glasgow area in Scotland. They performed neutron activation analysis on the samples and found arsenic levels ranging from 0.02 to 8.17 mg/kg dry weight with a geometric mean of 0.46 mg/kg. Geometric mean arsenic concentrations in hair of about 0.3 mg/kg were reported by Boylen & Hardy (1967) and Cornelis (1973). The first authors used a colorimetric method with SDDC as a reagent while Cornelis (1973) used neutron activation analysis. Leslie & Smith (1978) also used neutron activation analysis and reported hair arsenic levels of 0.01—0.40 mg/kg (median 0.11 mg/kg) in 52 persons with no known exposure to arsenic.

Elevated arsenic levels in hair have been noted in persons exposed to airborne arsenic in industrial or ambient air as well as in persons exposed to arsenic-rich drinking water. Arsenic in the hair can arise from 2 major sources: (*a*) the incorporation of absorbed arsenic into the growing portion of the hair root; and (*b*) external contamination. Lander et al. (1965) suggested that arsenic in the hair could also originate from sweat in cases of acute poisoning. They found high arsenic levels along the whole length of the hair at post-exposure times too short to have allowed the incorporation of arsenic into the hair root. Their findings are in contrast to those of other authors (Shapiro, 1967; Pearson & Pounds, 1971), the reason probably being the different methods and levels of arsenic administration. In acute arsenic poisoning, profuse sweating usually occurs, which could account for the data presented by Lander et al. (1965); this is not the case with lower doses. It is also possible that sweat and water can dissolve arsenic particles on the surface of the hair and in this way augment the possible binding of arsenic to SH-groups in the hair. It has been shown by Maes & Pate (1977) that the absorption of arsenic in hair soaked in a solution of radiolabelled arsenite is highly stratified on some subjects, showing zones of very high and very low absorption. To say that peaks in arsenic concentration along the length of the hair are indicative of days of high arsenic ingestion or inhalation is therefore risky, at least in some subjects.

Much effort has been made to develop techniques to remove possible external arsenic contamination from the hair. Atalla et al. (1965), after trying several different washing methods, concluded that it was not possible to distinguish between arsenic incorporated in the hair after absorption and arsenic settling on the hair from external contamination. The data seemed to indicate a saturation value of 70 mg/kg for linkage of arsenic to keratin in hair. When hair was impregnated with arsenic (pentavalent) from a water solution, almost all of the arsenic was easily washed off with dilute hydrochloric acid. However, when workers' hair containing 50 and 400 mg As/kg was washed, only about 50% of the arsenic was dissolved (van den Berg et al., 1969). Smith (1976) suggested a method to distinguish between arsenic in, and on the surface of human hair in which scanning was used on hair cut perpendicularly to the long axis. He concluded that most of the arsenic in the hair of residents in the vicinity of a smelter emitting arsenic(III) oxide was in, rather than on, the hair.

Arsenic levels in the hair of members of the general population exposed to arsenic-polluted air have been reported in a number of studies. Bencko & Symon (1977) determined hair concentrations in boys living in the vicinity of a power plant that burned local coal with a high arsenic content. In the most highly exposed groups, the values for arsenic in hair ranged from 0.6 to 10 mg/kg (SDDC

method; hair washed with detergent and 3% hydrochloric acid). At 36 km distance from the source of the emission, a mean value of 0.3 mg/kg (range from not detectable up to 0.9 mg/kg) was found. The value in a control group residing in a metropolitan city was 0.15 mg/kg. Hammer, et al. (1971) compared hair levels of arsenic in fourth grade boys living in cities representing exposure dose gradients for arsenic. In the city with the highest arsenic exposure (no data on air concentrations were given), a geometric mean hair concentration of 9.1 mg As/kg was found compared with 0.3 mg/kg in the city with the lowest arsenic exposure (analytical method reported as spectrophotometry). Head hair samples were collected from children aged between 5 and 12 years, who lived near an open cast metal mine in Ireland (Corridan, 1974). The mean arsenic concentration in the hair of these children was 2.1 mg/kg (SDDC method), which was more than 17 times higher than that in a comparable group of urban children. Suzuki, et al. (1974) measured the arsenic contents of head hair from primary-school boys living near a smelter in Japan. The concentrations showed a log-normal distribution with a geometric mean of 1.87 mg/kg (SDDC method), which was about 9 times higher than that in hair from children in a control city. Higher levels of arsenic in hair were also reported among children in various copper smelter towns in the USA (Baker, et al., 1977) where the median level was 0.38 mg As/kg (atomic absorption spectroscopy) compared with a median level of 0.08 mg/kg in the hair of children from control towns without copper smelters. Children, 5–9 years of age, in a gold-mining town in Canada had mean hair arsenic concentrations (neutron activation) of 1.76 mg/kg compared with 0.39 mg/kg in another town without a mine (Canadian Public Health Association, 1978).

The contents of arsenic in the hair of occupationally exposed persons can reach several hundred mg/kg (Smith, 1964; Atalla, et al., 1965; Porazik, et al., 1966; Leslie & Smith, 1978). A survey concerning the arsenic contents in hair was conducted on 703 residents in Yellowknife, Canada (Canadian Public Health Association, 1977). Of the 135 gold mine and mill workers participating in the survey, 33% had hair arsenic levels exceeding 10 mg/kg (analytical method not given). Among other residents, only 3.4% had hair levels of more than 10 mg/kg.

Reported studies do not include any information on the correlation between arsenic exposure via air (industrial or general environment) and arsenic concentrations in hair. The only conclusion that can be drawn is that the hair of exposed persons contains higher levels. Arsenic levels in the hair of persons exposed to inorganic arsenic through ingestion are a more relevant indication of exposure, providing that external contamination can be excluded. The influence on hair arsenic levels of ingested organic arsenic from seafood and drugs is not known.

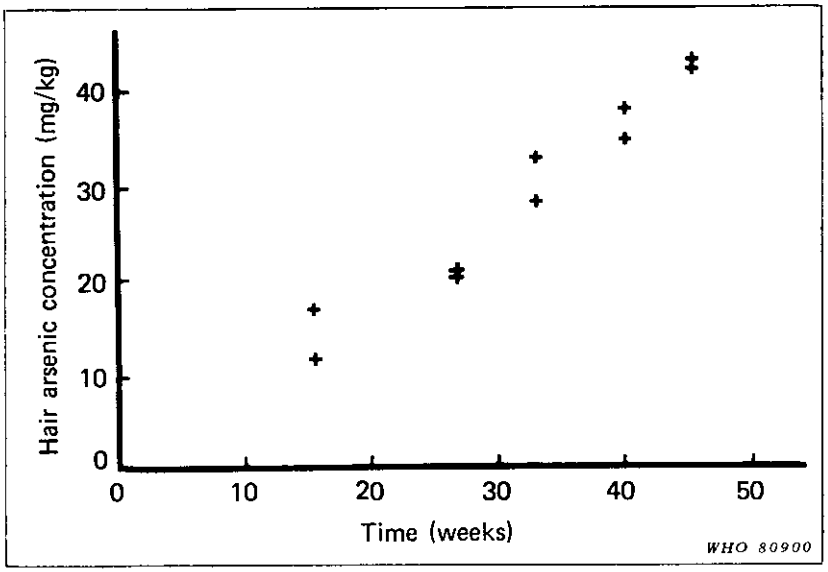

Fig. 5. The amount of arsenic found in hair plotted against the time elapsed since the beginning of treatment with Fowler's solution containing 1% As_2O_3 (corresponding to a daily intake of 6–10.5 mg As) (From: Pearson & Pounds, 1971).

A correlation between hair arsenic contents and the dose of inorganic arsenic ingested has been reported by Pearson & Pounds (1971) and Curry & Pounds (1977). It has also been shown that arsenic concentrations along the length of the hair can serve to indicate uptake over a period of time (Pearson & Pounds, 1971) (Fig. 5).

Hindmarsh, et al. (1977) measured arsenic concentrations in the hair of 110 people in Nova Scotia, Canada, who used drinking-water from wells with an arsenic content ranging from 0.01 to 1.4 mg/litre. The relationship between arsenic concentrations in drinking water and arsenic levels in hair (samples of hair cut close to the scalp) is seen in Fig. 6. The spread is quite substantial and the correlation was reported to be poor (without any quantification). Hair arsenic concentrations were determined using neutron activation analysis in a population in an area with elevated arsenic levels in the well water (Harrington, et al., 1978). Drinkers of well water with an arsenic concentration exceeding 0.1 mg/litre had a mean arsenic concentration of 3.3 mg/kg in hair, while those who drank well water containing less than 0.1 mg As/litre had a mean arsenic concentration in the hair of 0.46 mg/kg. There were indications of external contamination in the high exposure group, as bottled water drinkers, with a substantially lower intake of arsenic as shown by

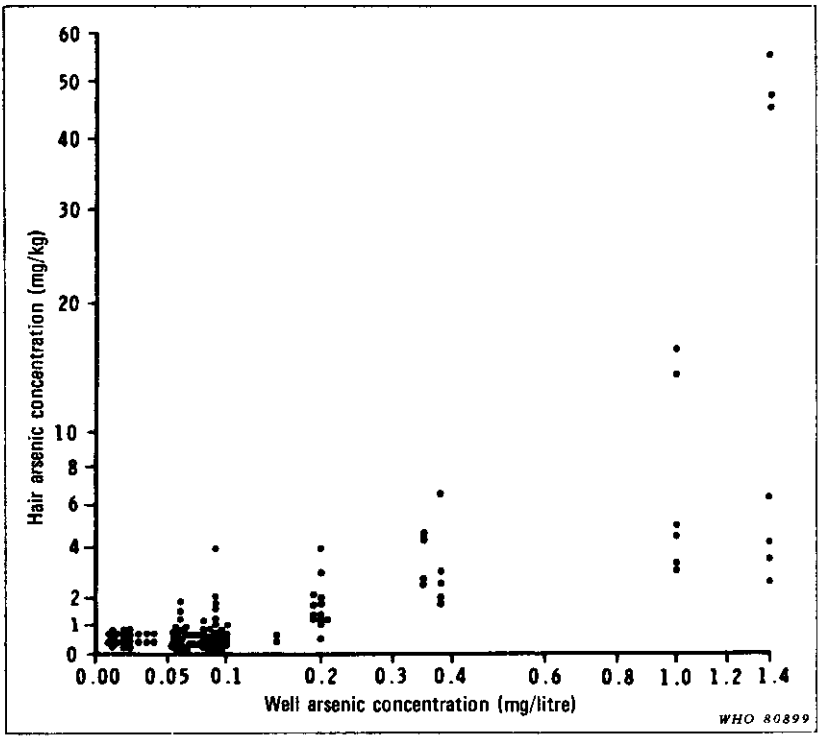

Fig. 6. Relationship between well water arsenic concentration and hair arsenic concentration (From: Hindmarsh et al., 1977).

comparatively low urinary arsenic concentrations, had hair arsenic concentrations similar to those of well water drinkers with arsenic levels exceeding 0.1 mg/litre in the drinking-water.

In conclusion, it can be stated that hair arsenic can be used on a group basis as an indicator of arsenic exposure through ingestion, providing that external contamination is only slight. The use of hair arsenic as an indicator of exposure to airborne arsenic is limited, as no reliable method exists of distinguishing arsenic from external contamination from arsenic that has been absorbed and metabolized in the body. However, it can be used on a group basis as an indicator of possible exposure situations.

7.4 Other Tissues

The concentrations of arsenic in various human tissues determined by neutron activation analysis and reported by Liebscher &

Table 8. Arsenic concentrations in human organs and tissues

Tissue or organ	Dry weight[a] (geometric mean values)	Arsenic concentration (mg/kg) Wet weight[b] (mean values)	Wet weight[c] (median values)
adrenal	0.03		
aorta	0.04		
whole blood	0.04		
brain	0.01		
hair	0.46		
heart	0.02		
kidney	0.03	0.007	0.004
liver	0.03	0.011	0.003
lung	0.08	0.010	0.008
muscle	0.06 (pectoral)	0.004	
nail	0.28		
ovary	0.05		
pancreas	0.05	0.005	
prostate	0.04		
skin	0.08		
spleen	0.02	0.003	
stomach	0.02		
teeth	0.05		
thymus	0.02		
thyroid	0.04		
uterus	0.04		

[a] Compiled from Liebscher & Smith (1968).
[b] Compiled from Larsen et al. (1972).
[c] Compiled from Brune et al. (1980).

Smith (1968), Larsen et al. (1972), and Brune et al. (1980) are shown in Table 8.

Arsenic levels in the lungs of 22 smelter workers, who had not been exposed occupationally to arsenic for the last 2–19 years, were reported by Brune et al. (1980). A median arsenic value of 0.048 mg/kg wet weight (range 0.014–0.21 mg/kg) was found compared with a median value of 0.008 mg/kg wet weight (range 0.001–0.018 mg/kg) in 9 controls. No such differences could be found in the arsenic contents of the liver and kidneys of 10 workers and 8 controls.

8. EFFECTS AND DOSE-RESPONSE RELATIONSHIPS OF INORGANIC ARSENIC

Occupational exposure to inorganic arsenic occurs mainly in the smelting industry, and in the manufacture and application of arsenic-containing pesticides (section 5.2) It is generally considered that smelter workers are exposed to trivalent inorganic arsenic compounds, while workers handling pesticides are exposed

primarily to pentavalent arsenic. In the general environment, high levels of arsenic may be found in drinking-water in various parts of the world, including, Argentina, Chile, China (Province of Taiwan), Japan, and Mexico. It is believed that arsenic occurs predominantly in an inorganic form in water; however, the oxidation state of the arsenic associated with adverse health effects is not known at present. Substantial exposure to arsenic also results from medication with inorganic (mainly trivalent) and organic arsenic compounds. The use of inorganic arsenic in drugs is now limited in most countries.

8.1 Acute and Subacute Effects after Short-Term Exposure

8.1.1 Man

Acute effects caused by the ingestion of inorganic arsenic compounds, mainly arsenic(III) oxide, are well documented in the literature. The major lesion is profound gastrointestinal damage resulting in severe vomiting and diarrhoea, often with blood-tinged stools. Other acute symptoms and signs include muscular cramps, facial oedema, and cardiac abnormalities. Shock can develop rapidly as a result of dehydration. Symptoms may occur within a few minutes of the exposure if the arsenic compound is in a solution but may be delayed for several hours if it is solid or taken with a meal. When taken orally, the toxicity of the arsenic compound largely depends on its solubility (Done & Peart, 1971). Human data on the differences in toxicity between trivalent and pentavalent arsenic are limited. The fatal dose of ingested arsenic(III) oxide for man has been reported to range from 70—180 mg (Vallee et al., 1960).

Effects resulting from exposure to quantities of arsenic sufficient to cause acute symptoms and signs, but inadequate to produce systemic collapse, are of particular interest. Unfortunately, the doses that have resulted in such symptoms and signs have rarely been reported. Subacute effects mainly involve the respiratory, gastrointestinal, cardiovascular, nervous, and haematopoietic systems. Exposure to irritant arsenic compounds, such as arsenic(III) oxide, in air can acutely damage the mucous membranes of the respiratory system and exposed skin. This can result in severe irritation of the nasal mucosa, larynx, bronchi, and ear canal, as well as in conjunctivitis and dermatitis (Holmqvist, 1951; Pinto & McGill, 1953). Nasal septum perforation may appear within two weeks.

Peripheral nervous disturbances, primarily of a sensory type, are frequently encountered in individuals surviving acute poisoning with inorganic arsenic compounds (Heyman et al., 1956; Jenkins,

1966; Nagamatsu & Igata, 1975; O'Shaughnessy & Kraft, 1976; Le Quesne & McLeod, 1977). These disturbances usually become manifest 1—2 weeks after ingestion. Recovery is slow, usually starting between 1 and 2 months after the onset of symptoms. The degree of recovery depends on the severity of the symptoms. The lower extremities are often more severely affected than the upper ones.

Histological examination of the peripheral nerves in a case of arsenic poisoning showed Wallerian degeneration, especially in the longest axons (Ohta, 1970). Clinical and electrodiagnostic recordings made over an extended period of time were consistent with the histological changes.

The haematopoietic system may also show effects, characterized by anaemia and leukopenia, especially granulocytopenia (Hamamoto, 1955; Heyman et al., 1956). These effects are usually reversible within 2—3 weeks.

Reversible changes in the electrocardiogram have frequently been encountered following acute exposure to arsenic compounds (Hamamoto, 1955; Weinberg, 1960; Barry & Herndon, 1962; Chhuttani et al., 1967). In these situations, the doses have generally been high enough to produce other symptoms and signs of acute intoxication. The observed effects usually include extensions of the QT-time and T-wave abnormalities.

Two instances of mass poisoning by inorganic arsenic in Japan give a good picture of the diversity of symptoms associated with acute and subacute poisoning, though the nature of the clinical investigations on the victims makes it difficult to interpret some the findings. The first episode occurred when over 12 000 infants were poisoned with dried milk contaminated with inorganic arsenic (Hamamoto, 1955: Nakagawa & Ibuchi, 1970). The milk powder contained 15—24 mg As/kg and the arsenic was reported to be in the pentavalent state, although no data exist on its form at the time of ingestion. It was estimated that the infants ingested 1.3—3.6 mg of arsenic daily depending on age, and 130 deaths were reported. Symptoms usually appeared after a few weeks of exposure and often included fever, insomnia, and anorexia. Liver swelling and melanosis were present in all but one of 61 hospitalized patients examined by Hamamoto. The blood picture showed anaemia and leukopenia with relative lymphocytosis. Acute renal damage was indicated by a high incidence of microscopic haematuria. Although swelling of the liver was characteristic among the poisoned infants, liver function tests were normal in all cases. Disturbance of the heart function was another common finding, and was characterized by rises in the ST, decreases in the T, and extensions of the QT-time. Most symptoms were rapidly reversible upon cessation of exposure and the beginning of therapy; however, the changes observed in the electrocardiograms took longer to disappear than the other clinical symptoms.

It must be emphasized that this group of patients constituted a limited sample of the intoxicated population and was selected according to certain diagnostic criteria, i.e., liver swelling and melanosis. Consequently, little emphasis should be put on the abundance of these symptoms; however, the coexistence of a high degree of other symptoms is noteworthy.

Mizuta et al. (1956) examined 220 out of 417 patients, who had been poisoned by soy sauce contaminated with inorganic arsenic at a concentration of 100 mg/litre. The average estimated ingestion per person was 3 mg of arsenic (valence state unknown), daily, for 2–3 weeks. The main findings were facial oedema, anorexia, and upper respiratory symptoms followed by skin lesions and neuritic signs at a later stage, i.e., after 10–20 days. Though the livers of most patients were enlarged, relatively few abnormalities were found in the liver function tests and liver size gradually decreased after cessation of exposure. Abnormal electrocardiograms were found in 16 out of 20 cases tested. The arsenic content of hair in 5 patients about 2 weeks after arsenic intake ceased was between 3.8 and 13 mg/kg near the roots and 0–1.8 mg/kg at the ends. Levels in control subjects ranged from 0.4 to 2.8 mg/kg.

