ARSENIC AND ARSENIC COMPOUNDS (Group 1*)

A. Evidence for carcinogenicity to humans (*sufficient*)

Many cases of skin cancer have been reported among people exposed to arsenic through medical treatment with inorganic trivalent arsenic compounds, particularly Fowler's

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group (see also Methods, p. 38).

solution[1], and further reports have confirmed these findings[2-9]. In some instances, skin cancers have occurred in combination with other cancers, such as liver angiosarcoma (after six months' treatment with Fowler's solution giving a total intake of 0.24 g arsenic)[6], intestinal and bladder cancers[7] and meningioma[9]. Liver angiosarcomas have also been associated with medicinal exposure to arsenic[1,6,10].

Epidemiological studies of cancer following medical treatment with arsenic have shown an excess of skin cancers, but no clear association with other cancers has been obtained[1], as confirmed by a recent cohort study on individuals treated with Fowler's solution[11]. No relation was found between prostatic cancer and treatment of syphilis with arsenicals[12].

An association between environmental exposure to arsenic through drinking-water and skin cancer has been observed[1] and confirmed[13,14]; two cases of bladder cancer were also described, with latent periods of eight to 20 years[15]. The latent periods for two cases of skin cancer related to arsenic in drinking-water were 20 and 23 years, and the concentrations or uptake of arsenic were reported to be 1.2 and 1 mg per day, respectively, with an estimated total ingested dose of about 8 g in one study[14].

Epidemiological studies in areas with different frequencies of black-foot disease and where drinking-water contained 0.35-1.14 mg/l arsenic revealed elevated risks for cancers of the bladder, kidney, skin, lung, liver and colon in both men and women[16,17].

A case of liver angiosarcoma was reported in the 20-month-old child of an exposed worker living in the vicinity of a copper mine and smelter[18]. Four rather inconsistent studies describing the effect of air pollutants containing arsenic[1,19,20] were followed by further reports that indicated an effect on lung cancer incidence of arsenic in polluted air from smelters and pesticide production, with risk ratios of 2.0-2.5 near smelters[21,22]. Two further studies near smelters showed no clear effect[23,24].

Occupational exposure to inorganic arsenic, especially in mining and copper smelting, has quite consistently been associated with an increased risk of cancer[1]. A number of studies of smelter workers relate to populations that have been reported previously[1] and represent both partial[25-27] and total[28,29] updates. An almost ten-fold increase in the incidence of lung cancer was found in workers most heavily exposed to arsenic, and relatively clear dose-response relationships have been obtained with regard to cumulative exposure[29] and especially with 30-day ceiling levels[27]. Sulphur dioxide in the smelter environment appeared to play a minor role, if any, in the development of lung cancer[27]. Other forms of cancer were considered, but their incidences were not found to be consistently increased[28]. Other US smelter worker populations have been shown to have consistent increases in lung cancer incidence, as well as increases of about 20% in the incidence of gastrointestinal cancer and of 30% for renal cancer and haematolymphatic malignancies[30,31]. The observation in an earlier study of an increase in lung cancer risk among a population of Swedish smelter workers[1] has been confirmed, with a risk of six to eight fold among roasters[32].

A decrease in lung cancer risk after cessation of exposure to arsenic has been observed in some studies[30,33], possibly indicating a late-stage effect of arsenic[34,35].

With regard to histological type of lung cancer, a significant, relative excess of adeno-carcinomas and a slight excess of oat-cell cancers were seen among smelter workers[36].

A multiplicative effect of arsenic exposure and smoking was observed among Swedish smelter workers[37]. A slightly increased risk was also indicated for exposure to sulphur dioxide in this study. Other studies have shown a lesser influence of smoking[25,33].

Relatively high concentrations of arsenic, as well as of antimony, cadmium, lead and lanthanum, were found in lung tissue of lung cancer cases, whereas the concentrations of selenium were low[38,39].

An approximately two-fold risk for lung and stomach cancers has been observed among (fine) glass workers with some exposure to arsenic but who were also exposed to other potentially carcinogenic metals and to asbestos. Stomach cancer was especially frequent among glass blowers, suggesting an association with oral contact with contaminated pipes[40].

Some excess of lung cancer was seen among female hat makers exposed to arsenic, but also to mercury[41].

Additional reports have suggested an increased risk of skin and lung cancers in vineyard workers[42,43] and have also suggested that ingestion of arsenic in wine byproducts may have contributed to this increase[42]. One case of lung cancer was reported in an individual involved in the production of lead arsenate and calcium arsenate[44]; multiple skin keratoses and chronic lymphatic leukaemia were reported in one person involved in the production of copper acetoarsenate[45].

Three studies of two populations of workers in pesticide production showed an increased risk ratio for lung cancer — up to about 3 — and some excess of malignant neoplasms of the lymphatic and haematopoietic tissues[1,46]. In a study of liver angiosarcomas, two of 26 cases had been in contact with arsenical pesticides occupationally[1].

