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The Carcinogenicity of Arsenic

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A carcinogenic role of inorganic arsenic has been suspected for nearly a century. Exposure to inorganic arsenic compounds occurs in some occupational groups, e.g., among smelter workers and workers engaged in the production and use of arsenic containing pesticides. Substantial exposure can also result from drinking water in certain areas and the use of some drugs. Tobacco and wine have had high As concentrations due to the use of arsenic containing pesticides.

Inorganic arsenic compounds interfere with DNA repair mechanisms and an increased frequency of chromosomal aberrations have been observed among exposed workers and patients.

Epidemiological data show that inorganic arsenic exposure can cause cancer of the lung and skin. The evidence of an etiologic role of arsenic for angiosarcoma of the liver is highly suggestive; however, the association between arsenic and cancer of other sites needs further investigation. No epidemiological data are available on exposure to organic arsenic compounds and cancer. Animal carcinogenicity studies involving exposure to various inorganic and organic arsenic compounds by different routes have been negative, with the possible exception of some preliminary data regarding lung cancer and leukemia. Some studies have indicated an increased mortality from lung cancer in populations living near point emission sources of arsenic into the air. The role of arsenic cannot be evaluated due to lack of exposure data.

Epidemiological data suggest that the present WHO standard for drinking water (50 μg As/l.) provides only a small safety margin with regard to skin cancer.

Introduction

Inorganic arsenic has had a classic reputation as a poison for centuries. Recent reviews on arsenic toxicity have associated long-term exposure to inorganic arsenic compounds with damage to the respiratory, cardiovascular, nervous, and hematopoietic systems, as well as lesions of the skin and liver (*1*, *2*). Health effects of organic arsenic compounds have not been adequately investigated.

Already in 1888, Hutchinson associated inorganic arsenic medication with skin cancer (*3*). Ever since, numerous reports have linked arsenic exposure to the development of tumors in various organs. An intriguing and unique feature has been that no animal model has been established for arsenic carcinogenicity, although strong epidemiological evidence exists to relate exposure to inorganic arsenic to lung and skin cancer. In 1980, after reviewing available experimental and epidemiological data, IARC concluded that inorganic arsenic compounds are skin and lung carcinogens in humans (*4*).

In the following, evaluation of dose response relationships with regard to lung cancer will be given special attention. Assessment of cancer risks of low exposure doses is often based on the assumption of a linear dose-response curve (*5*, *6*). The experimental and epidemiological evidence for this assumption is very weak; however, the usage of this model can be justified as a probably conservative estimate of the risk. Consequently, the extrapolations of cancer risks from high to low doses in this paper should be regarded as somewhat speculative and serve mainly as a basis for further discussion.

Exposure

Arsenic is a metalloid and is widely distributed in nature. The processing of some ores and minerals as well as the production and usage of arsenic containing pesticides have led to environmental

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pollution. Tobacco contained substantial amounts, e.g. up to 40 mg/kg As, some decades ago due to the use of arsenical pesticides in certain countries (*7*). Coal contains arsenic, sometimes up to 1500 mg/kg (*8*). In the U.S. in 1971, the average content of coal was 5 mg/kg (*9*). Arsenic particulate is released at combustion (*10, 11*). Burning of wood treated with arsenic containing preservatives can also result in a release of arsenic to air (*12*).

Water ordinarily contains low levels of arsenic (< 10 μg/l.), dominate in the inorganic form (*13-15*). In certain areas, however, natural concentrations may reach several hundred micrograms per liter (*16-18*). Contamination of water has resulted from industrial operations and the use of geothermal energy (*19, 20*).

Certain foodstuffs contain appreciable amounts of arsenic, e.g., some marine fish and crustaceans. Concentrations may exceed 10 mg As/kg (*21, 22*). The major part of the arsenic in marine organisms is present as organic arsenic compounds of high chemical stability (*23*). Accumulation of arsenic in the tissues of poultry and swine can result from the use of organic arsenic compounds as feed additives (*24, 25*). The use of arsenic-containing pesticides can give rise to increased arsenic levels in wine (*26*).