In a clinical study of 13 cases of polyneuropathy connected with arsenic poisoning, in Sri Lanka, Senanayake et al. (1972) found Mee's lines, i.e., transverse white bands across finger nails, to be the constant feature, at least 6 weeks after the onset of initial symptoms. In 7 of these cases, the source of arsenic was contaminated well water, 4 others had a long history of consuming illicit liquor.

Mee's lines are of value both in the diagnosis and in the assessment of the approximate time of exposure to arsenic. The time may be calculated by considering the distance of the line from the base of the nail and the rate of nail growth, which is of the order of about 0.3 cm per month or about 0.1 mm per day (Smith & Fiddes 1955).

Appearance of polyneuropathy, 3 days to 3 weeks after acute poisoning, was seen in all the cases reported by Senanayake et al. (1972). The first symptom of neuropathy in these cases was numbness of extremities. The lower limbs were affected earlier and more severly than the upper limbs.

8.1.2 Animals

The oral LD_{50} (or "certain fatal dose") for arsenic ranged from 15–293 mg As/kg body weight in rats and 11–150 mg/kg in other laboratory animals (Schwartze, 1922; Dieke & Richter, 1946; Harrison et al., 1958; Done & Peart, 1971). The lower values are generally found, when the arsenic is administered in solution. Sodium arsenite, which is more soluble in water than arsenic(III) oxide, has been

shown to be 10 times as toxic as arsenic(III) oxide (Done & Peart, 1971). Trivalent arsenic is generally more toxic than pentavalent arsenic. Franke & Moxon (1936) obtained a minimal fatal dose (the smallest dose which killed 75% of intraperitoneally exposed rats in 48 h) of 4–5 mg As/kg body weight for sodium arsenite and 14–18 mg As/kg body weight for sodium arsenate. The development of tolerance towards the acute effects of arsenic(III) oxide following pretreatment with arsenic was demonstrated by Bencko & Symon (1969b). The LD_{50} following subcutaneous injection of arsenic(III) oxide was significantly higher for hairless mice, pretreated for 15 weeks with inorganic arsenic in the drinking water at a concentration of 50 mg/litre than for mice not previously exposed to arsenic (14 and 11 mg/kg body weight, respectively). A discussion of tolerance to arsenic appears in section 6.1.2.2.1. The effects observed in acutely intoxicated animals resemble those found in human subjects and included gastroenteritis, diarrhoea, lowered blood pressure, and ECG changes (Nelson et al., 1971; Tsutsumi & Nozaki, 1973; Selby et al., 1977).

In addition to the experimental data, the results of a large epizootic survey on cattle accidentally given feed containing high levels of inorganic arsenic have been reported (González, 1977). Nearly 6000 cattle were fed for 1–2 days with a mixture containing arsenic(III) oxide at levels of between 490 and 2900 mg/kg. Acute signs were observed immediately, and the first deaths occurred after 3 days. More than 50% of the 1464 animal deaths took place during the first week following administraton of the feed. The rest of the deaths occurred over a 6-month period as the result of visceral damage. The main acute signs observed were: drastic reduction in milk production (85% reduction), diarrhoea, dehydration, dyspnoea, cyanosis, abortion, and central nervous effects. Among the chronic signs, the most frequently observed were: hyperkeratosis of the skin, rigidity and inflammation of the joints, and blindness with opacity of the cornea. With respect to the pathological observations the most serious were: haemorrages and ulcers of the gastrointestinal tract, fatty degeneration of the liver and kidney, nephritis, emphysema and pulmonary oedema, and albuminar degeneration of the heart.

Animal data on subacute effects, will be discussed in section 8.3 together with chronic effects.

8.2 Effects on Reproductive Function and Teratogenicity

8.2.1 Man

Human data on the teratogenicity of inorganic arsenic are very limited. Children born to women who worked during pregnancy at a

Swedish copper smelter and were exposed to airborne arsenic in some workplaces, showed a significantly higher frequency of congenital malformations (Nordström et al., 1979). The frequency of all malformations in the children of women at the smelter was twice as high as that in the children of other women in the region. A 5-fold higher frequency was noted for multiple malformations. Data were collected from the records of the regional hospital, and included a total of about 25 000 live births during the period 1955—76. The exposure environment of the smelter was very complex, involving a number of heavy metals and sulfur dioxide. No conclusions can be drawn with regard to the specific cause of the observed excess of malformations.

Nordström et al. (1978) studied the frequency of spontaneous abortions during 4427 pregnancies in women living in the vicinity of this copper smelter. The smelter had emitted many potentially genotoxic substances in to the environment including arsenic and lead. The frequency of abortions was significantly higher in women living nearest the factory than in a reference population living more than 50 km from the plant. The abortion rates in the 2 areas were 11% and 7.6%, respectively. Obviously, no firm conclusions could be drawn with regard to the role of the inorganic arsenic exposure in these cases; but the results indicate that further research in this field is needed.

8.2.2 Animals

Teratogenic effects of inorganic arsenic have frequently been reported in laboratory animals. Ridgway & Karnofsky (1952) reported that sodium arsenate gave rise to nonspecific effects in chick embryo tests. Ferm & Carpenter (1968) were the first to describe clear teratogenic effects of arsenic in laboratory animals. Pregnant golden hamsters were given an intravenous injection of sodium arsenate on the 8th day of gestation and the embryos were examined 4 to 5 days later. A dose of 2 mg As/kg body weight as sodium arsenate did not induce any malformations, while 3 mg As/kg body weight caused an increased incidence of resorption and malformation, especially exencephaly. A level of 16 mg As/kg body weight resulted in the death of all embryos. In a later study, Ferm et al. (1971) investigated the influence of the time of injection on the teratogenic profile in hamsters. Intravenous injections of 6—10 mg As/kg body weight as sodium arsenate at various times on the eighth and ninth days of gestation caused different types of lesions. The observed malformations included exencephaly, anencephaly, renal agenesis, and rib and genitourinary abnormalities. In addition, high resorption rates were present.

Results similar to those reported in hamsters were found in mice, intraperitoneally injected with sodium arsenate at 45 mg/kg body weight (11 mg As/kg body weight) on the 6th to 12th days of gestation (Hood & Bishop, 1972). Offspring of mice treated with 6 mg As/kg body weight as arsenate did not differ from those of the controls. Administration of sodium arsenite in doses of 10 or 12 mg/kg body weight (6 or 7 mg As/kg body weight) resulted in a lower incidence of malformations and a higher incidence, of resorptions than sodium arsenate at 11 mg As/kg body weight (Hood, 1972; Hood et al., 1977).

The teratogenicity of sodium arsenate in rats was investigated by Beaudoin (1974). Doses of 5—12 mg As/kg body weight were given as a single intraperitoneal injection on the 7th to 12th day of gestation. All dose levels produced malformations such as eye defects, exencephaly, renal agenesis, and gonadal agenesis.

The route of administration was shown to have a significant influence on the teratogenic action of arsenic in mice (Thacker et al., 1977). A much higher oral dose of an aqueous solution of arsenate was needed to induce the same effects as found after intraperitoneal injection. The doses given were 120 and 40 mg arsenate per kg body weight, respectively.

In all the studies mentioned so far, single high doses of arsenic were used to produce teratogenic effects. Schroeder & Mitchener (1971) exposed 3 generations of mice to low doses of arsenite but did not find any abnormalities other than reduced litter size. The mice were exposed to arsenic in feed (5 mg As/kg diet) in the form of arsenite. Without supplementary data on food consumption it is difficult to estimate the actual dose level.

8.3 Noncarcinogenic Effects After Long-Term Exposure and Sequelae of Short-Term Exposure

8.3.1 Effects on the respiratory system

8.3.1.1 *Man*

Effects of arsenic on the respiratory system have been reported primarily as a result of occupational exposure. In the smelting industry, where high levels of airborne inorganic arsenic are frequently encountered, lesions of the mucous membranes in the respiratory system, including perforation of the nasal septum, have been observed (Pinto & McGill, 1953; Lundgren, 1954; Birmingham et al., 1965; Ishinishi, 1973; Hine et al., 1977). Lundgren performed medical examinations on 1276 workers at a copper smelter in Sweden. The levels of airborne arsenic were as high as 7 mg/m^3 in some workplaces, but generally did not exceed 0.5 mg/m^3. Two

types of respiratory syndromes were seen, each of them characteristic for a certain group of workers. Symptoms of the upper respiratory passages with septum perforation and rhino-pharyngo-laryngitis were found chiefly among workers exposed to arsenic in the crude or refined form. In some workplaces, over one third of the workers showed changes in the nasal mucosa. The other syndrome included symptoms of tracheobronchitis and signs of pulmonary insufficiency, often due to emphysematous lesions. This picture was found especially among those who had worked at the roasters, reverberatory furnaces, and in converter halls, where mixed exposure to arsenic and sulfur dioxide took place. This study did not include data on smoking habits, which probably played a role in the symptoms and signs noted. No controls were used.

It has been claimed that exposure to arsenic via routes other than inhalation can affect the respiratory system. A high frequency of chronic cough and a history of bronchopulmonary disease were reported by Borgono et al. (1977) among 180 inhabitants of Antofagasta in Chile who had abnormal skin pigmentation attributed to arsenic exposure in the drinking water. From the same area, Rosenberg (1974) found diffuse interstitial fibrosis of the lungs in 2 out of 5 children with systemic arterial lesions. When evaluating these 2 reports, the suspected role of arsenic as a suppressant of the immune response should be kept in mind, since this could impair resistance to infections (Gainer & Pry, 1972). It is also important to consider the very low socioeconomic status of this population, which resulted in various nutritional deficiencies.

8.3.1.2 Animals

There is a lack of data regarding the chronic effects of arsenic on the respiratory system in experimental animals. In view of the many different effects observed in workers exposed to airborne arsenic, and the difficulties in controlling various confounding factors, it is of great importance to develop animal model systems. The studies should preferably involve exposure via inhalation over long periods.

8.3.2 Effects on skin

8.3.2.1 *Man*

A number of skin lesions have been attributed to chronic exposure to inorganic arsenic compounds. Symmetric verrucous hyperkeratosis of the palms and soles is a characteristic finding after long-term ingestion of inorganic arsenic via drinking-water or drugs

Hyperpigmentation (melanosis) of the skin, often associated with paler spots (depigmentation), is also commonly encountered and occurs mainly in the areas of the skin not exposed to the sun, i.e., axillae and trunk. These lesions have been reported from regions in Argentina, Chile, China (Province of Taiwan), Japan, and Mexico, where the contents of arsenic in drinking-water were elevated (Arguello et al., 1938; Yoshikawa et al., 1960; Alvarado et al., 1964; Tseng et al., 1968; Borgoño et al., 1977). Arguello et al. (1938) reported that the keratodermia appeared insidiously between the second and third year of intoxication and did not disappear after cessation of exposure. Some individuals were followed for more than 30 years after termination of exposure.

As stated earlier, substantial exposure has also resulted from the ingestion of arsenic-containing drugs. The compound most often used was sodium arsenite in daily doses of up to 10 mg of arsenic, and the treatment could extend over decades. In a study by Fierz (1965), a dose-response relationship was found between the amount of arsenic ingested and the incidence of palmoplantar hyperkeratosis in 262 patients treated 6—26 years earlier for chronic dermatoses with diluted (1 : 1) Fowler's Solution, containing 3.8 g As/litre. In the patients who had received the equivalent of more than 400 ml of Fowler's Solution (3 g of arsenic), the prevalence of hyperkeratosis was more than 50%, and the author stated that as little as 60 ml of Fowler's Solution (about 0.46 g of arsenic) resulted in keratosis in one patient after 2.5 years of treatment. Melanosis was present in only 5 of the patients at the time of examination, but 3 others recalled that they looked "dirtyish" during the periods of arsenic treatment and that this had regressed over the years. It should be noted that this study did not include a control group and could have had a substantial selection bias, but the findings with regard to palmoplantar hyperkeratosis are worthy of note in view of the rarity of this lesion.

Hyperkeratotic lesions of the palms and soles and melanosis are uncommon among smelter workers exposed to airborne arsenic (Pinto & McGill, 1953) the most common lesion in these situations being dermatosis due to local irritation.

One third of a group of 31 workers manufacturing sodium arsenite had "warts", which, unfortunately, were not further described (Perry et al., 1948). All but 3 of these workers showed hyperpigmentation of the skin. Less than 4% of the controls at a factory with low exposure to arsenic had warts and 9 out of 56 showed melanosis of the skin.

Typical cutaneous manifestations of chronic arsenic poisoning were detected in 7 out of 28 male Japanese workers, who had been exposed to arsenic in the form of lead arsenate and calcium arsenate in the manufacture of insecticides (Hamada & Horiguchi, 1976). The lesions were symmetric punctuated palmo-plantar hyperkeratosis

and "bronze" hyperpigmentation. The authors did not find any correlation between the intensity of cutaneous manifestations and the length of exposure to arsenic. Similar conclusions were reached with regard to the skin lesions found following arsenic exposure among German wine growers (Wolf, 1974). Sixteen cases of typical arsenic-induced keratosis, which appeared from 3 to 31 years after the beginning of exposure, were reported. The total intake of arsenic through contaminated beverages was estimated to be between 5.7 and 133 g.

Sensitization of the skin following exposure to inorganic arsenic compounds, such as arsenic(III) oxide, has been reported among smelter workers (Holmqvist, 1951).

8.3.2.2 *Animals*

Skin effects have been observed in rats given oral intubations of aqueous solutions of arsenic(III) oxide in daily doses of 1.5 and 7.6 mg As/kg body weight (Ishinishi et al., 1976). The exposure was started when the rats were 2 weeks old and lasted for 40 days with an observation time of 30 weeks. Rats given the lower dose did not differ from the controls, while the rats given 7.6 mg As/kg body weight, lost the glossy appearance of their pelage, especially on the back and nape of the neck. Moist eczema developed into severe skin changes with ulcerations and crust formations in 9 out of 21 animals. Histopathological findings included ulcers and scarring of the epidermis and subcutaneous tissues, hyperkeratosis, and acanthosis. Enlargement and hyperplasia of the hair bulbs were also observed.

8.3.3 Effects on the liver

8.3.3.1 *Man*

Exposure to inorganic arsenic compounds has been associated with the development of chronic pathological liver changes. Several authors have reported cases of liver damage following treatment with arsenic in the trivalent inorganic form (Neale & Azzopardi, 1971; Knolle et al., 1974; Morris et al., 1974; Huet et al., 1975; Szuler et al., 1979). A common finding in these reports was portal hypertension without signs of liver cirrhosis. All patients had been on the arsenic medication, mostly Fowler's solution, for several years. Typical cutaneous signs of long-term arsenic exposure were also observed in some of the patients. There have also been case reports on liver cirrhosis following medication with inorganic arsenic compounds (cf. review in Franklin et al., 1950). It was claimed that alcohol could be ruled out as the causative agent in most of the

cases. Zachariae et al. (1974) took liver biopsies from 44 psoriatic patients who had received potassium arsenite and from 37 psoriatic patients who had not. Histopathological changes were common in both groups; however, no statistical differences could be established between the two. No cases of cirrhosis were demonstrated.

Exposure to arsenic-containing pesticides and contaminated wine was claimed to be the causative factor in the large number of cases of liver cirrhosis among German vintners in the forties and fifties (Roth, 1957). The number of cases diminished in the late fifties; however, less severe liver changes continue to be found regularly among the vintners (Lüchtrath, 1972; Wolf, 1974). It is probable that the heavy wine consumption, often 3—4 litres daily, among the vintners played an important role in the development of the lesions.

Kodama et al. (1976) made various biochemical determinations on the blood of 42 copper smelter workers belonging to 3 different occupational categories (14 subjects in each group, matched for sex, age, and period of employment). The average urinary arsenic concentrations in the 3 groups were 82.6, 40.6, and 45.2 μg/litre, respectively. Workers with the highest arsenic concentrations in the urine showed an increase in serum GOT and LDH, even though the levels were within normal limits. It should be noted that exposure to arsenic was fairly moderate in all the groups (< 13 μg/m^3, as a 6-h average).

An increased mortality from liver cirrhosis was reported in 2 studies on smelter workers heavily exposed to inorganic arsenic by Lee & Fraumeni (1969) and Axelson et al. (1978) (section 8.4.1.1). However, the total number of cases was quite small and a confounding effect of alcohol consumption cannot be ruled out.

8.3.3.2 *Animals*

Liver lesions have frequently been observed in animals following long-term exposure to trivalent or pentavalent inorganic arsenic. Liver cirrhosis and necrosis as well as bile duct proliferation were found in rabbits after administration of arsenate as lead, copper, or sodium salts (von Glahn et al., 1938). The arsenic was mixed in the feed and administered in daily doses of 1.4—9.3 mg of arsenic per animal for 50—250 days. Liver damage has also been observed in domestic animals exposed to arsenic (Selby et al., 1977). Histopathological findings included fatty changes and necrosis. Ishinishi et al. (1980b) gave 4 goups of male adult Wistar-King rats distilled water, per os, containing arsenic(III) oxide at arsenic levels of 0, 0.125, 12.5 or 62.5 mg/litre, respectively, for 7 months. The animals were then given distilled water without the addition of arsenic(III) oxide for 4 months. Though no differences were observed in growth

and in general physiological condition between the 4 groups, light liver injuries and dose-dependent proliferation of the bile duct with some chronic angitis in Glisson's capsules were found. Ultrastructural changes were studied in the hepatocytes of mice in the course of arsenic exposure via drinking water (50 mg As(III) per litre) over 4–64 days (Mohelská et al., 1980). The results obtained showed 2 types of response: the first (maximum on the 4th day) was enlargement of inner membranous structures (invaginations of the nuclear membrane and undulation of the mitochondrial structures) and disappearance of glycogen. The second type of response was represented by a gradual appearance of dense lamellar structures in the peroxisomes that persisted till the end of the exposure.

Disturbances of liver function have also been seen in animals exposed to arsenic. Impaired liver function, including delay in BSP excretion and increase in serum transaminases, was noted in rabbits given intravenous injections of arsenious acid in doses of 0.6 mg As/kg body weight, 3 times a week for up to 3 months (Shibuya, 1971). Mice exposed to arsenite in drinking water in daily doses of 12 mg As/kg body weight showed a progressive decrease in relative liver weight as well as a partially reversible decrease in liver oxygen consumption (Bencko & Němečkova, 1971). This finding was also noted in animals receiving a daily dose of about 6 mg As/kg body weight in the form of arsenic(III) oxide dissolved in drinking water. The oxygen consumption of liver homogenates decreased somewhat during the first month of exposure, but after 2 months it did not differ from that of the controls (Bencko, 1972). No differences in the metabolic oxygen consumption of liver homogenates were observed during 2 months in mice exposed to about 0.8 mg As/kg body weight per day. In a later study on liver dehydrogenase activity by Bencko et al. (1975), who used the same exposure groups, a decrease was revealed in the highest exposure group only, i.e., animals receiving a daily dose of 12 mg As/kg body weight. The concentration of free SH-groups in the liver decreased to a minimum level during the eighth day of exposure in all groups, and again reached the level of the control group by two months of exposure (Bencko et al., 1978a). The activity of liver glutathione reductase, on the other hand, showed a tendency to increase during the treatment period, especially in the highest exposure group.

