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Volume 23

Some Metals and Metallic Compounds

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ARSENIC AND ARSENIC COMPOUNDS

VOL.: 23 (1980) (p. 39)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Arsanilic acid, arsenic trioxide, sodium arsenite, potassium arsenite (Fowler's solution) and dimethylarsinic acid were tested by the oral route in mice. Lead arsenate, calcium arsenate, arsenic trioxide, sodium arsenate and sodium arsenite were tested by the oral route in rats. Sodium arsenate and arsenite were tested orally in dogs.

Potassium arsenite, arsenic trioxide and sodium arsenate were tested by skin application in mice. Sodium arsenite was tested by inhalation in mice; and arsenic trioxide, a calcium arsenate-copper mixture and copper ore or flue dust containing arsenic were tested by intratracheal administration in rats. Sodium arsenate was tested by intravenous administration in mice. Dimethylarsinic acid was tested by subcutaneous injection in mice; and calcium arsenate was tested by subcutaneous injection in rats. Metallic arsenic was tested by intramedullary injection in rats and rabbits.

In addition, sodium arsenate was tested by subcutaneous injection in mice in an experimental model which included exposures extending from the prenatal to the postnatal period.

Of all these studies, only one involving the subcutaneous administration to mice of sodium arsenate throughout pregnancy and one involving the intratracheal administration of a calcium arsenate-copper mixture to rats provided some evidence of a carcinogenic effect. However, all of the studies, both positive and negative, suffer from some inadequacies.

There is evidence that arsenite and arsenate cross the placenta in mammals. Sodium arsenate and arsenite have embryo-lethal effects and a teratogenic potential in several mammalian species. A variety of malformations can be induced. When given orally, high doses of arsenate are required to induce a small percentage of abnormalities.

The evidence that arsenic compounds cause mutations and allied effects in bacteria is inconclusive. However, arsenic compounds induce chromosomal aberrations and morphological transformation in mammalian cells.

5.2 Human data

A large number of cases of skin cancer have been reported among people exposed to inorganic arsenic through drugs, drinking-water or pesticides. The clinical presentation and sites of these tumours are different from those of cancers caused by other known skin carcinogens, suggesting that they are causally associated with exposure to arsenic. In one epidemiological study, skin cancer was positively correlated with high arsenic levels in the drinking-water; a second study showed no such correlation, however, the water arsenic levels were substantially lower than those in the first study.

Three cohort studies of workers manufacturing arsenical pesticides showed an excess mortality from respiratory cancer. A further cohort study of workers exposed to lead arsenate during spraying showed no excess mortality from any cancer; however, these people may have been exposed to lower levels than were manufacturing workers.

Case-control and cohort studies in copper smelters demonstrated a significantly increased mortality from respiratory cancer among the workers; however, smelter workers are exposed not only to arsenic compounds but also to other factors in the working environment, some of which may be carcinogenic. An attempt was

made to control for exposure to sulphur dioxide, copper, lead, nickel, selenium, antimony and bismuth in one case-control study, and the excess lung cancer remained. Smoking habits were examined in two of the studies and could not account for the excess.

The descriptive epidemiological studies on the mortality of people living in the neighbourhood of copper, lead and/or zinc smelters suggest increased mortality from respiratory cancer. One indicated excess mortality from lung cancer for both men and women, which was not associated with socioeconomic or geographical factors and could not be explained by occupational exposure alone. In the other, the excess mortality from respiratory cancer (which was present only for men) became insignificant when the deaths of workers in the smelter were excluded. These data are inadequate to evaluate the risk of nonoccupational exposure to low levels of airborne arsenic.

Four cases of haemangiosarcoma and one case of carcinoma of the liver have been reported in individuals exposed to medicinal arsenical preparations. One additional case of haemangiosarcoma of the liver was reported in association with general environmental exposure, and two further cases in workers exposed to arsenical pesticides; four cases of liver sarcoma and three of liver carcinoma were associated with vineyard exposure. An excess of lymphomas has been reported in workers in arsenic pesticide manufacture; and excesses of leukaemia, myeloma and colon and liver cancer have been found in smelter workers. An excess of oral cancers has been reported in a population exposed during the spinning of wool which may have been contaminated with arsenical sheep-dip.