When considering the carcinogenity of arsenic it is of importance to distinguish between exposure to inorganic and organic forms of arsenic. Only exposure to inorganic arsenic compounds have been associated with cancer. Although data on the content of inorganic arsenic in various foodstuffs is limited, an estimation can be made of the total daily intake of inorganic arsenic based on data on metabolism and urinary excretion of various arsenic species. In individuals not excessively exposed to arsenic either via food, drinking water, or occupation, the total daily absorption should not exceed 50 μg of inorganic arsenic (*27*). For an average smoker a few micrograms of arsenic may be inhaled. The high content of arsenic in some tobaccos especially from the U.S. in the 1950's, may have caused inhalation of more than 100 μg of As daily. The daily arsenic intake in areas with high concentrations of arsenic in water can be several hundred micrograms (*28*). Up to 10 mg of inoorganic trivalent arsenic could be ingested daily by patients taking certain drugs (*29*).

Occupational exposure to inorganic arsenic compounds occurs primarily among smelter workers and workers engaged in the production and use of arsenic containing pesticides. Airborne arsenic concentrations of several hundred micrograms per cubic meter have been reported in the workroom atmosphere (*30*).

Epidemiological Studies

Inorganic arsenic compounds have been implicated as human carcinogens, both occupationally and following the use of arsenic containing drugs. Ingestion of arsenic-rich water has been associated with skin cancer in some areas. The form of arsenic in the water was not determined, however. Data from other areas show that arsenic in water primarily is present in inorganic forms. Epidemiological studies on carcinogenic effects of organic arsenic compounds are lacking.

A number of epidemiological studies have investigated the role of occupational exposure to arsenic for the development of cancer of the respiratory tract. With few exceptions these reports do not lend themselves to discussions of dose-response relationships, and consequently many reports will only be discussed briefly here. As a rule the exposure environment in occupational situations involving arsenic is very complex, but unfortunately the exposure to other agents, as well as smoking habits, has only rarely been reported.

An increased lung cancer mortality among workers engaged in the production of insecticides containing inorganic arsenic compounds has been observed in three epidemiological studies (*31-33*). Ott et al. (*32*) were able to show a positive dose-response relationship with estimated degree of arsenic exposure among workers in a plant producing lead arsenate and calcium arsenate. The increase in the lung cancer mortality with increasing dose was, however, consistent only in the highest exposure categories i.e. those where the dose exceeded 40 $\mu g/m^3$ as a daily 8 hr time-weighted average airborne arsenic concentration during 40 years [exposure categories in original publication recalculated by Blejer and Wagner (*34*) to correspond to exposure during a whole "working life"].

The spraying of pesticides containing inorganic arsenic compounds, predominantly of very low solubility, has also been associated with lung cancer among vintners in Germany and France (*35, 36*). Unfortunately these reports are only case studies with some macroepidemiological evidence and cannot be used for dose-response discussions. A U.S. study on orchardists spraying lead arsenate failed to show an increased cancer mortality (*37*). NIOSH, however, later claimed that an elevated lung cancer mortality was at hand in this occupational group (*38*). Poor or nonexistent data on arsenic exposure preclude further evaluation of these reports.

Workers involved in copper smelting, where substantial arsenic exposure can occur, have been reported to experience an increased risk of dying

from lung cancer (*39-44*). Epidemiological evidence has come from Japan, Sweden and the U.S., and as a rule a positive gradient for lung cancer mortality with increasing dose of arsenic has been presented. Lee and Fraumeni (*39*) and Tokudome and Kuratsune (*40*) reported 8- and 12-fold excess lung cancer mortalities, respectively, in the highest exposure categories in two cohort studies on smelter workers. No actual data on arsenic exposure were given. Axelsson et al. (*43*) in a case-control study revealed a relative risk of five for death due to cancer of the lung as well as a positive dose-response relationship among Swedish copper smelter workers exposed to high levels of airborne arsenic. Smoking habits could not account for this excess mortality (*44*).

Pinto et al. (*41*) found a correlation between total life time exposure to arsenic and excess mortality from lung cancer in a cohort study among workers at a U.S. copper smelter. From the data it could be estimated that exposure to airborne arsenic levels of around 50 $\mu g/m^3$ for more than 25 years corresponded to a nearly 3-fold excess mortality in lung cancer at an age over 65 years. This should be regarded as a high estimate of the risk as the assessment of exposure in the study was based on urinary excretion of arsenic in various departments of the smelter in 1973, and the exposure during the relevant time period was, according to the authors, probably five to ten times higher. Smoking habits were recorded from a sample of the subjects under study and apparently were not responsible for the excess mortality (*45*).