Swollen mitochondria and biochemical changes in the form of altered enzyme activity in the hepatocytes were reported in rats given drinking water containing 20, 40 or 85 mg As/litre as arsenate for up to 6 weeks (Fowler et al., 1977; Schiller et al., 1977; Woods & Fowler, 1977). Inhibition of enzymes responsible for haem biosynthesis was observed. An increased urinary level of uroporphyrin was suggested to be a possible early indication of effects due to arsenic exposure (Woods & Fowler, 1977).

8.3.4 Effects on the cardiovascular system

8.3.4.1 *Man*

Though reversible changes in the electrocardiogram have often been encountered following acute exposure to inorganic arsenic (section 8.1), such effects have rarely been reported after chronic exposure. However, Zettel (1943) described an incident of arsenic intoxication among 170 German soldiers, who had ingested water contaminated with inorganic trivalent arsenic for several months. Unfortunately, the content of arsenic in the water was not reported, but was high enough to produce gastrointestinal symptoms. A broadening of the QRS-complex was observed on the electrocardiograms of 45 out of 80 soldiers examined. Other, less frequent changes included ST-depressions and flattening of the T-wave. In a check-up 3 months after cessation of exposure, electrocardiograms were normal in all but 6 cases. Myocardial damage as determined from electrocardiograms was described by Butzengeiger (1949) in 28.7% of 192 persons exposed to arsenic-containing insecticides before 1942. Marked electrocardiogram changes were observed in 55 patients, 65% of which were ascribed to arsenic. Neither of the 2 investigations related here included control groups, which makes it difficult to assess the significance of the findings. When considering effects on the heart, among vintners, their heavy alcohol consumption must also be kept in mind.

An increased mortality from cardiovascular disease has been observed in 2 epidemiological investigations on smelter workers exposed to high levels of airborne arsenic (Lee & Fraumeni, 1969; Axelson et al., 1978) (section 8.4.1.1). In the study by Axelson et al., a dose-response relationship between arsenic exposure and cardiovascular effects appeared. The excess mortality in both studies was 2-fold or less, and has not been confirmed in other, similar studies on workers occupationally exposed to arsenic.

Peripheral vascular lesions have been reported in some arsenic exposure situations. Such effects were first described by Geyer (1898) in residents of Reichenstein (now Silesia, Poland), who were exposed to arsenic via contaminated drinking water. Butzengeiger (1940) described peripheral vascular lesions in 23% of 180 vintners with chronic arsenic intoxication. In 6 cases, the inadequate peripheral circulation caused gangrene. In a study by Grobe (1976), the author examined 100 vinedressers over 30 years after arsenic exposure had been terminated (mode of selection not determined), the exposure having lasted 20 years on an average. He reported distinct peripheral vascular lesions, including symptoms and signs of endangiitis obliterans and acrodermatitis atrophicans, in between 60% and 95% of those in various age groups from 50 to 80 years of age. These symptoms were found in only 1—2% of a control group

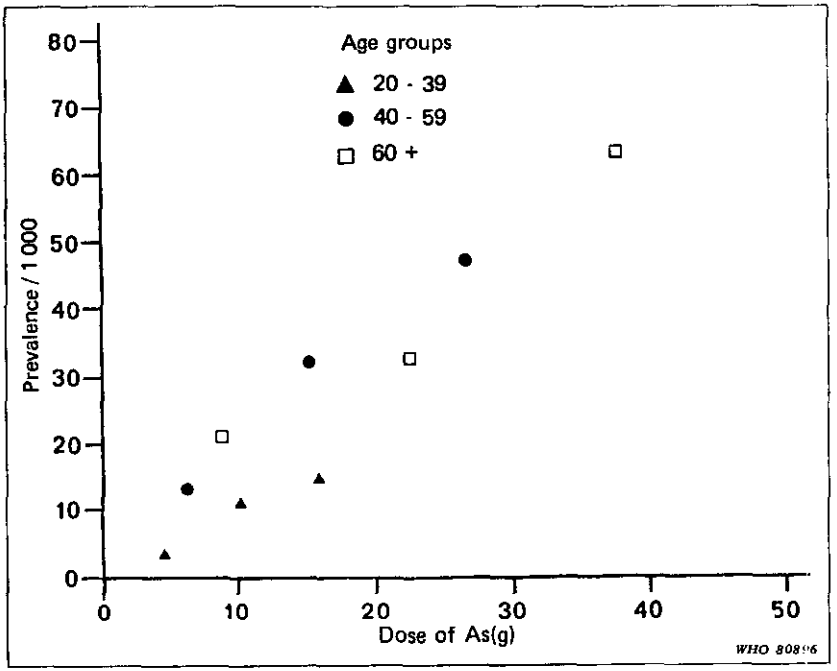

Fig. 7. Prevalence of blackfoot disease in relation to estimated total ingested dose (assuming a daily intake of 2 litres of water) in various age groups in an area of China (Province of Taiwan) with increased levels of arsenic in the drinking water (Modified from: Tseng, 1977).

that had not been exposed to arsenic, but unfortunately was not described further. The authors stated that the most important source of arsenic exposure was contaminated wine.

A high prevalence of a peripheral vascular disease called "blackfoot disease" was found in a population living in China (Province of Taiwan), where the arsenic levels in well water used for drinking purposes ranged from 0.01—1.82 mg/litre but were mainly between 0.4 and 0.6 mg/litre (Tseng et al., 1968; Tseng, 1977). The overall prevalence rate of the disease of 8.9 per 1000 increased with age and with the arsenic content of the water. From Fig. 7, it can be seen that there is a roughly linear increase in the prevalence rate with increasing total ingested dose of arsenic. Exposure for many years resulting in a total ingested dose of about 20 g corresponds to a prevalence rate of 3%. It shoud be noted that a control group was not included in the study and that there would be a rise in prevalence of peripheral gangrene with increasing age. If the most mildly ex-

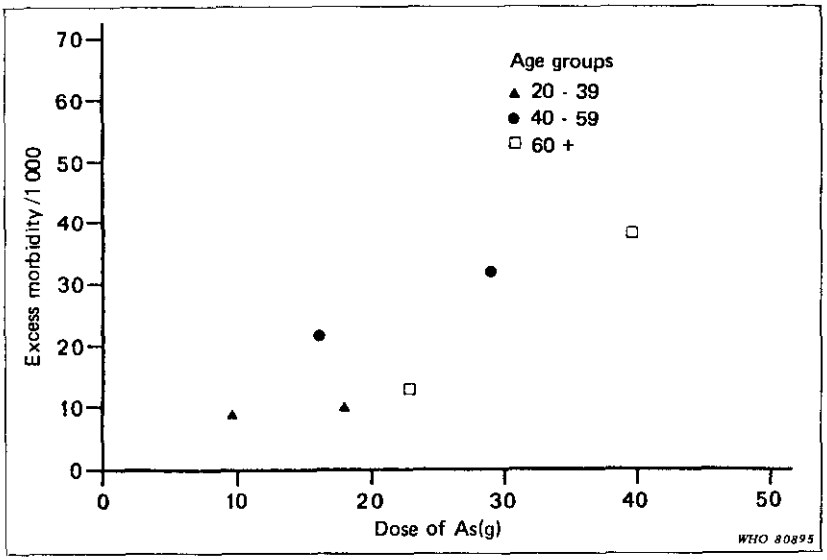

Fig. 8. Excess morbidity from blackfoot disease in various age groups in relation to estimated total ingested dose of arsenic (assuming a daily intake of 2 litres of water) in the endemic area of China (Province of Taiwan) (Modified from: Tseng, 1977).

posed group, i.e., the group that consumed well water with an arsenic content below 0.3 mg/litre, is taken as a control group, a roughly linear increase in excess morbidity expressed as prevalence rate of between 9.6 and 41.1 per 1000 still exists in various age groups (Fig. 8). Obviously this excess cannot be explained by the age factor or other concurrent diseases, and appears to be the result of arsenic exposure.

The severity of the disease was related to duration of water intake. Furthermore, the average age at death was lower in the group of "blackfoot disease" patients exposed to high arsenic levels in the water than in those exposed to lower levels. Carcinomas were the cause of 18.8% of the deaths in patients with "blackfoot disease" compared with 13.1% of deaths in the general population of the endemic area and 7.9% of deaths in the whole population of the Province of Taiwan. Further supporting evidence that arsenic in drinking water was a causative factor in "blackfoot disease" is that no new cases of the disease have appeared in children in the area, since the installation of tap water systems with low levels of arsenic in the water.

The occurrence of various fluorescent compounds in well water samples from the "blackfoot disease" area had been reported (Lu

et al., 1975). The authors suggest that an ergot-like action of the fluorescent substances may have been a cause, or contributing cause, of "blackfoot disease". Collectively, however, the data presented are not adequate to provide firm support for the authors' hypothesis.

Peripheral vascular disease was also reported in inhabitants of the Antofagasta region of northern Chile, who had been exposed to arsenic levels of about 0.6 mg/litre in the drinking water for 15 years. A clinical investigation among 180 inhabitants revealed several effects associated with chronic arsenic exposure, including hyperkeratosis, and a high prevalence of cardiovascular disturbances (Borgoño et al., 1977). Most common were peripheral vascular phenomena, i.e., Raynaud's syndrome and acrocyanosis, which were present, respectively, in 38.8% and 24.3% of the persons with abnormal skin pigmentation attributed to arsenic exposure, compared with 9.3% and 12.5% of persons with normal skin. Infants and children showed more pronounced symptoms than adults. Systemic arterial disease resulting in myocardial infarction was reported in 2 children (Rosenberg, 1974). The small and medium-sized arteries of most organs showed marked thickening of the intima. Similar microscopic findings have been reported in 2 men (32 and 36 years of age) from the same area who had myocardial infarctions but lacked the risk factors usually associated with coronary sclerosis (Moran et al., 1977).

It is noteworthy that effects on the peripheral vascular system have not been reported among patients undergoing medication with inorganic arsenic or among workers exposed to high levels of airborne arsenic. It is not clear, however, whether investigators have looked for such effects in these groups.

8.3.4.2 *Animals*

In order to study the chronic effects of arsenic, Massmann & Opitz (1954) fed 12 cats about 1.5 mg As/kg body weight as sodium arsenite and sodium arsenate mixed with the feed. T-wave abnormalities, mainly flattening, were found in the electrocardiograms of 9 of the animals and the QT-time was prolonged in some animals. No control group was used, which makes it difficult to interpret these findings. The animals were allowed to die spontaneously, at which time histological analysis of the heart was performed. No marked changes were found. No differences in effects were observed between the 2 forms of arsenic used.

Data are lacking with regard to the extent to which experimental animals develop the peripheral vascular lesions observed in human subjects following chronic inorganic arsenic exposure.

8.3.5 Effects on the nervous system

8.3.5.1 *Man*

As noted in section 8.1, reversible peripheral neurological damage has often followed acute and subacute exposure to inorganic arsenic. Recovery is slow and may take several months or even years.

Some studies have shown that long-term exposure to arsenic in the workplace and through drugs has resulted in peripheral neuropathy. Very few studies have dealt with possible neurological effects following occupational exposure to arsenic.

Heyman et al. (1956) reported 41 cases of suspected arsenic-neuropathy in the USA. At least 7 of these cases were caused by occupational exposure to arsenate sprays. Cases of occupational arsenic polyneuropathy have also been reported from Japan (Oida, 1957; Hara et al., 1968). The first report included 4 male workers, 24—54 years of age, employed for 11—32 years in the manufacture of arsenic (form not stated) at a copper refinery. The symptoms and signs included peripheral nervous disturbances and neuritis retrobulbaris as well as chronic rhinitis combined with septum perforation. The other report described 9 persons, aged 20—32 years, employed in the desulfurization of coal gas and exposed to arsenic in both the trivalent and pentavalent inorganic forms, who had developed symptoms and signs of sensimotor polyneuropathy. The symptoms and prognosis of chronic occupational arsenical polyneuropathy in these 2 studies resembled those of the neuropathy following acute exposure; some recovery was seen following cessation of exposure.

Tay & Seah (1975) examined 74 patients who had taken anti-asthmatic herbal preparations containing inorganic arsenic at levels of up to 107 g/kg. The recomended daily dose resulted in an intake of 3.3 mg from a pill, which contained arsenic (III) oxide, and an intake of 10.3 mg from a pill, which contained arsenic sulfide. Arsenic levels in the hair of over 1 mg/kg were found in 45% of the patients. Cutaneous manifestations of arsenic exposure were observed in 92% of patients including 6 cases of skin cancer. Over half of the patients presented neurological complications, the most common being sensimotor polyneuropathy.

Two case reports attribute peripheral neuropathy of the sensimotor type to cutaneous exposure to arsenic. In one case a worker was splashed with arsenic acid in an industrial accident and visual symptoms appeared (Garb & Hine, 1977). The source of the arsenic in the other case was the topical application of a caustic paste in which the form of arsenic was not specified (Robinson, 1975).

Severe hearing loss ($>$ 30 dB) was observed in 18% of 415 children examined in a follow-up study of the poisoning episode in

Japan in 1955, where infants were given powdered milk containing inorganic pentavalent arsenic (Yamashita et al., 1972). According to the local health statistics, the portion of the population in the same age groups with corresponding hearing losses was less than 1%. Moreover, the percentage of brain wave abnormalities observed in the arsenic-exposed children (14%) was twice as high as would be expected. Children exposed during the first 6 months of their life showed a higher rate of abnormalities (17%) than those exposed later (11%). Another follow-up investigation of the same incident of arsenic poisoning, made on a different part of the population and independently of the first study, showed a statistically significant increase in electroencephalographic abnormalities in children fed arsenic-contaminated powdered milk compared with breastfed infants (Ohira & Aoyama, 1972). This study also revealed a number of pathological eye changes in the powdered milk group, including a case of bilateral optic atrophy.

Hearing losses associated with exposure to arsenic have also been reported from Czechoslovakia. Bencko et al. (1977) examined a group of 56 10-year old children living near a power plant burning local coal that had a high arsenic content. When compared to a control group of 51 children in the same age group living outside the polluted area, the exposed children showed significant hearing losses in both air and bone conduction at a high frequency range, indicating inner ear damage. A higher proportion of children who had suffered middle ear inflammation was found in the control group, while the 2 groups did not show any major differences as far as most other medical conditions affecting hearing were concerned. A study carried out near a copper smelter in the USA, which emitted considerable amounts of arsenic, failed to show any impairment of hearing in children living in the area (Milham, 1977).

Electromyographic examinations were made on 33 people living in an area of Canada with a high content of arsenic in the well water (more than 0.05 mg/litre) and 12 controls from the same community who used water sources with a lower content of arsenic (Hindmarsh et al., 1977). EMGs were abnormal in 33% of the exposed persons, but not in any of the controls. Of persons using well water with an arsenic content exceeding 0.1 mg/litre, 50% exhibited abnormal EMGs. A similar relationship was found when hair concentrations of arsenic were correlated with abnormal EMGs. Of persons with hair levels exceeding 1 mg/kg, 52.6% had abnormal EMG findings. The way the results in this study are presented makes their interpretation somewhat difficult. It is not clear how well the controls matched the exposed persons in the various exposure groups with regard to such factors as age, alcohol consumption, and diseases that would predispose them to have EMG abnormalities.

Effects on the nervous system have not been reported in the investigations from Argentina, Chile, or China (Province of Taiwan),

where the subjects studied used drinking-water containing appreciable amounts of arsenic. Clinical and subclinical neurological effects do not seem to have been looked for. It would be of great value to conduct adequate neurological studies in these areas as well as in occupational exposure situations.

8.3.5.2 *Animals*

A one-year toxicity study was performed in which rhesus monkeys were given arsenic in the form of a complex arsenate salt ($2Na_3(PO_4AsO_4VO_4)NaF \cdot 18H_2O$) as a suspension in milk (Heywood & Sortwell, 1979). This is the same arsenic compound that was reported to be present in the dried milk resulting in massive infant poisoning in Japan (Tsuchiya, 1977). Five out of 7 infant monkeys survived daily oral doses of 2.8 mg of arsenic per kg body weight for one year and did not show any neurological abnormalities or other signs of toxic effects. It is, however, difficult to estimate the amount of arsenic absorbed as the substance was given as a suspension, indicating that it had a low solubility.

Dysfunction of the blood-brain barrier was indicated in rats fed arsenite at a concentration of 500 mg/kg diet in a cereal diet for 35 days (Tamura & Nozaki, 1972).

Effects on the ear have been reported in experimental animals treated with inorganic arsenic. Destruction of the Corti organ and loss of Reissemer's membrane, causing deafness, were observed in guineapigs given sodium arsenate intraperitoneally for 2 months (Aly et al., 1975). The dose was reported as 0.2 mg sodium arsenate per kg body weight. Further investigations by Aly et al. (1975) revealed diminished acetyl cholinesterase [EG 3.1.1.7] activity in the temporal lobe and decreased blood cholinesterase levels in exposed animals.

Inhibition of cholinesterase activity was also observed in rats exposed for 3 months to arsenic(III) oxide in the form of condensation aerosols containing 46 μg As/m^3 (Rozenshtein, 1970). Disturbances in the functional state of the CNS were reflected as changes in conditioned reflexes and in chronaximetry. Histopathological changes in the brain included pericellular oedema, plasmatic impregnation of the vascular walls, plasmolysis, and karyolysis of the neurons. Several of the effects mentioned, although less marked, were also observed in a group of rats exposed to an aerosol containing 3.7 μg As/m^3. Osato (1977) gave suckling rats 2 and 10 mg of arsenic(III) oxide through a stomach tube for 40 days. That the central nervous system had been affected was indicated by a significantly poorer performance in the avoidance conditioning test in both groups of exposed animals. No histopathological changes of note were found in the brains of these animals.

8.3.6 Effects on other organs

8.3.6.1 *Man*

Long-term exposure to inorganic arsenic, through drinking-water, medication, or in occupational situations, has resulted in disturbances of the haematopoietic system (Terada et al., 1960; Kyle & Pease, 1965; Westhoff et al., 1975; Feussner et al., 1979). The blood picture in these situations often resembles that in acute intoxication. Bone marrow examination shows disturbed erythropoiesis, and occasionally megaloblastic changes. Severe granulocytopenia may also be present, with possible effects on resistance to bacterial infections. As in acute intoxication, the blood picture has been reported to return to normal, 2—3 weeks following cessation of exposure.

8.3.6.2 *Animals*

Results of animal experiments show effects on the haematopoietic system similar to those observed in man. A decrease in haematocrit and in haemoglobin has been observed in female rats exposed to arsenite in the feed (250 mg As/kg diet) for 2 years (Byron et al., 1967) and in rats given sodium arsenate in the feed (50 mg As/kg diet) for 10 weeks (Mahaffey & Fowler, 1977). The same effects were observed in cats given arsenite or arsenate in the diet in doses of 1.5 mg As/kg body weight (Massmann & Opitz, 1954).