Arsenite crosses the placenta. Smelter workers exposed during pregnancy to arsenic compounds (and possibly to other toxic substances) had an excess of infants with low birth weights, an increased frequency of abortions and an increased occurrence of multiple malformations.

An increased incidence of chromosomal aberrations was observed in patients treated with arsenical compounds and in workers exposed occupationally to arsenic compounds in a smelter environment.

5.3 Evaluation

There is *inadequate evidence* for the carcinogenicity of arsenic compounds in animals. There is sufficient evidence that inorganic arsenic compounds are skin and lung carcinogens in humans. The data suggesting an increased risk for cancer at other sites are inadequate for evaluation.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluations: [Vol. 1 \(1972\)](#); [Vol. 2 \(1973\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

LEAD AND LEAD COMPOUNDS

VOL.: 23 (1980) (p. 325)

5. Summary of Data Reported and Evaluation

5.1 Animal carcinogenicity data

Lead acetate, lead subacetate and lead phosphate are carcinogenic to rats and lead subacetate to mice: these compounds induced benign and malignant tumours of the kidney following oral or parenteral administration. Gliomas occurred in rats given lead acetate or lead subacetate by the oral route.

When tetraethyllead was administered by subcutaneous injection to neonatal mice, an increased incidence of lymphomas occurred in female animals only; additional studies are required before an evaluation of the carcinogenicity of this compound can be made.

No evaluation could be made of the carcinogenicity of lead arsenate, lead carbonate, lead oxide, metallic lead powder, lead naphthenate or lead nitrate.

Lead chloride gave positive results in DNA misincorporation tests. Lead acetate induced morphological transformations in Syrian hamster cells. There is no evidence that lead acetate or lead chloride induces mutations or allied effects in bacteria; some chromosomal aberration tests in mammalian systems (either *in vitro* or *in vivo*) have given positive results. There was insufficient evidence to evaluate the mutagenicity of organometallic lead compounds.

Lead salts have been reported to cross the placenta and to induce embryo- and fetomortality. They also have a teratogenic effect in some animal species. No teratogenic effects have been reported with exposure to organometallic lead compounds.

5.2 Human carcinogenicity data

Three epidemiological studies have been made of workers who were exposed to either lead and inorganic lead compounds or to tetraethyllead. One of the two studies on metallic lead workers showed no excess of cancer deaths. The other showed a slight (although not significant) excess of deaths due to cancers of the digestive system and respiratory system among smelter workers but not among workers in a lead-acid battery factory. As 60% of the members of the smelter workers cohort were hired after 1950, further follow-up of this cohort is warranted, in order to determine more reliably if there is an excess risk. In the third study, a slight but not significant increase of skin cancer was observed among workers exposed to tetraethyllead.

Several case-control studies have investigated the possibility that there is a causal link between paternal occupation and childhood cancer. The one study that specifically links lead-related occupations with the occurrence of Wilms' tumour cannot be considered to exhibit a causal link in view of the disputable appropriateness of the occupation subcategories used.

In nine studies, chromosomal aberrations were found in peripheral lymphocytes of lead-exposed populations whose blood lead levels ranged from 100-1000 $\mu\text{g/l}$. Negative results were obtained in six studies in which blood lead levels ranged from 40-500 $\mu\text{g/l}$.

In numerous reports, lead has been shown readily to cross the placenta. Good correlations have been reported between maternal and fetal blood levels. Adverse effects of lead on human reproduction, embryonic and fetal development and postnatal (e.g., mental) development have been reported.

5.3 Evaluation

Experimental and epidemiological data on metallic lead and organic lead compounds were either unavailable or inadequate, and no evaluation of their carcinogenicity was possible.

There is *sufficient evidence* that lead subacetate is carcinogenic to mice and rats and that lead acetate and lead phosphate are carcinogenic to rats. In the absence of adequate human data, it is reasonable, for practical purposes, to regard these compounds as if they presented a carcinogenic risk to humans.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluations: [Vol. 1 \(1972\)](#); [Vol 2 \(1973\) \(Tetraethyl- and tetramethyllead\) \(Arsenic and arsenic compounds\)](#); [Vol. 12 \(1976\)](#)

Subsequent evaluation: [Suppl. 7 \(1987\)](#)

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