Ambient exposure to airborne arsenic has also been considered as a possible causative agent for lung cancer. Four epidemiological studies on populations living near point emission sources of arsenic to air have revealed moderate increases in lung cancer mortalities (*46-49*). Data on airborne arsenic concentrations was only reported in one of the studies (*47*) and information on the fraction of the population and lung cancer cases occupationally exposed (which would be expected to contribute to the excess lung cancer mortality) was only given in two of the studies (*48, 49*). In one of these (*49*) the excess mortality from lung cancer was no longer significant when workers employed at a smelter with high levels of airborne arsenic in some workplaces were excluded. It is not possible from the evidence presented to assess the role of arsenic in ambient air as a possible contributor to lung cancer in the community.

Histological classification of the lung cancers associated with occupational arsenic exposure has been performed in two of the above mentioned studies (*43, 47*). A tendency towards poorly differentiated carcinomas was evident in both reports, but this finding needs to be validated before any definite conclusions can be drawn.

Skin cancer has been associated with exposure to arsenic, mainly via drugs and drinking water (*50-53*). Only two reports lend themselves to discussions of dose-response relationships. Fierz (52) found a prevalence of 8% of skin cancer among 262 patients treated with arsenic for various chronic dermatoses. Arsenic was taken as Fowler's solution in inorganic trivalent form. An increased prevalence of skin cancer, predominantly of the multiple basal cell type, seemed to be present among patients who had ingested a total of 1000 ml or more of the solution (1000 ml corresponds to 7600 mg of arsenic). In this group the prevalence was over 20%. The prevalence of palmo-plantar hyperkeratosis, a characteristic feature of chronic arsenic poisoning increased with increasing dose of arsenic, i.e., from less than 10% in the lowest exposure group to over 90% among patients who had taken more than 9 g of As. Caution must be taken in the interpretation of the results in this study in view of the lack of a control group and the low response rate. Only 18% of the total number of patients intended for the study appeared for physical examination. Tseng (*53*) found a positive dose-response relationship between the content of arsenic in well water and skin cancer in a region of Taiwan with high concentrations of arsenic in well water. The content of arsenic in the well water ranged from 0.01 to 1.82 mg/l., with an average of about 0.5 mg/l. (*17*). A total of 428 cases of skin cancer was recorded in a population of 40, 421, giving an overall prevalence of about 1%. Assuming a daily intake of 2 liters of water, it could be estimated from the data presented that a total ingested dose of arsenic of about 20 g corresponded to a prevalence of skin cancer of approximately 6%. The increase in prevalence with increasing arsenic dose was partly due to a higher background prevalence of skin cancer in older age groups, although it was also evident that this could not explain the whole increase. Morton et al. (*54*) found no increase in incidence of skin cancer in an area in the U.S. with elevated levels of arsenic in water. As the concentrations of arsenic in the water were only moderately increased, ranging from 0.004 to 0.033 mg/l., the absence of a positive finding in this area does not necessarily contradict the previous data. The difference in nutritional status between Taiwanese and U.S. populations might also be of importance.

The neoplastic changes of the skin associated with exposure to arsenic are of several types, e.g., Bowen's disease, basal and squamous cell carcinoma. Bowen's disease, and basal cell carcinomas of arsenic origin are usually multiple and occur on all

parts of the body, often on the trunk (*52, 53*). Squamous cell carcinomas develop from the keratoses on the extremities. Histologically neither of the lesions possess any unique features when associated with arsenic (*54, 55*).

Angiosarcoma (or hemangioendothelioma) of the liver has been reported following exposure to arsenic via contaminated wine (*57*), drinking water (*58*), or Fowler's solution (*59-62*). The total ingested dose of arsenic could be estimated to be at least several grams. Only case reports of this rare tumour exist; the evidence, however, is highly suggestive of an etiologic role of arsenic.