Studies on laboratory animals indicate that arsenic can impair resistance to viral infections. Increased mortality from viral infections among mice exposed to arsenic was reported by Gainer & Pry (1972). The mice were given arsenic subcutaneously at the time of inoculation or in drinking water for 2 weeks before inoculation. The subcutaneous doses were 2—4 mg As/kg body weight as sodium arsenite or arsenic(III) oxide and the drinking water doses 75—150 mg As/litre as sodium arsenite or sodium arsenate. The viruses used were pseudorabies, encephalomyocarditis, and St. Louis encephalitis viruses. Mice given intraperitoneal injections of sodium arsenite (1.8 mg As/kg body weight) were less protected by poly I/poly C (a synthetic homopolynucleotide complex) against encephalomyocarditis virus than the controls (Gainer, 1972). The protective action of poly I/poly C against viruses was reported to be associated with interferon formation.

Minor changes in kidney function and histology have been reported in laboratory animals. Rats exposed to calcium and lead arsenate in daily doses of 2 mg/animal in the food for 2 years showed casts in the straight collecting tubules and swollen cells with large vesicular nuclei in groups of convoluted tubules (Fairhall & Miller, 1941). Rats given arsenic in the drinking water (deionized

water; 40, 85, or 125 mg As/litre as sodium arsenate), for 6 weeks, showed increased kidney weights in relation to body weights (Brown et al., 1976). The proximal tubular cells contained electron dense lysosome-like bodies and swollen mitochondria. Indications of impaired kidney function, including decreased urea clearance and increased serum creatinine have been reported in rabbits given intravenous injections of arsenious acid. The doses (0.6 mg As/kg body weight) were administered 3 times a week for 2—12 weeks (Shibuya, 1971).

8.4 Carcinogenicity

Exposure to arsenic has been associated with the induction of cancer for nearly a century. In 1888, Hutchinson discussed the possibility that medication with inorganic arsenic was an aetiological factor for skin cancer. Ever since, arsenic has been implicated as a causative agent for cancer in other organs also. In 1979, an IARC working group concluded that there was sufficient evidence that inorganic arsenic compounds were skin and lung carcinogens in man, but that the data for other sites were inadequate for evaluation (IARC, 1980).

8.4.1. Man

8.4.1.1 *Cancer of the respiratory system*

Several investigations concerning occupational populations exposed to inorganic arsenic have indicated an association with lung cancer. Many early reports in this field do not lend themselves to evaluation of dose-response relationships and will not be discussed in detail.

An excess of deaths due to respiratory cancer has been observed among workers exposed to inorganic arsenic in the production and use of pesticides, gold mining, and in the smelting of nonferrous metals, especially copper (Hill & Faning, 1948; Osburn, 1957, 1969; Roth, 1958; Lee & Fraumeni, 1969; Ott et al., 1974; Beatjer et al., 1975; Tokudome & Kuratsune, 1976; Pershagen et al., 1977; Pinto et al., 1977; Rencher et al., 1977; Axelson et al., 1978; Mabuchi et al., 1979). The composition of the environment in most occupational situations involving arsenic is very complex, but the extent of exposure to other agents has rarely been reported. In the following discussion, the various exposure situations will be dealt with separately. The effects observed should be considered in the context of the total exposure in these workplaces.

The mortality experience among workers engaged in the production of insecticides containing inorganic arsenic compounds has been the subject of 3 major epidemiological studies. Hill & Faning (1948) found a significant excess proportion of deaths attributable to cancer among workers producing sheep dip powder from sodium arsenite. Atmospheric concentrations of arsenic in this plant in 1946 averaged between 78 and 1034 $\mu g/m^3$ in different workplaces during sampling periods of 10 min or more (Perry et al., 1948). Analysis of 179 cancer deaths showed that 31.8% of the factory workers had died from cancer of the respiratory organs (larynx, lung, mediastinum, and bronchus), compared with 15.9% of the deaths in other occupational groups from the environs of the plant, i.e., agricultural workers, general labourers, artisans, and shopworkers (Hill & Faning, 1948). Smoking habits, which of course may have had a substantial influence on deaths from cancer of the respiratory organs, were not recorded. If considerable differences in smoking habits existed between the factory workers and the other occupational groups, the findings might be invalidated.

Ott et al. (1974) examined the causes of death for the period 1940—72 with reference to proportionate mortality rates in nearly 2000 workers, who had been engaged in the production of insecticides including lead arsenate, calcium arsenate, copper acetoarsenite, and magnesium arsenite. Various forms of inorganic arsenic, including trivalent compounds were used in the processes. Airborne arsenic levels in 1943 ranged from 0.18 mg/m^3 to 19 mg/m^3 (time interval for measurement not stated) in the packaging department. In 1952, concentrations between 0.26 mg/m^3 and 40.8 mg/m^3 were recorded. On the basis of work histories, 173 of the workers were classified as workers who had been exposed to arsenic, i.e., engaged in formulating and packaging arsenic-containing insecticides for one or more days. "Respiratory malignancies" accounted for 16.2% of the deaths in the exposed group compared with 5.7% in the rest of the workers. It should be noted that 16 of the 28 deaths from "malignant neoplasms of the respiratory system" in the exposed group occurred in individuals with an arsenic exposure of less than 1 year. Only men who died during employment or following retirement from the company were included in the survey, and hence both the exposed and unexposed categories could be biased samples of the actual population of employees. A positive dose-response relationship between the degree of arsenic exposure and lung cancer mortality was indicated (Fig. 9). The ratio of observed to expected respiratory cancer deaths ranged from 0.6 in the lowest exposure category to 7.0 in the highest. The degree of exposure was based on available industrial hygiene data, annual personnel lists and assessment by 2 experienced industrial hygienists.

Blejer & Wagner (1976) calculated the daily 8-h time-weighted average (TWA) airborne arsenic concentrations over a 40-year work-

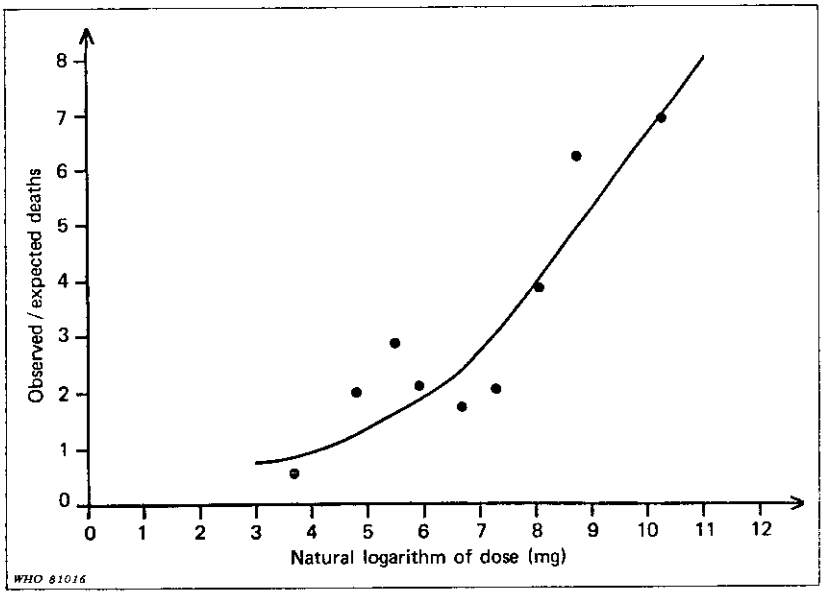

Fig. 9. Ratio of observed to expected respiratory deaths by dose among workers exposed to arsenic in the manufacture of pesticides (From: Ott et al., 1974).

ing life that would correspond to the various exposure categories used by Ott et al. (1974). The results are shown in Table 9. It was suggested that a "no-effect level vis-à-vis an increased respiratory cancer mortality risk might lie in the very low microgram range of arsenic per m^3." If, however, workers exposed to arsenic for less than one year are excluded, no deaths due to "respiratory cancer" occurred in the categories with daily TWA concentrations of up to 90 $\mu g/m^3$ over 40 years. It should also be noted that a consistent dose-response relationship was not observed below this level. Great

Table 9. Observed and expected deaths due to "respiratory cancer" by exposure category [a]

Daily TWA dose ($\mu g/m^3$)	Respiratory cancer deaths		
	Observed	Expected	Observed/ Expected
1	1	1.77	0.6
3	2	1.01	2.0
6	4	1.38	2.9
10	3	1.36	2.2
20	3	1.70	1.8
40	2	0.97	2.1
90	3	0.77	3.9
160	5	0.79	6.3
740	5	0.72	7.0

[a] Modified from: Ott et al. (1974) and Blejer & Wagner (1976).

care should be taken not to draw too firm conclusions from these data in view of the substantial unreliability involved in the computations of expected "respiratory cancer deaths", which were based on proportionate mortality rates. Furthermore, smoking histories could not be obtained for the workers included in the study.

Mortality rates were studied, according to cause, in 1393 workers employed from 1946–74 in a factory where pesticides were manufactured (Mabuchi et al., 1979). The workers were exposed to many arsenic compounds including arsenic(III) oxide, lead arsenate, calcium arsenate, and various arsenites as well as to copper sulfate, chlorinated hydrocarbons, organic phosphates, and carbamates, and other organic herbicides. In 1972, an atmospheric concentration of 0.5 mg As/m^3 was reported; however, the concentrations at the pertinent time of exposure were not known. By August 1977, 197 males and 43 females had died (the vital status of 18% of the total cohort was not available). The observed number of deaths from all or selected causes were compared with the numbers expected from the death rates for the general population in the city where the plant was located. The overall standardized mortality ratios[a] (SMR) were close to 100, and the only statistically significant excesses of deaths were seen for cancer of the trachea, bronchus, and lung in males (23 observed, 13.7 expected; SMR = 168) and anaemias in males (2 observed, 0.2 expected; SMR = 1000). Furthermore, though based on small numbers of deaths, there was also an increase in the SMR for lung cancer with increasing duration of exposure to arsenic compounds, but not with nonarsenic products. No data were given on smoking habits.

Cases of lung cancer have also been reported among workers engaged in the spraying of insecticides containing inorganic arsenic, in the Federal Republic of Germany and France (Roth, 1958: Galy et al., 1963). Among 47 vintners with signs of chronic arsenic intoxication, Roth found bronchial cancer in 19 at autopsy. Nine of these also had primary tumours of other organs, most notably the skin. A selection bias cannot be excluded; however, the frequently observed simultaneous development of primary tumours in the bronchus and skin should represent an excess morbidity. When looking at the mortality statistics of the region between 1950 and 1956, the same author noted that the death rates of bronchial carcinomas was a markedly higher in the wine producing districts than in other areas i.e., 5.1% and below 1%, respectively. Besides exposure through inhalation, the consumption of arsenic-contaminated wine must be considered. In 1938, 43% of 336 samples of wine from the area studied by Roth contained more than 5 mg As/litre (Koelsch, 1958).

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[a] The standardized mortality ratio is the ratio of observed to expected deaths multiplied by 100.

In a follow-up of more than 1200 orchard workers, who were registered in a medical survey in the USA in 1938–39, no excess was detected either for total deaths or for deaths from cancer (Nelson et al., 1973). The male workers had been exposed to lead arsenate resulting in an average urinary arsenic concentration of 0.14 mg/litre in 1938. No data on exposure other than the duration of employment of each individual as an orchardist could be obtained, when the follow-up was made. The mortality data were analysed for the counties in which the orchardists surveyed by Nelson et al. had lived, and a respiratory cancer mortality 7% higher than that in the state as a whole was found (NIOSH, 1975). When looking at death records of the whole state from 1961–71, a significant increase in respiratory cancer mortality was observed among decedents classified as orchardists. The data in the NIOSH document cannot be evaluated in detail because of lack of information concerning such factors as the methods and numbers of people.

An increased respiratory cancer mortality has been observed in many studies on smelter workers exposed to high levels of inorganic arsenic, mainly in the form of arsenic(III) oxide. Lee & Fraumeni (1969) compared the mortality rate among more than 8000 smelter workers in the USA with that of the white male population of the states in question. The mortality was followed from 1938–63 and a total of 1877 deaths were recorded. About 10% of the original cohort was lost in the follow-up. An excess mortality was found for cancer of the respiratory system (lung and bronchus, larynx, and mediastinum) with an overall standardized mortality ratio, SMR, equal to 329. A positive relationship between SMR and estimated degree of exposure was indicated, with an SMR of 800 in the highest arsenic exposure group. A positive relationship was also found between exposure to sulfur dioxide and respiratory cancer mortality with a SMR of over 700 in the highest exposure groups. Unfortunately, data were not available concerning the actual exposure levels and it was difficult to separate the effects associated with arsenic from those associated with sulfur dioxide, since both types of exposure occurred in most work areas. Smoking histories were not obtained, and if large age distribution differences were at hand between the different exposure groups the comparison of SMRs would be unreliable.

The mortality among 2675 Japanese metal workers from 1949–1971 was examined by Tokudome & Kuratsune (1976), using the cohort technique. Workers were divided into 5 cohorts depending on their work histories, i.e., copper smelting, ferronickel smelting, maintenance or transport, copper or lead electrolysis or production of sulfuric acid, and clerical work. Among the 839 copper smelters, an almost 12-fold increase in the number of deaths was observed for cancer of the trachea, bronchus, and lung in comparison with the expected number, which was derived from the national rates for

Japanese males during the period at issue. A positive correlation was observed between length of employment and excess of deaths from cancer of the trachea, bronchi, and lung as well as between estimated levels of arsenic exposure and excess mortality. The exposure was not described in detail and smoking habits and age distributions in the various exposure groups were not reported.

Pinto et al. (1977), in a follow-up of an earlier study in 1963, analysed the cause-specific mortality experience above 65 years of age among 527 retired workers at a large copper smelter in Washington, USA. Expected deaths were computed from the mortality rates of the male population in the state of Washington during the time period at issue, i.e., 1949—73. Exposure occurred, mainly to arsenic(III) oxide, and was assessed on the basis of the determination of arsenic concentrations in the urine of workers in each department of the factory in 1973. It was emphasized that the relevant exposure levels, i.e., those during the active working life of the decedents, were higher. Each worker was assigned an exposure index that was calculated by multiplying the period of time spent in the various departments by the 1973 urinary arsenic levels of workers in these departments.

A highly significant increase in mortality from cancer of the respiratory system (ICD 160—164)[a] was found for the whole group of former smelter workers under study (SMR = 304.8), which had a roughly linear relationship with the estimated time-weighted average total life-time exposure (Fig. 10). The comparison between the different SMRs should be made with caution, as their magnitudes depend partly on the age distribution of the index population for each SMR.

A group of workers with more than 25 years of exposure to airborne arsenic at concentrations associated with urinary arsenic levels of 50—200 μg/litre, i.e., (according to Fig. 4) up to approximately 40 $\mu g/m^3$ or a rough average of about 25 $\mu g/m^3$, showed an SMR of 277.8. As previously stated, the exposure was probably underestimated because of higher levels of airborne arsenic in earlier years. Urinary arsenic data from Pinto et al. (1978) indicate that the exposures were higher by perhaps a factor of 2 than those given in the previous paragraph. This would mean that exposure to airborne arsenic at levels of around 25 $\mu g/m^3$, according to the original estimates, or perhaps more appropriately 50 $\mu g/m^3$ according to the revised value, would lead to a nearly 3-fold (increase in) mortality from lung cancer. It should be emphasized that the uncertainty in the estimated exposure could well amount to a factor of 2.

Smoking habits were recorded on a sample of the cohort (Pinto et al., 1978), i.e., directly from all men still living and from the friends and relatives of men who died after 1961, a total of 377 sub-

[a] WHO (1965) International Classification of Diseases (8th revision).

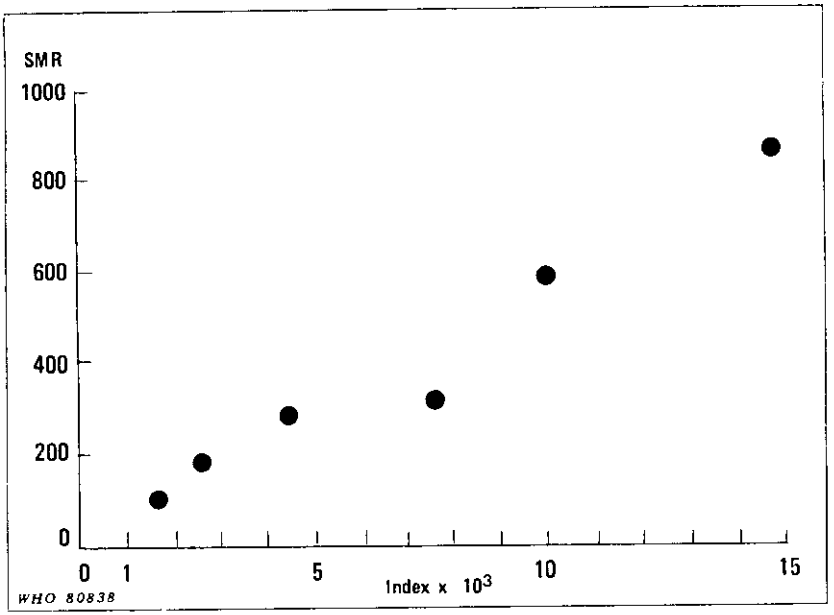


Fig. 10. Standardized mortality ratio (SMR) for respiratory cancer deaths in relation to arsenic exposure index among 527 males retired from a US copper smelter. It should be noted that normal SMR is 100 and that the arsenic exposure index for normal arsenic concentration in urine (50 µg/litre; Pinto et al., 1976) and a working period of 25 years is 1250 (Modified from: Pinto et al., 1977).

jects. Observed respiratory cancer deaths among smokers, ex-smokers, and nonsmokers were compared with data on expected deaths in these smoking categories. The SMR in the study population was elevated in both the smokers and ex-smokers (245.1—506.5) indicating that smoking habits in the study population as a whole were not responsible for the increased mortality rate from cancer of the respiratory system. In fact, the highest SMR was noted among the nonsmokers, although it must be stressed that its magnitude is unstable due to the fact that the number of observed respiratory cancer deaths was small.

Rencher et al. (1977) examined the lung cancer mortality at a smelter with high levels of airborne arsenic in the USA. A higher proportional mortality was obtained for smelter workers than for mine workers or for males in the state as a whole (7.0, 2.2 and 2.7%, respectively). Estimated cumulative exposure indices for sulfur dioxide, arsenic, and lead were higher among those dying from lung cancer than among those dying of nonrespiratory causes. No indication of a smoking synergism could be found.

An increased mortality from lung cancer has also been reported at a Swedish copper smelter (Holmqvist, 1964; Pershagen et al., 1977; Axelson et al., 1978). Employing the case control technique, Axelson et al. examined the death records of 369 men aged 30—74, who had died in the years 1960—1970 and who had been residing in the parish surrounding the smelter at the time of death. A total of 44 subjects were omitted because of vague diagnoses and diseases that might have excluded them from employment at the smelter, e.g., mental deficiency and diabetes mellitus.

"Cases" included men who had died from malignant tumours of the lung, other malignancies, cardiovascular disease, cerebrovascular disease, or cirrhosis of the liver. The "controls" were men who had died from all remaining causes.

Assessment of exposure at the smelter was based on employment registers that had been kept since the start of operations at the smelter in 1928. These records included detailed information regarding the time spent at various workplaces by all workers. The exposure levels at these workplaces, from 1928 onwards, was estimated by an experienced safety engineer. Using this information and a calculated half median latency period for lung cancer of 17 years, the men were divided into 4 different exposure categories. The 2 highest exposure categories were chosen to include subjects exposed, before death, for more than half of the latency period, to levels of airborne arsenic exceeding 0.5 mg/m^3. A rate ratio of about 5 for death due to lung cancer was observed for workers exposed to arsenic compared with unexposed workers and subjects never employed at the smelter. A positive dose-response relationship was also indicated. Pershagen (1978) showed that the excess mortality could not be explained by smoking habits. It was not possible to establish detailed dose-response relationships because of the rough measurements of exposure and the small number of subjects in these studies.

In recent years, a number of reports have associated exposure to arsenic in the ambient air near point emissions with an increased risk of lung cancer. Blot & Fraumeni (1975) found an increased mortality rate from lung cancer in the period 1950—69 for white males and females (averaging 17% and 15%, respectively) in counties in the USA with copper, lead, or zinc smelting and refining industries compared with the rest of the country. The increase could not be explained by differences in population density, urbanization, or socioeconomic status. No data on the actual exposure levels of arsenic in ambient air were given. Caution must be applied when associating arsenic exposure with the excess of deaths, because of considerable variations in emissions among the smelting and refining operations in the various counties in question.

The vital statistics of 2 copper mining and smelting counties in Montana, USA, were reviewed for the years 1969—71 by Newman

et al. (1976). Respiratory cancer death rates were significantly elevated in both men and women in the mining as well as in the smelter town but not in the counties as a whole, when compared with national rates during the same period. Annual mortality rates for cancer of the bronchus and lung among persons from the age of 21 years upwards were 20.4 and 3.2 per 10 000 among men and women, respectively, in the smelting town and 13.8 and 6.0 per 10 000 in the mining town. Unfortunately, the data obtained on smoking habits were not compared with data on smoking habits for the nation as a whole. Furthermore, the authors did not report which fraction of the population under study was also employed at the mines or smelters. Atmospheric concentrations of arsenic were reported to be markedly higher in the smelter town, and a figure of 0.45 μg As/m^3 was given (measurement period not stated).

Matanoski et al. (1976), in analysing the mortality data from 1970—72 in white men who had lived in a heavily industrialized area surrounding a plant producing pesticides containing arsenic, found an excess of deaths from lung cancer which was between 3 and 4 times that in men in adjacent areas. The populations in the areas were matched for age, race, and sex. The observed excess in the number of deaths remained statistically significant, when the pesticide plant workers were excluded from the population. There were indications of a decrease in lung cancer deaths with increasing distance from the plant. No significant excess in lung cancer deaths was observed among women in the area. No data were given on the levels of arsenic or other contaminants in the ambient air and further information on occupation and personal characteristics such as smoking habits is needed to validate the findings.

A study has been reported by Pershagen et al. (1977) on the lung cancer mortality between 1961 and 1975 in an area around a large smelter in northern Sweden. During the period 1930—60, arsenic was emitted into the air in amounts of 1—3 tonnes by day. Other pollutants of interest were sulfur dioxide and, in lower amounts, lead, cadmium, mercury, and nickel. No emmission data were obtained. A total of 28 male cases of death from lung cancer were found, which constituted a 2 to 3-fold increase in the number of deaths (SMR = 250) compared with control population with a similar degree of urbanization and a similar occupational profile. The increase in the number of deaths was no longer significant, when the occupational population exposed at the smelter was excluded, though the tendency remained (SMR = 173). No corresponding increases in death from lung cancer could be detected among women.

Some reports have claimed an association between exposure to inorganic arsenic as medication and lung cancer (Sommers & McManus, 1953; Robson & Jelliffe, 1963; Goldman, 1973). This association was based on the occurrence of lung cancer in patients receiving trivalent inorganic arsenic in daily doses of several milli-

grams, for decades. Unfortunately, these are only case histories, and epidemiological studies in this field are greatly needed.

The respiratory tract tumours associated with arsenic exposure have been classified according to histological type in some studies (Robson & Jelliffe, 1963; Newman et al., 1976; Axelson et al., 1978). A clustering of poorly differentiated types is evident in all these reports. Poorly differentiated or undifferentiated types were noted in 5 out of 6 patients with lung cancer, who had received medication with inorganic arsenic (Robson & Jelliffe, 1963). Half of the patients were nonsmokers. In the previously described report on lung cancer mortality from 1954–72 in 2 mining and smelting counties in Montana, USA (Newman et al., 1976), the histological types of 143 respiratory tumours in men and women were presented. Microscopic slides were examined independently by a panel of 4 experienced pathologists on a "blind" basis, i.e., they did not know the residence or occupation of the individual from whom the specimens were obtained. Information on smoking habits, place of residence, and occupation was obtained from a tumour registry, hospital records, or relatives. Smelter workers showed a high number of poorly differentiated epidermoid carcinomas (40.0%) that did not appear in mine workers or other men in the area. The difference could not be explained by smoking habits, which were very similar in all 3 groups, a high percentage (36.0%) of poorly differentiated carcinomas also occurred among women from the mining town in association with elevated lung cancer rates.

Out of the 24 persons with lung cancer at the Swedish copper smelter investigated by Axelson et al. (1978) (reported earlier in this section), 18 were classified as having been exposed to arsenic. In this group, 22.2% of the tumours were classified as poorly differentiated epidermoid carcinomas, whereas this type of tumour was not found among lung cancer-stricken employees not exposed to arsenic. There also appeared to be an increase in other types of epidermoid carcinoma as well as of the small cell undifferentiated type; however, the numbers in all groups were too small to draw any definite conclusions.

8.4.1.2 *Cancer of the skin*

Several types of neoplastic changes of the skin, including Bowen's disease and basal and squamous cell carcinomas, have been associated with arsenic exposure. Neither of these lesions, when attributable to arsenic, possesses any unique histological features (Hundeiker & Petres, 1968; Sanderson, 1976; Deng & How, 1977). While the effects of other skin carcinogens such as UV-radiation and polyaromatic hydrocarbons are limited to areas of exposure, arsenic lesions, can occur on every part of the body. Bowen's disease and

basal cell carcinomas of arsenical origin are usually multiple and located on the the trunk (Fierz, 1965; Yeh et al., 1968). Squamous cell carcinomas develop primarily from the keratoses on the extremities.

Skin cancer has been associated with inorganic arsenic exposure in reports from many parts of the world, i.e., Argentina, Canada, China (Province of Taiwan), Czechoslovakia, France, Federal Republic of Germany, Israel, Japan, South Africa, Switzerland, the United Kingdom, and the USA (Hutchinson, 1888; Arguello et al., 1938; Neubauer, 1947; Hill & Faning, 1948; Sommers & McManus, 1953; Berlin & Tager, 1962; Fierz, 1965; Schulz, 1967; Thiers et al., 1967; Tseng et al., 1968; Bartak & Kejda, 1972; Wolf, 1974; Jackson & Grainge, 1975; Hamada & Horiguchi, 1976). The total number of cases reported is well over 1000 with exposure occurring most frequently via the oral route, either through contaminated drinking-water or medication. Ingestion has usually taken place over several decades, with daily doses of several mg of arsenic. As a rule, the skin tumours appear earlier in life than is ordinarily encountered. In the medication, the arsenic was mainly in the form of arsenite, while the oxidation state in arsenic-contaminated water is unknown.

In the following discussion, it is assumed that the response is related to the total ingested dose of arsenic. In the study by Fierz (1965), mentioned in section 8.3.2, 8% of 262 patients treated with arsenic compounds mainly in the form of arsenite, for up to 26 years, showed various types of skin cancer, the most common being multiple basal cell carcinoma. The prevalence of skin cancer increased as the total ingested dose of Fowler's solution increased. In patients who had ingested between 200 and 800 ml of Fowler's solution (= 1.5 and 6.0 g of arsenic), the prevalence rate ranged from 5% to 10%. No firm conclusions can be drawn regarding dose-response relationships in view of the possible selection bias in this study. A control group, which would have enabled an estimation of the "background" morbidity in skin cancer to be made, was also lacking. Obviously, however, an increased morbidity did occur among patients who received a total of more than 1000 ml of Fowler's solution (= 7.6 g of arsenic). The prevalence rate in this group was over 20%.

In the survey on more than 40 000 inhabitants in China, Province of Taiwan, reported in section 8.3.4, Tseng (1977) established a positive dose-response relationship between the contents of arsenic in well water and the prevalence rate for skin cancer. The overall prevalence was 10.6 per 1000, and the male to female ratio, 2.9. The prevalence of skin cancer in relation to increasing doses of arsenic is depicted in Fig. 11. Assuming a daily intake of 2 litres of water a total ingested dose of about 20g of arsenic over a life-time corresponds to a prevalence of roughly 6%. This is an average between the 2 lowest exposure groups for age 60 and over. The oldest age

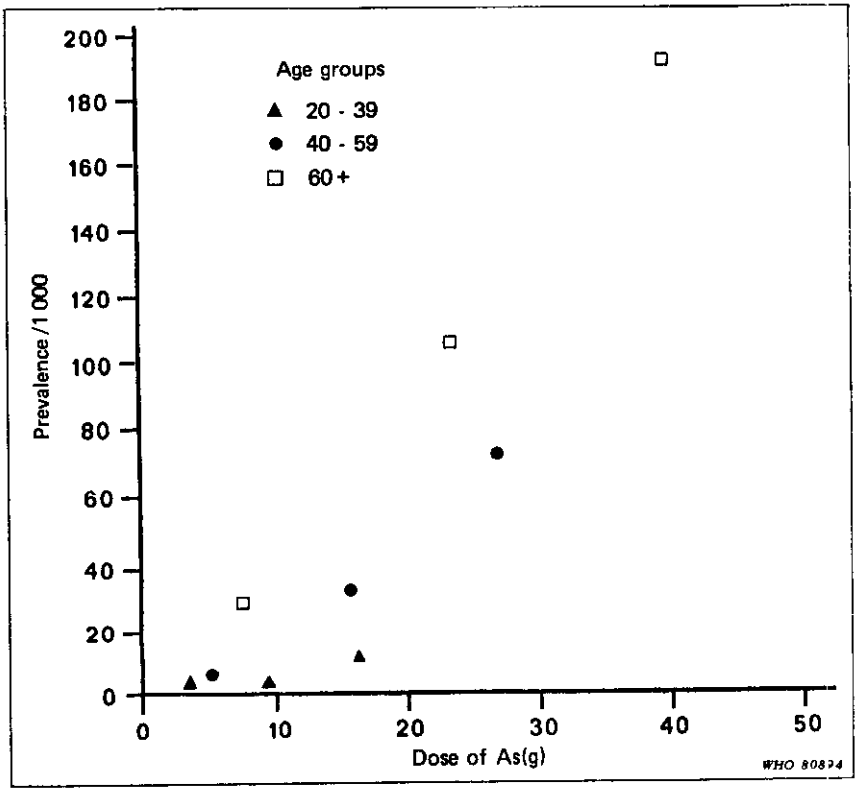


Fig. 11. Prevalence of skin cancer in relation to estimated total ingested dose of arsenic (assuming a daily intake of 2 litres of water) in various age groups in an area of Taiwan with increased levels of arsenic in the drinking water (Modified from: Tseng, 1977).

was selected in order to ensure that the maximum tumour response was achieved for a given dose. Because the tumours were of low malignancy, they would be expected to persist for a long period and hence prevalence would be a reasonable approximation of life-time cumulative incidence. The increase in prevalence with increasing arsenic dose is partly due to a higher background prevalence of skin cancer in older age groups. Unfortunately, no control group was included, but if the lowest exposure group using well water with an arsenic content below 0.3 mg/litre, is taken as a control group, a roughly linear increase in excess morbidity expressed as prevalence rate of between 0.9 and 164.9 per 1000 is still seen in various age groups (Fig. 12). As was concluded in section 8.3.4.1 with regard to "blackfoot disease", the increase in age could not explain the observed increase in skin cancer with estimated dose of arsenic.

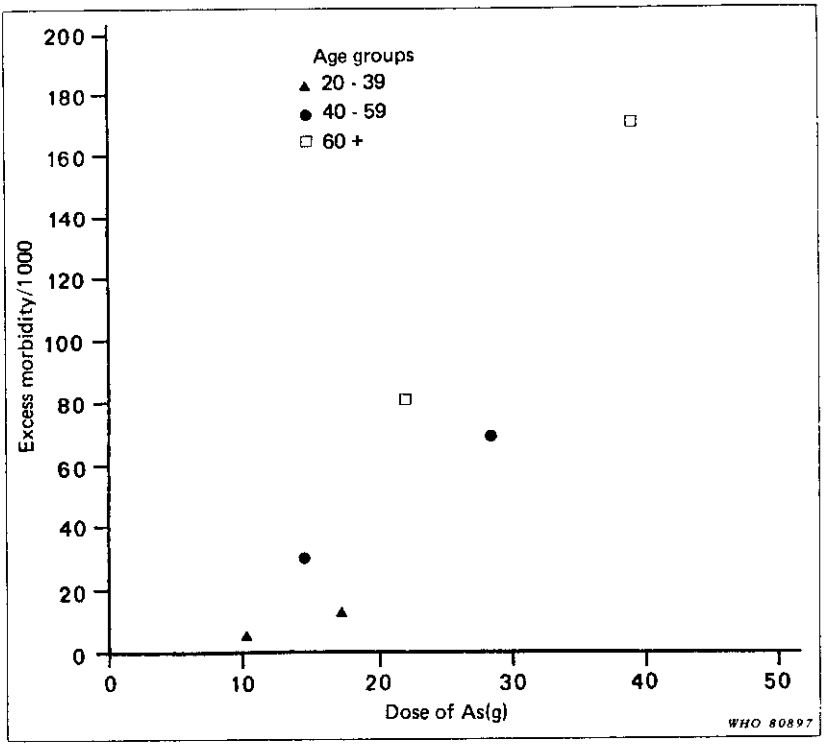


Fig. 12. Excess morbidity in skin cancer in various age groups in relation to estimated total ingested dose of arsenic (assuming a daily intake of 2 litres of water) in the endemic area of China (Province of Taiwan) (Modified from: Tseng, 1977).

The extrapolation to low doses is very uncertain, as indicated by the discrepancies between prevalence rates in the reports of Fierz (1965) and Tseng (1977). While the patients who had been on the arsenic-containing medication showed a prevalence of 20% (after an estimated total intake of arsenic of 7.6 g), the corresponding prevalence among the Chinese in Taiwan was less than 3%. None of the reports, however, included a control group, and at least the first one could have had a substantial selection bias. The medicated patients probably had a higher dose rate than the Taiwanese.

Morton et al. (1976) examined the incidence of skin cancer in Lane County, Oregon, where high levels of arsenic had been found in water supplies. No relationship was detected between arsenic levels in water and the appearance of squamous or basal cell carcinomas. However, these data do not necessarily contradict previous

findings as drinking water sources with high arsenic concentrations were fewer than expected. The mean levels in the different regions of the community ranged between 0.004 and 0.033 mg As/litre.

8.4.1.3 *Cancer of the liver*

Haemangioendothelioma of the liver has been associated with exposure to inorganic arsenic in a number of cases. The exposure has come from contaminated wine, drinking-water, or Fowler's solution. Roth (1957) reported 5 cases of haemangioendothelioma of the liver among former vintners, who died between 47 and 58 years of age. The workers had been handling arsenic-containing insecticides (type not specified) for a number of years and had typical cutaneous manifestations of arsenic intoxication, i.e., palmo-plantar hyperkeratosis and melanosis. All cases also suffered from liver cirrhosis, which the author ascribed to arsenic ingestion (section 8.3.3). The latent period, from the beginning of arsenic exposure ranged from 20 to 28 years. No data were given on the actual doses, but it can be estimated that the total ingested dose of arsenic was 10–20 grams (Grobe, 1976).

Rennke et al. (1971) described a case of malignant haemangioendothelioma in a 22-year old male from the Chilean province of Antofagasta. Cutaneous signs of arsenic exposure were also present. The decedent had been exposed to arsenic in drinking water for 12 years at an average level of 0.8 mg/litre, i.e., a total of 5.46 grams. An arsenic level of 20 mg/kg was found in the hair.

Some cases of haemangioendothelioma have also been reported following prolonged ingestion of Fowler's solution. Liver haemangioendothelioma was found in a patient who had been taking Fowler's solution over 20 years for psoriasis (Rosset, 1958). Regelson et al. (1968) described a psoriatic patient who had taken Fowler's solution for 17 years, so that the total ingested dose amounted to approximately 10 grams of inorganic trivalent arsenic. This patient also displayed palmo-plantar hyperkeratosis. The tumour was diagnosed 24 years after initiation of treatment with the drug. A 43-year-old psoriatic patient, who developed haemangioendothelioma 21 years after the initiation of a 15-year-long treatment with Fowler's solution has been reported by Lander et al. (1975). The total ingested dose was estimated by the authors to have been 15g (not stated whether this was calculated as As or As(III) oxide). Popper et al. (1978) compiled 5 cases of haemangioendothelioma in the US each with a history of ingestion of Fowler's solution. The duration of exposure ranged from 10 to 17 years. It is not clear whether the cases reported by Regelson et al. (1968) and Lander et al. (1975) were included in this series.

Although only case reports of this extremely rare tumour exist, it is noteworthy that the reported latency times seem to be similar, i.e., 20—25 years. If trivalent arsenic plays a role in the development of haemangioendothelioma, it can be concluded that large doses, at least several grams, are required and that the effect is rare in view of the large number of people who have been exposed through drinking water or medication.

8.4.1.4 *Leukaemia and tumours of the haematopoietic system*

A carcinogenic effect on the haematopoietic system in situations of occupational exposure to inorganic arsenic compounds cannot be ruled out. In 2 studies on the mortality of workers exposed to high levels of airborne arsenic, an increased mortality due to malignant neoplasms of the lymphatic and haematopoietic tissues was indicated compared with unexposed control groups (Ott et al., 1974; Axelson et al., 1978). It should be pointed out that the numbers of deaths due to these causes were small in both studies.

The data need further confirmation, especially in view of the lack of supporting evidence from other instances of exposure to inorganic arsenic, i.e., through drinking water and medication.

8.4.1.5 *Cancer of other organs*

Exposure to inorganic arsenic through medication, mostly as Fowler's solution, has been associated with the development of various malignant neoplasms. Sommers & McManus (1953) compiled a total of 27 cases of multiple primary tumours of the skin and internal organs. In 24 of the cases, there was a history of excessive arsenic exposure and all but one of the patients had palmoplantar hyperkeratosis. Nineteen of the patients had been exposed through ingestion of Fowler's solution, mostly for treatment of psoriasis. Unfortunately, exposure doses were not given. Multiple skin cancers, predominantly basal cell carcinomas, were observed in 17 patients (section 7.3.2). In another 10 cases, skin cancers were combined with primary tumours of other organs, e.g., lung, oesophagus, and bladder. The average latency between commencement of arsenic exposure and diagnosis of a tumour was 24 years. The data presented in this study do not lend themselves to statistical analysis. The 10 cases with simultaneous skin cancer and internal malignancy could have involved a selection artefact.