Two epidemiological studies on occupational exposure to inorganic arsenic compounds have shown an increased mortality from cancer of the lymphatic and hematopoietic systems (*32, 43*). The number of deaths due to these causes was small in both studies and the findings have not been confirmed in other studies on occupational exposure or exposure via drinking water or drugs.

Experimental Studies

Inorganic arsenic compounds have been tested for carcinogenicity by various routes of exposure. In the following the different exposure routes will be treated separately. Finally investigations on carcinogenicity of some organic arsenic compounds will be discussed.

Only two preliminary reports are available on exposure to inorganic arsenic compounds via the respiratory tract. Ishinishi (*63*) gave 15 intratracheal instillations to rats of arsenic trioxide, copper ore and flue dust. The total arsenic doses ranged between 1.5 and 3 mg in the groups. One adenocarcinoma appeared in the group receiving the flue dust. When the exposure was combined with benzo(a)pyrene instillations a tendency towards a positive, although not statistically significant, interaction on tumour induction appeared. Only between seven and ten animals in the various groups survived the 15 instillations. Ivankovic et al. (*64*) were able to produce lung tumors in 9 of 15 rats surviving a single intratracheal instillation of a mixture of calcium arsenate, copper sulfate and calcium oxide. The exposure dose to As was 0.07 mg. No lung tumors appeared in a control group receiving an intratracheal instillation of 0.9% saline. This study indicates a carcinogenic potential of the mixture given; however, the role of arsenic cannot be evaluated in detail.

Several experimental studies have investigated the carcinogenicity of inorganic trivalent (*65-72*) and pentavalent (*68, 73, 74*) arsenic by oral administration. The compounds tested were arsenic trioxide (*65, 67, 70, 72*) sodium arsenite (*68, 69, 71*), potassium arsenite (*66*), sodium arsenate (*68, 73, 74*), and lead arsenate (*73, 74*). None of the studies provide positive evidence of arsenic carcinogenicity. Inorganic arsenic compounds have also been tested for carcinogenicity by skin application (*66, 67, 75-77*). Neither tumor-initiating nor tumor-promoting activities of arsenic could be demonstrated with arsenic trioxide (*76, 77*), sodium arsenite (*75*), potassium arsenite (*66, 78*) or sodium arsenate (*67*).

An experimental system involving weekly subcutaneous injections in mice with sodium arsenate (corresponding to a total of 10 mg As/kg body weight) indicated a role of arsenic for the development of lymphocytic leukemia and lymphoma both in treated animals and their offspring (*79*). The interpretation of the results in this experiment is difficult as the control animals were not sham treated by injection of the vehicle solution and because some exposed and control animals were still alive at time of reporting.

Organic arsenic compunds such as carbarsone (*80, 81*), arsanilic acid (*66, 82*) and 3-nitro-4-hydroxyphenylarsonic acid (*83*) have been tested for carcinogenicity. The exposure routes included peroral administration, skin application or subcutaneous injection. All studies were essentially negative, with the possible exception of one report on hepatomas in trout fed carbasone (*80*). This finding could not be evaluated in detail as the original data were not available.

Metabolism and Mechanism of Effects

The metabolism of various arsenic compounds has recently been reviewed (*1, 2*). Only data pertinent to the carcinogenicity of arsenic, e.g., *in vitro* and *in vivo* studies on interactions with the genetic material, will be mentioned here.

Inorganic arsenic compounds may interfere with DNA repair mechanisms. Incorporation of radioactively labelled nucleotides in dermal cells and lymphocytes was reduced by sodium arsenate (*84, 85*). Post-replication repair in bacteria was decreased by arsenite (*86*).

One mutagenicity test *in vitro* was positive for sodium arsenate, sodium arsenite and arsenic trichloride (*87*) while another failed to show any mutagenic response for inorganic trivalent and pentavalent arsenic (*88*).

An increased frequency of chromosomal aberrations has been observed among workers exposed to inorganic arsenic compounds, as well as in patients who had taken drugs containing arsenic (*85, 89*). Chromosomal aberrations have also been produced

in vitro by inorganic arsenic salts (*90, 91*).

No data are available on interactions of organic arsenic compounds with DNA.