In a study by Reymann et al. (1978), a total of 389 patients were followed, who had been on arsenic therapy, primarily with Fowler's solution. Fifty-three of the patients had typical arsenical keratosis. A total of 41 cases had developed cancer of internal organs during

the period 1943—74, as traced from the Danish Cancer Registry. It was found that this was not statistically different, in terms of the life table method, from the national average. Neither the estimated total dose of arsenic ingested, nor the nature of the agent was correlated with the incidence of internal cancer. In the group of patients with arsenical keratosis, 9 died from cancer of internal organs (type not specified) during the period under study, as opposed to 5.2 expected (increase not statistically significant).

The data relating to arsenic exposure and malignancies other than lung and skin cancer are inadequate. Further studies are needed before any conclusions can be drawn.

8.4.2 Experimental animal studies

8.4.2.1 *Cancer of the respiratory system*

Only a few studies have been performed on the carcinogenic effects of inorganic arsenic following exposure of the respiratory tract in experimental animals. Ishinishi, et al. (1977) administered copper ore, metal refinery flue dust, or arsenic(III) oxide, alone or together with benzo(*a*)pyrene in a saline suspension, intratracheally to male rats. Another group received benzo(*a*)pyrene alone. The doses of arsenic in the various groups were 1.5, 3.0, and 3.0 mg per animal, divided into 15 weekly instillations. A total of 6 mg of benzo(*a*)pyrene was given. Altogether, 161 animals were treated, including a control group of 23 animals that received saline only. The mortality in the various groups during the exposure period ranged from 30% to 50%, the lower value being recorded in the control group. The results indicated a positive interaction between benzo(*a*)pyrene and arsenic(III) oxide in the induction of lung tumours, but the number of animals in this study was too small to permit any firm conclusions. Ishinishi, et al. (1980a) gave 30 male adult Wistar strain rats intratracheal instillations of arsenic(III) oxide in a suspension once a week for 15 weeks. Sixteen untreated rats acted as controls. Observation of these rats over their life span revealed only one malignant lung tumour (squamous cell carcinoma) in the 19 rats that survived 15 instillations. No lung tumours were found in the control group. This report does not provide definite evidence of arsenic respiratory carcinogenicity in animals.

In a study by Ivankovic et al. (1979), 25 rats were given a single intratracheal instillation of 0.1 ml of a mixture of calcium arsenate, copper sulfate, and calcium oxide. The preparation was similar to that of a pesticide used on vines between the 1920s and 1940s. The dose of calcium arsenate administered was reported to correspond to 0.07 mg of arsenic. During the first week after treat-

ment, 10 of the animals died due to pneumonia or lung necrosis. Of the 15 surviving animals, 9 developed lung tumours (7 bronchogenic adenocarcinomas and 2 bronchiolar-alveolar cell carcinomas). The average induction time was 470 days. No lung tumours were observed in 25 control animals, instilled with 0.1 ml of 0.9% saline, and observed throughout their life span (mean survival time: 670 days). The data in this report indicate that the mixture given was carcinogenic, but no firm conclusion can be reached as to the causative agent, because of the design of the experiment. It seems, however, that arsenic might have played an important role and further studies should clarify whether calcium arsenate alone is sufficient to evoke a carcinogenic response and also the possible modification of effects by the other components in the mixture.

8.4.2.2 *Skin application*

Inorganic arsenic has been tested repeatedly in skin applications and not been found to be carcinogenic. Leitch & Kennaway (1922) produced one metastasizing squamous cell carcinoma of the skin in 100 mice painted 3 times weekly with a solution of sodium arsenite in alcohol. The first skin applications contained 1.8% of arsenic(III) oxide (about 13.7 g As/litre), but the concentration was reduced to 0.12% (about 0.9 g As/litre) because of the high mortality induced by the higher dose. In 3 months, two thirds of the animals had died, and, by that time, a tumour appeared in one of the survivors at the site of application of the arsenic. At autopsy after 5 1/2 months, a lung metastasis was observed. No control group was included in the study.

The cocarcinogenicity of sodium arsenite was tested in a series of experiments by Boutwell (1963). Each of 20 female mice was given a total of 1.24 mg potassium arsenite in 80% ethanol, in 8 skin applications over a 5-day period. From 2 days after completion of the arsenic treatment, the mice were treated twice weekly with croton oil. After 18 weeks, it was observed that previous exposure to sodium arsenite did not make the treated mice more responsive to croton oil than the controls which had been treated with croton oil only. A single skin application of 75 µg dimethylbenzanthracene and subsequent, twice-daily applications potassium arsenite (2.2 mg $KAsO_2$/week) for the duration of the experiment (30 weeks) did not result in tumour formation. Thus neither tumour initiating nor tumour promoting activity could be shown for sodium arsenite.

In 1956, Salaman & Roe painted 14 mice with a total of 30 mg of potassium arsenite (8.7 mg As), dissolved in methanol, once a week for 10 weeks. Croton oil was also applied weekly, starting 25 days later. Three papillomas were observed in mice treated with

potassium arsenite, while 4 papillomas appeared in 19 animals receiving croton oil only.

The skin of 10 rabbits was painted with 10% arsenic(III) oxide in vaseline (about 76 g As/kg). After daily applications for 70 days 1 epithelioma and 4 papillomas had appeared. A control group was not used (Raposa, 1928). Friedewald & Rous (1944) repeated this study and failed to produce any malignant tumours. They did observe verrucous lesions in 3 out of 7 animals surviving a 22-month treatment. During the first 6 months, 12 rabbits were painted with 10% arsenic(III) oxide in vaseline on one ear and vaseline only on the other ear. For the subsequent 13.5 months, the rabbits were painted with a 2% solution of arsenic(III) oxide (15 g As/litre) in water mixed with acetone in the proportion of 1:2. Three out of 6 lesions were excised and proved to be papillomas. One of these appeared on a control ear.

Sodium arsenate at a concentration of 15.8 g/litre (about 3.8 g of As) in a 2.5% solution of Tween 60 in water was applied twice weekly to the skin of 54 male and 14 female mice. A total of 3 skin papillomas appeared in the exposed animals, and 4 in 69 control animals. Sodium arsenate applied to the skin in combination with croton oil treatments twice weekly, failed to show papilloma-initiating action. An absence of tumour promoting activity was noted when exposure to arsenic followed a single skin application of 200 µg dimethylbenzanthracene or a stomach tube dose of 60 mg urethane (Baroni et al., 1963).

8.4.2.3 *Oral administration*

Fairhall & Miller (1941) could not find any evidence of carcinogenicity of lead arsenate or sodium arsenate in 148 rats, fed daily doses of approximately 2 mg of arsenic, over a period of 2 years. Groups of 50 mice or rats were given arsenic(III) oxide dissolved in 12% ethyl alcohol or water at arsenic concentrations of 3.0 mg/litre at the beginning of an experiment by Hueper & Payne (1962). The level was successively raised over a span of 15 months and from then on kept at 25.5 mg As/litre. In the rats, these levels were reported to result in daily intakes of between 0.08 and 0.6 mg per animal. No differences in tumour incidence were found between the arsenic-exposed animals and the controls.

Boutwell (1963) gave each of 20 female mice a total of 2.4 mg potassium arsenite (corresponding to 0.7 mg As) by stomach tube. The dose was administered in 7 portions over a 5 day period. Other groups were given potassium arsenite mixed with the feed combined with tumour-initiation treatments with 5 µg dimethylbenzanthracene and tumour-promotion treatments with croton oil, both applied to the skin. There were no differences in the

production of papillomas and carcinomas between the arsenic-fed animals and controls.

Arsenic (III) oxide was given in the drinking water in a concentration of 76 mg As/litre to 15 female and 62 male mice. No skin tumours were observed in the animals, 21 of which survived for 60 weeks. The tumour incidence in other groups, treated in addition with croton oil, dimethylbenzanthracene, and urethane, respectively, as described in section 8.4.2.2, did not differ from that in control animals given these substances separately (Baroni et al., 1963).

In studies by Byron et al. (1967), groups of 50 rats each were fed for up to 2 years with sodium arsenite at arsenic levels in the diet of 0, 15.6, 31.3, 62.5, 125, and 250 mg/kg and sodium arsenate at arsenic levels of 0, 31.3, 62.5, 125, 250 and 400 mg/kg. The arsenic was mixed in the standard laboratory diet. After the 2 years, both the incidence and type of tumours were similar in exposed animals (4—15 survivors/group) and controls (8—12 survivors/group). In the same studies, groups of 6 dogs (3 male and 3 female) were fed sodium arsenite or sodium arsenate at arsenic levels in the diet of 5, 25, 50, and 125 mg/kg. In the group receiving the highest dose of sodium arsenite, no animal survived 2 years, while only one of the 6 dogs given the highest level of sodium arsenate died during this time. All of the other animals were killed at the end of 2 years. No tumours were observed in any of the animals.

Kanisawa & Schroeder (1969) reported a study in which sodium arsenite was administered in the drinking-water to 103 mice at a concentration of 5 mg As/litre, throughout their lifetime. A total of 170 mice received double-deionized water. In 67 animals surviving 15 weeks in the exposed group, 11.9% subsequently died with tumours compared with 34.5% in the control group. The death rates during this period were similar in both groups.

Mice of 3 different strains were exposed by Milner (1969) to arsenic(III) oxide in the drinking water at a concentration of 100 mg/litre (corresponding to 76 mg As/litre) over periods of 4 to 11 weeks. Cutaneous tumours were initiated by the topical application of 1,2-dihydro-3-methylbenz[j]accanthrylene (methylcholanthrene) and promoted by transplantation. The results were contradictory, as arsenic treatment seemed to increase the number of papillomas in one strain, i.e., 5 papillomas in 16 arsenic-treated animals compared with one papilloma in 10 controls, while it seemed to decrease the incidence in another strain (9/28 in exposed versus 17/29 in unexposed).

Schrauzer & Ishmael (1974) exposed 30 mice of a strain with a high incidence of spontaneous mammary tumours to sodium arsenite in the drinking-water at a concentration of 10 mg/litre (3.6 mg As/litre). Tumours appeared between 6 and 9 months of age only and were seen in 27% of the animals In control

animals, tumours did not occur before the eleventh month, but affected 82% of the animals after the sixteenth month. The growth rate of the spontaneous tumours, as well as of transplanted mammary tumours, was significantly enhanced in arsenic-fed animals. When a similar experiment was performed on 30 mice exposed to 2 mg As/litre as arsenic(III) oxide in drinking-water, mammary tumours started to appear at the age of 9 months, while in control animals, the age of onset was 4.5 months (Schrauzer et al., 1978). The tumour incidence was lower in the arsenic-exposed group, i.e. 36% compared with 41% in the controls (not statistically significant). As in the previous study, the growth rate of the tumours was higher in the arsenic-treated animals. When the administration of arsenite was accompanied by administration of 2 mg selenite per litre of drinking water, a higher incidence of spontaneous mammary tumours occurred (62%) than when selenite was administered alone (17%). The tumour growth rate was similar in the arsenic/selenite and arsenic groups and was significantly higher than in the selenite only and control groups.

Lead arsenate was administered at levels of 463 and 1850 mg/kg (100 and 400 mg As/kg diet) and sodium arsenate at 416 mg/kg (100 mg As/kg diet), in both cases mixed with the feed, to rats in groups of 48—110 animals (Kroes et al., 1974). For 5 days per week exposure to arsenic was combined with oesophageal intubations of diethylnitrosamine at a dose of 5 µg/day. Mortality was comparable in all groups except the group given 1850 mg lead arsenate/kg which showed a marked increase after 26 weeks. After 120 weeks all survivors were killed and the animals were examined for tumours. In the control groups, the incidence of malignant tumours ranged from 10% to 17%, and in the exposed groups from 0% to 13%. Similarly, there were no differences in the development of of benign tumours between the groups.

8.4.2.4 *Other experimental systems*

Hueper (1954) injected metallic arsenic in lanolin into the femur marrow of 25 male rats and 6 rabbits. The doses were 0.43 mg and 0.65 mg, respectively. Only 4 rats survived 18 months and one of these developed a spindle cell sarcoma at the site of injection. None of the rabbits showed any metaplastic reactions. No tumours were produced at the site of injection in 25 rats injected intrapleurally once a month for 6 months resulting in a total dose of 0.65 mg of arsenic. Similar results were obtained after nasal sinus injection of 0.65 mg of arsenic in 20 rats.

In studies by Osswald & Goerttler (1971), 24 pregnant mice were injected daily with 0.5 mg of arsenic per kg body weight in the form of sodium arsenate for 20 days. Half of the 22 animals

that died during a subsequent 24-month period of observation had developed lymphocytic leukaemias or lymphomas. Two animals were still alive at this time. None of 16 dead female controls had developed such lesions. Four controls were still alive. Some of the offspring of the arsenic-treated mothers (41 males and 56 females) received 20 weekly subcutaneous injections of sodium arsenate in doses of 0.5 mg As/kg body weight. Leukaemias and lymphomas had developed in 50% of the males and 42.0% of the females that had died at the time of reporting. Seven males were still alive at this time. In 71 untreated progeny, leukaemias and lymphomas were present in 13.3% of males and 20.7% of females that had died at the time of reporting. Four out of 34 males and 8 out of 37 females were alive at this time. Lymphomas appeared in 11 out of 20 mice injected intravenously with 0.5 mg of arsenic in the form of sodium arsenate once a week, for 20 weeks.

8.5 Mutagenicity

Several studies have indicated an effect of inorganic arsenic on human chromosomes, both *in vivo* and *in vitro*. An increased frequency of chromosomal aberrations has been found among persons exposed to arsenic, mainly in inorganic trivalent form, both as medication and in the workplace. Petres et al. (1977) examined lymphocytes from 62 dermatology patients, 31 with a history of extensive arsenic contact, displaying typical palmo-plantar hyperkeratosis, and 31 controls. The exposed group consisted of 14 psoriasis patients and 17 wine-growers. The control group also included 14 psoriasis patients but these did not have any history of arsenic medication. The frequency of chromosome aberrations, both structurally and numerically, in the arsenic-exposed group was significantly higher than that in the controls, especially as regards chromatid aberrations. An *in vitro* addition of sodium arsenite to lymphocyte cultures from healthy subjects induced the same chromosomal changes. Similar results were earlier obtained by Oppenheim & Fishbein (1965) after adding potassium arsenite to a culture of human leukocytes and by Paton & Allison (1972) following exposure of human diploid cells to arsenic salts, including sodium arsenate.

The chromosomal aberrations in lymphocytes from 39 employees at a Swedish copper smelter with high levels of airborne arsenic in some workplaces were counted (Nordenson el al., 1978). The workers were divided into 4 exposure categories based on type and duration of work with arsenic compounds and presence or absence of septum perforation and arsenic dermatitis. Controls were apparently healthy individuals living about 100 km from the smelter. A total of 4106 cells from arsenic-exposed workers and 1312 from

the controls were examined. The frequency of chromosomal aberrations was significantly higher in the arsenic-exposed workers than in the controls. However, the correlation between the chromosomal aberrations and the estimated arsenic exposure was poor.

An interaction effect of tobacco smoking and arsenic exposure on the frequency of chromosomal aberrations was indicated. The effect of arsenic alone cannot be assessed in this study, as simultaneous exposure to other agents occurred.

An elevated sister chromatid exchange rate was found by Burgdorf et al. (1977) in the lymphocytes of 6 patients treated with Fowler's solution (daily doses of up to 3 mg of arsenic as arsenite).

The mean sister chromatid exchange rate per mitosis in the arsenic-treated patients was 14.0, and only 5.8 in healthy controls. It should be noted that all 6 arsenic-treated patients had developed skin cancer and that at least 2 of them had received X-ray treatment. No information of this sort was given regarding the control subjects.

Several studies have indicated that inorganic arsenic affects DNA repair mechanisms. Jung (1971) examined the effectiveness of the dark repair enzyme system in human skin biopsies treated with sodium arsenate after irradiation with a Xenon lamp. The repair activity, which was determined in terms of incorporation of a radioactively labelled nucleotide, was significantly reduced in arsenic-treated cells. These results have been confirmed by Petres et al. (1977), who showed that doses of about 1.0 mg sodium arsenate per litre of culture medium, reduced the incorporation of radioactively labelled nucleotides into RNA and DNA in lymphocytes. These 2 studies were performed on dermal cells and lymphocytes, respectively, but other cell systems could also be expected to be affected by arsenic in a similar manner.

A significant increase was found in the frequency of dominant lethals in the F_3 generation of mice given sodium arsenite in the drinking water at a level of 100 mg As/litre, when this exposure was combined with intraperitoneal injection of tris-l-aziridinylphosphine oxide (TEPA) in a dose of 1 mg/kg body weight prior to mating. No increase was observed in animals exposed to 1 mg As/litre (Šrám & Bencko, 1974).

Rossman et al. (1975) showed that survival of *Escherichia coli* following UV-radiation was decreased by arsenite. Studies on different strains of bacteria, deficient in various repair mechanisms, indicated that arsenic particularly affects post-replication repair.

The incidence of early fetal deaths is determined in the dominant-lethal assay, and may be an indication of genetic damage. Sodium arsenate (5 mg/kg bodyweight) and sodium arsenite (5 mg/kg bodyweight), when given to male mice in a single dose intraperitoneally, has been shown not to elicit a dominant-lethal effect (Hodge & Embree, 1977). An effect on chromosomes by a toxic

agent might cause malformations or spontaneous abortion, if it occurs at the germ cell level. Malformations can also result from interference with fetal development without necessarily damaging the genetic material (section 8.2).

Nishioka (1975) carried out mutagenicity tests *in vitro* for 56 inorganic metal compounds using the DNA recombination assay of *Bacillus subtilis*. Sodium arsenite, sodium arsenate, and arsenic (III) chloride gave positive results in the test. On the other hand, Löfroth & Ames (1978) failed to show any mutagenic activity of inorganic trivalent and pentavalent arsenic in the *Salmonella* plate incorporation test.

8.6 Mechanisms of Toxicity

Inorganic arsenic has been shown to cause impaired tissue respiration *in vivo* in the liver and kidneys of mice and rats (Bencko & Nemeckova, 1971; Bencko, 1972; Brown et al., 1976; Fowler et al., 1977). To affect the enzymatic activity responsible for respiration, arsenic has to pass the mitochondrial membranes and membrane damage appears to play a prominent role in the emergence of some of the observed effects. *In vitro* studies have shown that rat liver mitochondria can accumulate arsenite (Harris & Achenjang, 1977) and arsenate through energy-dependent processes (Kagawa & Kagawa, 1969). Arsenic-bound components with properties similar to those of a low relative molecular mass arsenate ester have been isolated from rat liver mitochondria (Chan et al., 1969).

It was recognized many years ago that inorganic arsenic inhibits enzyme activity and that *trivalent* inorganic arsenic reacts with the sulfhydryl groups of proteins. Many enzymes containing such groups have been shown to be affected by arsenite (Thompson, 1948; Webb, 1966). In particular, the marked inhibitory effects of As(III) on mitochondrial respiration mediated by NAD-linked substrates, appear to play a critical role in the toxicity of this agent. Suppression of NAD-linked substrates (pyruvate, glutamate, and a-ketoglutarate, in particular) in rat liver mitochondria is thought to occur through the reaction between the arsenite ion and the dihydrolipoic acid cofactor, necessary for oxidation of the substrate (Fluharty & Sanadi, 1960, 1961). A depression in the activity of succinic acid dehydogenase [EC I. 3.99.1] in various tissues has also been demonstrated (Tsutsumi et al., 1974). Arsenite has been shown to decrease or uncouple mitochondrial oxidative phosphorylation. This phenomenon is associated with the stimulation of mitochondrial ATPase activity, which in turn, is usually a factor in the distortion of mitochondrial membranes. The dithiol-containing compound, 2,3-dimercapto/propanol (BAL) has been shown to potentiate the uncoupling action

of arsenite in rat liver mitochondria, suggesting that dithiols have a function in the transport of arsenite to the enzyme site (Fluharty & Sanadi, 1960, 1961; Fletcher & Sanadi, 1962). Addition of BAL or dithiols in excess was found to recouple the phosphorylation. At high, *in vitro* concentrations, arsenite also inhibited respiration in rat thymus nuclei (Konings, 1972).

In vitro studies on rat heart and liver mitochondria and *in vivo* studies have shown that pentavalent and trivalent arsenic exert similar effects in the inhibition of mitochondrial respiration and uncoupling of oxidative phosphorylation (Crane & Lipmann, 1953; Azzone & Ernster, 1961; Packer, 1961; Wadkins, 1961; Fowler, 1975). The mechanism of this inhibition is not clear and several possibilities exist. One is that arsenate is reduced by the mitochondria to As(III) and that inhibition occurs through the formation of a complex with the lipoic acid cofactor. The increasing inhibitory effect on NAD-linked substrates with time found by Crane & Lipmann (1953) indicates that this could be the case. From studies on rat liver and beef heart mitochondria, Mitchell et al. (1971) proposed that inhibition of mitochondrial energy-linked functions by arsenate occurs in 2 ways: competition with phosphate during oxidative phosphorylation and inhibition of energy-linked reduction of NAD.

9. EFFECTS AND DOSE-RESPONSE RELATIONSHIPS OF ORGANIC ARSENIC COMPOUNDS

9.1 Acute and Chronic Toxicity

The form of organic arsenic determines the tissue distribution and hence affects the pattern of toxicity (section 6.2.2.2). Some organic arsenic compounds have a high toxicity for certain organs, while the organic arsenic compounds in seafood are apparently of low toxicity.

9.1.1 Man

Organic arsenic compouds are still used widely as antiparasitic drugs (section 5.3.3). Side-effects have been reported in many organ systems, most notably the central nervous system. Encephalopathy

was observed in 1.5% of 1066 patients treated with arsobal (tryparsamide) for trypanosomiasis (Sina et al., 1977). The mortality was high (62.5%) among those with encephalopathy. Encephalopathy also also occurred in patients treated with glycobiarsol, another organic arsenic compound (Cole et al., 1966). A well-known side-effect of tryparsamide treatment is optical atrophy. Visual effects arise in 3%—4% of patients treated with this drug, according to Neujean et al. (1948). Other, less frequent, side-effects include dermatitis, liver damage, and disturbances of the haematopoietic system.

Organic arsenic compounds may be found in high concentrations in some seafoods (section 5.2). Although there have not been any scientific studies published on the acute and subacute toxicity of these forms of arsenic for man, experience indicates that it is very low. Chronic effects, however, cannot be ruled out. Walkiw & Douglas (1975) described 2 women who had been on health food supplements prepared from kelp (duration of intake not stated). The women had developed neuropathy, one of them having foot drop and the other peripheral neuropathy. At the time of hospitalization, the urinary excretion of arsenic for the 2 patients was 138 μg and 293 μg/24 h, respectively. No information was given on the course of the symptoms following cessation of exposure. Clearly, this report cannot incriminate organic arsenic in the seaweed, beyond doubt, as the cause of the neuropathy.

9.1.2 Animals

The toxicity of the form of organic arsenic present in seafoods is of special interest with regard to general human exposure. From the very limited research performed to date it appears to be relatively low. Coulson et al. (1935) reported that rats fed a diet containing shrimp arsenic at a concentration of about 14 mg As/kg for 12 months did not have any defects in growth or physical appearance. No histological changes were found in the spleen, liver, or kidneys. In studies by Lancaster et al. (1971), lakeweed with a high arsenic content was given to sheep at a daily dose of 1.4 mg As/kg body weight for 3 weeks. The animals remained healthy, and examination of organs and tissues removed from the animals at slaughter (3 animals per week) did not reveal any gross morphological changes.

Aliphatic arsenic compounds such as dimethylarsinic acid and mono- and disodium methane arsenate, are used commercially as herbicides in noncrop areas. These herbicides have been reported to be a source of intoxication for domestic animals (Selby et al., 1977). The clinical symptoms and histological findings seem to

be the same as those induced by inorganic arsenic, discussed in section 8.1.

Experimental research on the acute inhalation toxicity of dimethylarsinic acid for rats was performed by Stevens et al. (1976). No mortality was found among rats, exposed to an aerosol containing a commercial product (Phytar 138) at a concentration of 2600 mg/m^3 for 2 h. The particle size of the dust was 3 μm (MMD). No other details of the product were specified in the report. Assuming a content of 65% dimethylarsinic acid (Gosselin et al., 1976), it can be calculated that the arsenic concentration in the aerosol was approximately 840 mg/m^3. Exon et al. (1974) fed rabbits a diet containing monosodium methane arsenate (MSMA) at a level of 50 mg/kg diet, equal to 27.5 mg As/kg diet, for 7 or 8 weeks. Toxic hepatitis was found in all of the 8 animals necropsied and reactive hyperplasia in 5 of them. Steers and heifers, weighing 100—200 kg, were given daily doses of pure MSMA at 10 mg/kg (5 mg As/kg body weight; aqueous solution) for up to 10 days (Dickinson, 1972). Two steers died during the treatment and the third, some days later. Of the 2 heifers, one was killed due to morbidity. The other recovered, when the exposure was ended. All the arsenic-exposed animals lost weight and developed severe diarrhoea, haemorrhagic gastritis, and intense hyperaemia. Liver necrosis and renal tubular degeneration were also found.

The short-term toxicity of phenoxarsine oxide (PXO) and phenarsazine oxide (PZO), 2 organic arsenic compounds used as industrial biocides, was studied by Ballantyne (1978). Acute oral toxicities, determined as the LD_{50} for guineapigs and rats, were 24 and 40 mg/kg body weight (equal to 7 and 12 mg As/kg body weight) for PXO and 77 and 83 mg/kg body weight (23 and 25 mg As/kg body weight) for PZO. PZO was more hepatotoxic, producing cellular infiltration and oedema of the portal tracts as well as periportal hepatocellular necrosis in rats receiving a single oral dose of 30 mg/kg body weight (10 mg As/kg body weight). Histological changes of the liver were not observed in animals receiving the same dose of PXO. Inhalation of PXO and PZO for 30 days in concentrations of 1—2 mg/m^3 (0.3—0.6 mg As/m^3) (MMD 4—5 μm), for 5 h a day, did not elicit any toxic signs except for transient cellular infiltration of the portal tracts of the liver. Both substances produced eye and skin irritation in guineapigs with a local application of a 25% suspension in water. Increases in intraocular pressure in rabbits were concentration dependent.

The toxicity of derivatives of phenylarsonic acid, such as arsanilic acid, is a subject of great interest, since these compounds are commonly used as feed additives for poultry and swine. Ledet et al. (1973) studied the effects of a diet containing arsanilic acid at a concentration of 1000 mg/kg (350 mg As/kg) in pigs. This was reported

to be 10 times the level recommended for growth stimulation. Roughened haircoat and mild diarrhoea were the first signs of toxicity. Cutaneous hyperaemia and hyperaesthesia usually occurred after a few days, and the animals often stumbled and staggered about. Histopathological lesions were confined to peripheral and optic nerves. The same dietary level of arsanilic acid was found to cause blindness and optic disc atrophy in pigs within 25–30 days (Witzel et al., 1976). Sodium arsanilate injected subcutaneously into guineapigs in doses exceeding 70 mg/kg body weight caused degeneration of the sensory cells of the inner ear (Anniko & Wersäll, 1977). Retention of arsenic in the cochlea and delayed elimination from the inner ear compared with elimination from the blood have been reported (Anniko & Plantin, 1977).

9.2 Teratogenicity

Teratogenic effects were not observed in 7 generations of rats fed 0.01, 0.02, or 0.05% arsanilic acid (3.5, 7 or 17.5 mg As/kg diet) (Frost et al., 1964). On the contrary, both the litter sizes and the survival of pups increased significantly.

9.3 Carcinogenicity

No human epidemiological investigations have been conducted on the carcinogenicity of organic arsenic compounds. Consequently, only data concerning laboratory animals can be considered.

9.3.1 Animals

Twelve mice belonging to a strain with a high incidence of spontaneous mammary tumours were injected with neoarsphenamine in doses of 6.7 mg/kg body weight, twice weekly, for up to 10 weeks (Hueper & Itami, 1933). Exposed and control animals were found to have similar average life spans. The arsenic-exposed animals showed an increased growth rate, and histologically, a higher grade of malignancy.

In an experiment in which 50 trout were fed a synthetic diet containing carbarsone at 4.8 g/kg diet for 20 months, 5 trout developed hepatomas (Halver, 1962; cited in Kraybill & Shimkin 1964). A control group of 300 trout given the same diet but omitting the carbasone, did not develop any hepatomas. The original data in this

report were not available, and consequently a thorough evaluation could not be made of the findings.

Frost et al. (1962) fed groups of 60 rats (30 males and 30 females) diets containing arsanilic acid at 0, 0.1, 0.5 and 1 g/kg diet for 106 weeks. Tumour incidence was similar in all the groups. In studies by Boutwell (1963), arsanilic acid was given to 30 mice for a 2-week period at a level corresponding to 200 mg As/kg diet and to another group for 48 weeks at a level of 100 mg/kg diet. The arsenic exposures were combined with a skin application of the tumour initiator 7,12-dimethylbenz(*a*)anthracene (5 μg) and the tumour promoter, croton oil. No differences were noted in tumour incidence between the arsenic-fed animals and controls.

3-Nitro-4-hydroxyphenyl-arsonic acid was incorporated into the feed of groups of 100 rats and 100 mice (50 animals of each sex in each group) at levels of 0, 50, and 200 mg/kg diet for the rats and 0, 50, and 100 mg/kg diet for the mice. Tumours occurred in essentially similar numbers of animals in all groups over a 2-year period (Prier et al., 1963). The same authors also exposed groups of 6 dogs (3 male and 3 female) to 4-hydroxy-3-nitrophenylarsonic acid added to the feed at levels of 50 and 200 mg/kg. In this study also, no differences were seen between exposed and control groups. A solution of 4-hydroxy-3-nitrophenylarsonic acid in ethanol acetone (1:4), at a concentration of 10 g/litre, was painted on the skin of 100 mice, 3 times weekly, for 1 year. No skin tumours developed during this and the following year. Subcutaneous injections of 10 mg of 4-hydroxy-3-nitrophenylarsonic acid were given to 100 female mice and 5 mg to 100 male mice. Neither of the 2 groups differed from control animals with regard to tumour incidence during a 2-year period of observation.

The diets of 5 groups of 100 rats (equal numbers of each sex in each group) were supplemented with carbarsone, (*p*-ureidobenzene arsonic acid) to provide daily intakes of 2.5, 5, 25, 50, and 100 mg/kg body weight, respectively. After 72 weeks, the group receiving the highest level of carbarsone in the feed was given an unsupplemented diet. Survival was similar in all groups except the one with the highest exposure, in which there was a marked increase in the death rate before the transfer to the unsupplemented diet. A total of 13 malignant tumours was observed in a control group of 200 rats followed for 2 years. In the 3 groups receiving the highest levels of carbarsone, the number of malignant neoplasms varied between 0 and 14 and was not related to dose (Oser et al., 1966).

9.4 Mutagenicity

No increase in the incidence of early fetal deaths was observed by Hodge & Embree (1977) in the offspring of male mice given a

single dose intraperitoneally of [(dimethylarsino)oxy] sodium As-oxide (sodium dimethylarsonate) (200 mg/kg body weight) arsenodiacetic acid (arsenoacetic acid) (50 mg/kg body weight), and methanearsonic acid (250 mg/kg body weight).

9.5 Mechanisms of Toxicity

The mechanisms by which arsenic compounds exert their action in biological tissues have been thoroughly described and reviewed (Barron & Singer, 1945; Barron et al., 1947; Thompson, 1946, 1948; Gordon & Quastel, 1948; Stocken & Thompson, 1949; Peters, 1955; Vallee et al., 1960; Johnstone, 1963). Arsenic compounds do not constitute a homogeneous group and the effects in biological systems, caused by reactions between the arsenic compounds and functional groups of different enzymes, are highly dependent on the chemical character of the compound involved in each particular case.

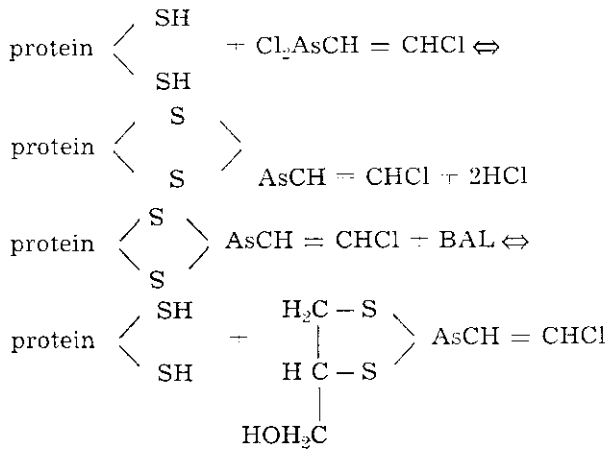
The first distinction to be made is that between trivalent and pentavalent organic arsenic compounds. Pentavalent arsenic compounds ($R\text{-}AsO_3H_2$) have little effect on enzyme activity but can be reduced *in vivo* to more toxic trivalent compounds (Peters, 1955; Johnstone, 1963).

Trivalent organic arsenic compounds include, according to the nomenclature used by Johnstone (1963), arseno and arsenoso compounds. Arseno compounds, (R—As = As—R) are readily oxidized, even by trace amounts of oxygen, and their action has been suggested to be due to their conversion to the corresponding arsenoso derivatives. These can be divided into monosubstituted and disubstituted compounds according to their reaction with sulfhydryl groups (Peters, 1955). The monosubstituted compounds, exemplified by R As = O, react with enzymes containing sulfhydryl groups:

$$R - As = O + 2\,R'SH \Leftrightarrow R - As \begin{matrix} SR' \\ \diagup \\ \diagdown \\ SR' \end{matrix} + H_2O$$

Inhibition of different enzyme systems by these arsenic compounds was shown to be reversed by addition of an excess of a monothiol, e.g., glutathione. Some enzymes contain 2 thiol groups, which can react with the monosubstituted arsenic compound, thereby yielding a 5-membered ring structure. This reaction is reversed by dithiols, e.g., 2,3-dimercaptopropanol (BAL), but not by monothiols. Lipoic acid, necessary for the initial stages in the oxidation of

pyruvate, is inhibited in this way by lewisite (used as a war gas), and the reaction is successfully reversed by 2,3-dimercaptopropanol (BAL).



The disubstituted arsenoso compounds, $\begin{matrix} R \\ \diagdown \\ \diagup \\ R \end{matrix}$ As — OH, exerts its action by combining with enzymes containing monothiol groups. The resulting enzyme poisoning can probably be reversed by the monothiol defence mechanisms present in the body. One complication, however, is the possible conversion of disubstituted to monosubstituted arseno compounds. This is indicated by the finding that dithiols are needed for reversing the reaction between diphenylchloroarsine and certain enzyme systems in brain and kidney.

10. INTERACTIONS WITH OTHER CHEMICALS

Until recently, studies on the toxicity of different chemical agents have been based almost exclusively on the administration of a single substance as the point of departure. Considering that man is exposed simultaneously to a wide variety of agents, it is urgent that the interactions between these agents should be investigated. In the case of arsenic, attention has been paid to its interaction with dithiol-containing substances such as BAL, because of the introduction of BAL as an antidote to the arsenic-containing war gas lewisite. Investigations concerning combined exposures to arsenic and other chemicals may, in the future, explain some of the data which appear controversial at present. Interactions between arsenic and other

agents have been dealt with by the Scientific Committee on the Toxicology of Metals under the Permanent Commission and International Association on Occupational Health at its Stockholm meeting on "Factors Influencing Metabolism and Toxicity of Metals", held in July, 1977. Among the items discussed were interactions between arsenic and selenium, cadmium, and lead (Nordberg, 1978). Because of the lack of data on human exposure situations, the following discussion will refer exclusively to experimental animal studies.

10.1 Thiol Compounds

The toxicity of arsenic compounds, the influence of mono- and dithiol-containing compounds, and the introduction of 2,3-dimercaptopropanol (BAL) as an antidote in arsenic poisoning have been reviewed by Stocken & Thompson (1949). The mechanism for the interaction was discussed in terms of the biochemical aspects of arsenic toxicity (sections 8.6 and 9.5). It should be noted that organic and inorganic arsenic react differently with dithiols. The toxic effects of arsenite can be potentiated by dithiols, as these can serve as vehicles for the transport of arsenite to the enzymes. The distribution and excretion of inorganic arsenic in the form of arsenate, given orally to rats, can be influenced by BAL or thioctic acid (TA) (Tsutsumi & Kato, 1975). Five consecutive injections of either substance decreased the tissue levels of arsenic and increased its excretion more than a single dose.

In rabbits, given BAL or TA parenterally, the amount of arsenic(III) oxide absorbed in the blood from a ligated loop of the intestine was considerably lower than in control animals (Tsutsumi & Nozaki, 1975). Furthermore, when BAL and TA were added directly into the loop containing arsenic(III) oxide, the amount of arsenic absorbed in the blood was lower than that of the control group. It was suggested that BAL and TA, after being excreted into the intestine with the bile, can inhibit the absorption of arsenic.

BAL, TA, and to some extent diisopropylaminodichloroacetate (DADA), intraperitoneally injected in rats, increased the amounts of ^{74}As in the stomach and small intestine following orally administered ^{74}As-arsenate (Tsutsumi et al., 1976). When glucuronolacton (GL) and glutathione (GT) were injected into the animals, the ^{74}As-content in these organs was comparable to that of the control group. BAL, TA and DADA were also shown to suppress intestinal movements. The authors suggested that the delayed uptake of arsenic might be because of the inhibited transport of arsenic in the gastrointestinal canal, as it had been shown earlier that arsenic is absorbed preferentially in the small intestine.