Inorganic trivalent arsenic can inhibit enzymatic activity by reaction with the sulfhydryl groups of proteins (*92*). Both pentavalent and trivalent arsenic can inhibit mitochondrial respiration and uncouple oxidative phosphorylation. It has been suggested that arsenic may replace phosphorus in the DNA chain (*85*).

Discussion and Recommendations for Future Research

A peculiarity with arsenic carcinogenicity is the discrepancy between the findings in epidemiological and experimental animal studies. Only recently some preliminary animal data indicate a role of inorganic arsenic for the development of lung cancer. A reason for the negative findings may be that insoluble arsenic compounds have not previously been tested in animal models involving exposure via the respiratory system. The inability of eliciting a carcinogenic response with soluble nickel and chromium compounds is well known, while compounds of low solubility readily produce lung cancer. The presence of inorganic arsenic compounds of low solubility has been indicated in the workroom air of smelters and the arsenic pesticides were often insoluble compounds (*36, 93*). Recently, data have also appeared indicating a retention of arsenic in the lung long after cessation of occupational exposure (*94, 95*). Experimental animal studies on exposure of the respiratory system to inorganic arsenic compounds of low solubility are thus greatly needed. There is also a lack of studies on cocarcinogenicity of arsenic following exposure of the respiratory tract.

A particular retention of inorganic arsenic in skin is indicated in both man and animals (*96, 97*). This may be explained by its high content of sulfhydryl groups. Skin cancer has been observed in humans after peroral exposure to arsenic and thus occurs in an indirectly exposed tissue. The effect is then dependant on processes of absorption, metabolism and excretion. This implicates that direct skin application to animals may not be adequate in producing cancer. The difference in hair growth and distribution between man and laboratory animals may also be of importance when animals are exposed perorally. It can thus be anticipated that the establishment of an animal model for arsenic skin carcinogenesis may be difficult.

Exposure to airborne arsenic compounds take place in many occupational groups. In the U.S., it was estimated that approximately 660,000 employees were involved in the commercial cycle of arsenic in 1978 (*98*). An even larger number of people are exposed to increased levels due to tobacco smoking or by living in the vicinity of smelters or other point emission sources of arsenic. Coal combustion as a source of arsenic in ambient air should also be considered. It would be of great importance to characterize in detail the airborne arsenic compounds in these exposure situations, in order to make it possible to assess the carcinogenic potential of the various forms of arsenic in future epidemiological investigations.

One of the studies discussed above can be used for estimations of lung cancer risks from exposure to arsenic in ambient air, assuming a nonthreshold linear dose-response relationship. At a recent WHO Task Group Meeting it was estimated from the data by Pinto et al. (*41*) that a 25% excess in lung cancer incidence would result from lifetime (70 yr) exposure to 1 μg As/m^3 (WHO Environmental Health Criteria: Arsenic. World Health Organization, Geneva, to be published). It is obvious that this constitutes only a rough estimate and that the major determinant of lung cancer, e.g., smoking habits, also needs to be considered. An ambient airborne exposure level of 1 μg/m^3 has been reported in some areas around point emissions of arsenic to air (*99-101*). As noted above, a few epidemiological studies have indicated an increased mortality from lung cancer in populations living in such areas, however, the lack of exposure data in these studies precludes an evaluation of the role of arsenic. Further surveillance of the cancer morbidity in areas with high concentrations of airborne arsenic is needed.

In reports relating arsenic exposure via drugs and drinking water to cancer of the skin (*52, 53*) it is indicated that ingestion of several grams of arsenic increases the prevalence of skin cancer. The present WHO drinking water standard of 0.05 mg As/l., which would lead to a total ingestion of about 2·g during 50 yr (2 liters water/day), does not give a large safety margin. It was estimated by the WHO Task Group on Arsenic that the lifetime (70 yr) risk of skin cancer from arsenic in drinking water would be 25% per mg As/l. of water (WHO, loc. cit.). This would correspond to about a 1% risk of skin cancer at the present WHO drinking water standard. As skin cancer following peroral exposure to arsenic occurs in an indirectly exposed tissue, the assumption of a nonthreshold linear dose-response relationship may not be appropriate. There is a great need for further data on the occurrence of skin cancer in populations exposed to arsenic.

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