BAL, subcutaneously injected in mice (50 mg/kg body weight), reduced the teratogenic action of simultaneous intraperitoneal injections of sodium arsenate at a level of 16 mg As/kg body weight (Hood & Pike, 1972).

10.2 Selenium

The interaction between selenium and arsenic has been reviewed by Levander (1977), who concluded that arsenic has a protective effect against the toxicity of a variety of forms of selenium. He found that this effect had been demonstrated in several species including rats, dogs, swine, cattle, and poultry. It was suggested that arsenic acts by enhancing the biliary excretion of selenium. Sodium arsenite was shown to be most potent, arsenate somewhat less potent, and various organic arsenic compounds least potent. The opposite course of events has also been observed, i.e., selenite can stimulate the excretion of arsenite in the bile of rats. The experiments referred to have been performed almost exclusively on rats. Taking into account what is known about the metabolism of arsenic in rats and especially about the partition of different forms of arsenic in the enterohepatic circulation, it must be concluded that research on the mechanism of interaction between selenium and arsenic is far from complete. Holmberg & Ferm (1969) observed that selenite decreased the teratogenic effects of arsenate when the 2 compounds were given to pregnant hamsters in simultaneous intravenous injections.

The protective effect of arsenic against selenium has also been noticed in studies on mouse fibroblasts (Rössner et al., 1977). A study carried out on mice demonstrated that arsenic (III) was more efficient in protecting against selenium toxicity than arsenic (V) (Benckc et al., 1978b).

10.3 Cadmium and Lead

Mahaffey & Fowler (1977) examined the effects of dietary cadmium (50 mg/kg diet) and lead (200 mg/kg) on the toxicity of arsenic administered to rats as sodium arsenate or arsanilic acid in the food (50 mg As/kg diet). The efficiency of food utilization was more reduced by the combination of arsenic and cadmium than by each metal alone. The combination of arsenic and cadmium also caused a greater decrease in serum alkaline phosphatase levels than either metal alone. Additive effects of arsenic and lead in coproporphyrin excretion were also noted. Increased uroporphyrin excretion in rats was reported (Fowler & Mahaffey, 1978), when lead, cadmium, and arsenic were combined compared with excretion levels following exposure to arsenic alone.

11. EVALUATION OF HEALTH RISKS TO MAN FROM EXPOSURE TO ARSENIC

11.1 Introduction

Arsenic can give rise to acute, subacute, and chronic effects. The adverse health effects of arsenic may involve the respiratory, gastrointestinal, cardiovascular, nervous, and haematopoietic systems. Effects may be local and systemic.

In the discussions of effects in the following sections, quantitative aspects on dose-response relationships are given, whenever possible. Unfortunately, such data are generally very scanty or nonexistent, and this makes risk evaluation difficult.

Various models have been developed for assessing the risk of cancer at low doses; however, the simple linear non-threshold dose-response extrapolation model is most often used. If this model is adopted, the pulmonary carcinogenicity of inorganic arsenic should constitute the basis for setting environmental standards for airborne exposure. In the case of oral exposure, several effects, including skin cancer, have to be taken into consideration.

Mutagenic and teratogenic effects will not be discussed separately in this section, as the significance of such data as a basis for environmental standards is not clearly recognizable.

11.2 Exposure

Exposure to arsenic may occur industrially as well as through ambient air, tobacco smoke, water, food and beverages. In addition, considerable exposure may take place through the ingestion of drugs, still in use in certain countries.

Occupational exposure occurs through the inhalation of particulate matter containing inorganic arsenic, which may be trivalent or pentavalent. Concentrations varying from a few micrograms to more than one milligram per cubic metre have been reported.

Most arsenic in particulate matter in ambient air is in the form of inorganic arsenic compounds. Concentrations in urban areas may range from a few nanograms per cubic metre to a few tenths of a microgram. In the vicinity of point sources emitting arsenic, concentrations exceeding 1 μg As/m^3 have been reported.

In the past, tobacco contained high concentrations of arsenic because of the widespread use of arsenic in pesticides and concentrations of up to about 40 mg/kg have been found. However, levels are now well below 10 mg/kg, in countries that restrict the use of pesticides containing arsenic.

In both ground and surface waters, the total arsenic concentration is usually below 10 μg/litre. In certain areas, levels of more

than 1 mg/litre have been recorded. Some studies indicate that arsenic is mainly present in inorganic forms. The oxidation state of the arsenic in waters depends on the prevailing redox potential. In surface waters, in the presence of dissolved oxygen, arsenic(V) is predominant. Under reducing conditions, particularly in deep well water, arsenic(III) is present.

Food and beverages are the most important sources of exposure to arsenic for the general population. The total daily intake of arsenic from the diet has been estimated to be less than 200 μg in the adult. The figure is greatly influenced by the intake of seafood, which may contain up to 100 mg As/kg. Most of the arsenic of marine origin is organic. The total daily intake of inorganic arsenic from food and water has been estimated to be under 50 μg.

11.3 Inorganic Arsenic Compounds

Exposure can occur to both trivalent and pentavalent inorganic arsenic compounds, the solubilities of which vary. The nature of the compounds present in different exposure situations has not been well identified. Furthermore, the absorption and retention, in the lungs for example, of compounds of different solubilities are virtually unknown.

Both arsenic(III) and arsenic(V) are methylated to a great extent after entering the body. The major metabolites in the urine are methylarsonic acid and dimethylarsinic acid. The possibility of dose-dependence in this respect should be considered. Furthermore, the conversion of arsenic(V) to arsenic(III) *in vivo* has been suggested, but data are not conclusive.

In view of these uncertainties, health evaluations, with few exceptions, have to be confined to inorganic arsenic in general.

11.3.1 Acute and subacute effects after short-term exposure

A fatal dose of ingested arsenic (III) oxide for man has been reported to range from 1 to 2.5 mg As/kg body weight. This is lower than the LD_{50} values generally reported for animals. Trivalent arsenic is considered to be more toxic than pentavalent.

Two recent mass outbreaks of arsenic poisoning due to the ingestion of inorganic arsenic have been described. In the first episode, more than 12 000 infants were poisoned with dried milk contaminated with inorganic arsenic compounds (oxidation state uncertain, although in one report it was given as pentavalent). The average exposure level for a baby of 3 months had been about 3.5 mg of arsenic daily and symptoms usually appeared after a few weeks. In all, 130 deaths occurred, and effects were observed in several organs.

The other episode concerned about 400 persons who ate contaminated soy sauce and were thus exposed to an average of 3 mg of arsenic, daily, for 2—3 weeks. Many acute symptoms were encountered but neurological symptoms usually did not appear until the 10th—20th day of illness.

Dose-response relationships are difficult to estimate from the incidents just described, but it appears that ingestion of 3 mg of inorganic arsenic per day, over a period of few weeks, may give rise to severe poisoning in infants and symptoms of toxicity in adults. The toxic effects cannot be related to any specific valence form of arsenic.

11.3.2 Noncarcinogenic effects after long-term exposure and sequelae of short-term exposure

Inhalation of inorganic arsenic compounds can result in local damage to the respiratory system, including perforation of the nasal septum. Systemic effects after inhalation and/or ingestion involve the skin, liver, and the cardiovascular and nervous systems.

In general, details of exposure in human situations have been inadequate, as a basis for dose-response evaluations. For certain effects, however, some estimations of dose-response relationships can be made and information about this is given in the following sections.

11.3.2.1 *Skin effects*

Skin effects in the form of hyperkeratosis, hyperpigmentation, and depigmentation have been observed in different parts of the world after exposure to drinking-water containing high levels of arsenic, and after treatment with drugs containing inorganic arsenic. The oxidation state of the arsenic in the water involved in these incidents is not known but, in drugs, the arsenic component has usually been in the trivalent state. Skin effects have also been reported following exposure to arsenic during the manufacture of insecticides and also among wine growers.

Very few of the data available are of much help in estimating dose-response relationships. It seems, however, that several years of exposure to approximately 1 mg of arsenic per day may give rise to skin effects. It is not possible to state to what extent effects are caused by exposure to trivalent arsenic alone or whether pentavalent arsenic may also be of importance.

11.3.2.2 *Cardiovascular effects*

Cardiovascular effects, in the form of electrocardiographic changes and peripheral vascular disorders have been observed in

persons exposed to arsenic. Peripheral vascular disorders have been reported in German vintners, and, in Chile and China (Province of Taiwan), in parts of the population consuming water containing 0.5—1 mg As/litre. In both the Taiwanese villagers and the German vintners, the inadequate peripheral circulation caused gangrene, referred to as "blackfoot disease" by the Taiwanese. A dose-response relationship was arrived at on the basis of the data concerning the Taiwanese villagers, in which a roughly linear increase in the prevalence with increasing arsenic dose was indicated. Exposure to arsenic for many years, resulting in a total ingested dose of about 20 g of arsenic, corresponded to a prevalence of "blackfoot disease" of about 3%.

11.3.2.3 *Neurological effects*

Peripheral neurological damage has been observed in persons consuming arsenic-containing antiasthmatic preparations on a long-term basis. The exposure corresponded to 3—10 mg of arsenic per day in the form of arsenic(III) oxide or arsenic sulfide.

Disturbances of the central nervous system function were noted in a follow-up of Japanese infants, fifteen years after exposure to an average daily arsenic dose of about 3.5 mg for one month. The occurrence of severe hearing loss and brain wave abnormalities was indicated. However, the data were considered not to be conclusive.

11.3.3 Carcinogenicity

It has already been mentioned that the pulmonary carcinogenicity of inorganic arsenic should constitute the basis for setting environmental standards for airborne exposure, and that in the case of oral exposure, several effects, including skin cancer, have to be taken into consideration. In reviewing available data in 1973, as well as in 1980, IARC concluded that there was sufficient evidence to associate exposure to inorganic arsenic with cancer of the lung and skin.

11.3.3.1 *Cancer of the respiratory system*

Arsenic has been associated with pulmonary cancer in the manufacture and use of arsenic-containing pesticides and in the smelting of copper. The carcinogenic potential of inorganic arsenic, mainly trivalent, in the smelter environment is evident from many epidemiological studies in different countries. One report revealed a roughly linear relationship between cumulative arsenic exposure

and the lung cancer risk. Though data are uncertain, it could be estimated that exposure to airborne arsenic levels of about 50 $\mu g/m^3$ (probably mostly arsenic(III) oxide) for more than 25 years would result in a nearly 3-fold increase in mortality due to lung cancer over the age of 65 years (section 8.4.1).

11.3.3.2 *Skin cancer*

Exposure to inorganic arsenic can cause skin cancer, mainly tumours of low malignancy. This has been observed following ingestion of arsenic-rich drinking-water and the consumption of arsenic-containing drugs. A total dose of several grams has usually been required for the development of cancer. The form of arsenic in the different types of drinking water in question has yet to be elucidated, while, in drugs, it has most often been inorganic trivalent arsenic.

There are very few dose-response data on arsenic and skin cancer that can be used for quantitative estimations. From one study on exposure to arsenic via drinking-water in China (Province of Taiwan), there was evidence that a total of about 20 g of arsenic over a lifetime resulted in a prevalence of skin cancer of about 6%.

11.4 Organic Arsenic Compounds

The application of organic arsenic compounds in medicine, most notably tryparsamide, has induced side effects, mainly in the central nervous system, in the form of encephalopathy and optical atrophy. Toxic effects on the nervous system have also been reported in experimental animals given high doses of arsanilic acid. This is a compound commonly used as a feed additive for poultry and swine in some countries. No data on dose-response relationships, which would be directly applicable to the long-term exposure of man, are available.

Human beings are exposed to organic arsenic compounds in seafood, certain types of which may contain arsenic concentrations of 20—50 mg/kg wet weight or even more. The form of arsenic in seafood is largely unknown, but it has been found to be readily absorbed (more than 80%) from the gastrointestinal tract in both animals and man. It is also rapidly excreted in the urine (70—80% within a week).

No adverse effects were found in a study in which rats were fed a diet containing "seafood arsenic" in the form of shrimps at a concentration of about 14 mg As/kg for 12 months. There are no data concerning the toxicity of "seafood arsenic" for man, apart from the fact that acute effects have not been reported. It seems obvious

that this question has not been studied sufficiently, especially considering that a large number of people are exposed to this form of arsenic. Another organic arsenic compound, dimelhylarsinic acid, has been shown to pass through the placental barrier of rats. Blood values of the fetus were comparable to those of the mother. Placental transfer should be investigated when the toxicity of "seafood arsenic" is studied.

There is no conclusive evidence that any of the organoarsenic compounds tested for carcinogenicity in laboratory animals are carcinogenic. Epidemiological studies are greatly needed on populations exposed to organic arsenic, especially in view of the discrepancy between animal and human data with regard to the carcinogenicity of inorganic arsenic compounds. Suitable groups for study are workers exposed in the manufacture, handling, and use of organoarsenic compounds as well as patients treated with such compounds. Data have not been reported concerning the possible carcinogenic effects of "seafood arsenic".

11.5 Assessment of the Cancer Risk for Man from Exposure to Inorganic Arsenic

The purpose of this section is to provide guidance for the estimation of the cancer risk to the lung and skin from the inhalation and ingestion, respectively, of inorganic arsenic. For the purposes of this risk assessment, it is assumed that both pentavalent and trivalent arsenic are carcinogenic.

It must be recognized that the assessment of cancer risks by currently available methods can provide only crude estimates and this should be borne in mind particularly in making regulatory decisions about permissible limits of exposure. The use of the linear non-threshold model is recommended for extrapolation of risks from relatively high dose levels, where cancer responses can be measured, to relatively low dose levels, which are of concern in environmental protection where such risks are too small to be measured directly either through animal or human epidemiological studies.

The linear non-threshold model has been generally accepted amongst regulatory bodies in the USA for chemical carcinogens (IRLG) and for ionizing radiation on an international basis (ICRP). The linear non-threshold philosophy was accepted by a Task Group on Air Pollution and Cancer in Stockholm in 1977 (Task Group on Air Pollution and Cancer, 1978). The scientific justification for the use of a linear non-threshold extrapolation model stems from several sources: the similarity between carcinogenesis and mutagenesis as processes which both have DNA as target molecules, the strong evidence of the linearity of dose-response relationships

for mutagenesis, the evidence for the linearity of the DNA binding of chemical carcinogens in the liver and skin, the evidence for the linearity in the dose-response relationship in the initiation stage of the mouse 2-stage tumorigenesis model, and the rough consistency with the linearity of the dose-response relationships for several epidemiological studies; for example, aflatoxin and liver cancer, leukaemia and radiation. This rationale for the linear non-threshold dose-response model is strongest for the genotoxic carcinogens.

The mechanism of the carcinogenesis of arsenic is not clear at present.

In the case of the lung cancer estimates for the inhalation of inorganic arsenic, based on epidemiological data from an occupational smelter population, it is assumed that the life-time cancer risk is a function of the total dose of arsenic. This is a necessary assumption because occupational exposures begin at maturity, whereas exposures to airborne arsenic in the general environment begin at conception. Furthermore, in the case of lung cancer risk estimates, it is assumed that there are no age or sex differences in susceptibility to cancer induced by arsenic. There is not much basis in scientific fact for assuring the validity of these assumptions. It is not unreasonable to assume that the cancer response is proportional to the total dose, since the occupational smelter exposures extended over a substantial portion of the life span. On the basis of animal data, it is possible that children may generally be somewhat more susceptible than adults to carcinogens, but it is not known whether this is the case for arsenic and lung cancer. It is also not known whether males and females are equally susceptible. It is possible that sulfur dioxide and smelter dusts other than arsenic potentiate arsenic in the workplace. Presumably there are more carcinogen co-factors in the occupational setting than in the general environment, but this is not certain.

Risk estimates for lung cancer from inorganic arsenic exposure can be based on the study of Pinto et al. (1977) on smelter workers, in which there was a standard mortality ratio of about 300 or a 200% excess of lung cancer at an average air concentration of 50 $\mu g/m^3$ for an average duration of exposure of more than 25 years. It was assumed that the 200% excess of lung cancer applied to the life-time risk even though the Pinto study was limited to observations in men over 65 years of age. This assumption of relative-risk model has a sound factual basis particularly for cancer response to protracted exposures. The 200% excess needs to be extrapolated for the same total dose to the average life span of the population under consideration; i.e., if the average life span is 70 years, then a 200% excess of cancer would be produced for the same total arsenic dose by a life-time exposure to 8 $\mu g/m^3$. It is assumed that the 200% excess of lung cancer, observed in the Pinto

study, corresponds to an exposure level of 50 $\mu g/m^3$ for 25 years. (This will lead to some overestimation of the risk as the duration of exposure in the original data was given as more than 25 years.) The calculation is based on an occupational air intake of 8 m^3 per day for 240 days a year, over 25 years compared with an environmental air intake of 12 m^3 per day for 365 days a year over 70 years. In other words, a life-time exposure to 8 $\mu g/m^3$ would be expected to produce a 200% excess in lung cancer. This excess risk can conveniently be expressed as a percentage increase per unit concentration of arsenic in air. Thus 1 $\mu g/m^3$ would produce 200/8 or a 25% excess in lung cancer incidence. Knowing the existing life-time cancer incidence for the population under consideration, the risk from the nominal concentration of 1 $\mu g/m^3$ can be expressed in terms of absolute excess risk. If the life-time risk of lung cancer is for example 3%, then the excess risk is 3% x 25% or 0.03 x 0.25 or 0.0075 per microgram of airborne arsenic per cubic metre or 0.8% per microgram of airborne arsenic per cubic metre.

There are relatively few assumptions that need to be made for the estimation of the skin cancer risk from the ingestion of arsenic in drinking water. These risk estimates can be based on the epidemiological data from China (Province of Taiwan) (Tseng, 1977), where the population at risk was exposed for at least 50 years and the data were obtained from more than 40 000 men, women, and children of all ages. Nevertheless, the response could have been affected by socio-economic, cultural, and racial factors such as skin pigment, which may not be comparable to other populations. The risk assessment for skin cancer from the ingestion of inorganic arsenic can be based on the data shown in Fig. 11. The skin tumour data in this study was given in terms of prevalence. However, since these tumours were of low malignancy and would be expected to persist for a very long time, it has been assumed that the characterization of tumour yield in terms of prevalence is equivalent to cumulative incidence. The middle dose group shown in Fig. 11 for the age range of 60 years and over was chosen as the point of departure for the downward linear non-threshold extrapolation because it is the one that is the best description of exposure; the choice of the oldest age group maximizes the tumour yield for a given total dose. The observed prevalence data were not modified to account for a control incidence, since Tseng stated that actinic skin cancers were not included in this series of cases. The slope of the resultant linear extrapolation is about 5% skin tumour prevalence per 10 grams of total ingested arsenic. Assuming a 2 litre/day average intake of drinking water, a concentration of 0.2 mg As/litre would result in a total dose of 10 grams in an assumed average life span of 70 years. Thus the life-time risk from arsenic in drinking-water is about 25% per mg As/litre (5%/0.2 mg As/litre).

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