B. Evidence for carcinogenicity to animals (*limited*)

Various arsenic compounds have been tested for carcinogenicity by perinatal treatment of mice, by intratracheal instillation in hamsters and rats and by implantation into the stomach of rats. Arsenic trioxide produced lung adenomas in mice after perinatal treatment[47], and induced low incidences of carcinomas, adenomas, papillomas and adenomatoid lesions of the respiratory tract in hamsters after its intratracheal instillation[48,49]. It induced a low incidence of adenocarcinomas at the site of its implantation into the stomach of rats[50]. A high incidence of lung carcinomas was induced in rats following a single intratracheal instillation of a pesticide mixture containing calcium arsenate[1]. Intratracheal instillations of calcium arsenate into hamsters resulted in a borderline increase in the incidence of lung adenomas, while no such effect was observed with arsenic trisulphide[51]. Oral administration of sodium arsenite enhanced the incidence of renal tumours induced in rats by intraperitoneal injection of *N*-nitrosodiethylamine[52].

No adequate data on the carcinogenicity of organic arsenicals were available to the Working Group.

C. Other relevant data

In one study of people exposed to trivalent arsenic in drinking-water, no increase in the incidence of sister chromatid exchanges or chromosomal aberrations was observed. A number of other studies published on people occupationally exposed to arsenic or patients treated with arsenic have shown increased levels of chromosomal aberrations or sister chromatid exchanges. The interpretation of these results remains uncertain because of methodological problems[53].

Trivalent arsenic did not induce dominant lethal mutations in mice, but it produced a small increase in the incidence of chromosomal aberrations and micronuclei in bone-marrow cells of mice treated *in vivo*. It induced chromosomal aberrations and sister chromatid exchanges in human and rodent cells *in vitro*, and transformation of Syrian hamster embryo cells; it did not induce mutation in rodent cells *in vitro*. It induced gene conversion in yeast but did not cause mutation or induce prophage in bacteria[53].

Pentavalent arsenic induced chromosomal aberrations in human and rodent cells *in vitro*; equivocal results were obtained in assays for the induction of sister chromatid exchanges. It induced transformation in Syrian hamster embryo cells but did not induce mutation or DNA strand breaks in rodent cells *in vitro*. It induced gene conversion in yeast but did not induce mutation in bacteria[53].

References

[1]*IARC Monographs*, *23*, 39-141, 1980

[2]Heddle, R. & Bryant, G.D. (1983) Small cell lung carcinoma and Bowen's disease 40 years after arsenic ingestion. *Chest*, *84*, 776-777

[3]Cowlishaw, J.L., Pollard, E.J., Cowen, A.E. & Powell, L.W. (1979) Liver disease associated with chronic arsenic ingestion. *Aust. N.Z. J. Med.*, *9*, 310-313

[4]Kastl, J. & Horáček, J. (1980) Arning's carcinoids in a psoriatic receiving long-term arsenic treatment (Czech.). *Čs. Dermatol.*, *55*, 89-93

[5]Kastl, J. & Horáček, J. (1985) Multiple basal cell carcinomas after long-term intake of arsenic (Ger.). *Dermatol. Monatsschr.*, *171*, 158-161

[6]Roat, J.W., Wald, A., Mendelow, H. & Pataki, K.I. (1982) Hepatic angiosarcoma associated with short-term arsenic ingestion. *Am. J. Med.*, *73*, 933-936

[7]von Roemeling, R., Hartwich, G. & König, H. (1979) Occurrence of tumours at different locations after arsenic therapy (Ger.). *Med. Welt*, *30*, 1928-1929

[8]Southwick, G.J. & Schwartz, R.A. (1979) Arsenically associated cutaneous squamous cell carcinoma with hypercalcemia. *J. surg. Oncol.*, *12*, 115-118

[9]Weiss, J. & Jänner, M. (1980) Multiple basal cell carcinomas and meningioma after long-term arsenic therapy (Ger.). *Hautarzt*, *31*, 654-656

[10]Falk, H., Caldwell, G.G., Ishak, K.G., Thomas, L.B. & Popper, H. (1981) Arsenic-related hepatic angiosarcoma. *Am. J. ind. Med.*, *2*, 43-50

[11]Cuzick, J., Evans, S., Gillman, M. & Price Evans, D.A. (1982) Medicinal arsenic and internal malignancies. *Br. J. Cancer*, *45*, 904-911

[12]Lees, R.E.M., Steele, R. & Wardle, D. (1985) Arsenic, syphilis, and cancer of the prostate. *J. Epidemiol. Commun. Health*, *39*, 227-230

[13]Armando, V.L. & Angel, A.O. (1979) Chronical arsenicism (Span.). *Bol. med. Hosp. Infant., 36*, 849-861

[14]Zaldívar, R., Prunés, L. & Ghai, G.L. (1981) Arsenic dose in patients with cutaneous carcinomata and hepatic haemangio-endothelioma after environmental and occupational exposure. *Arch. Toxicol., 47*, 145-154

[15]Nagy, G., Németh, A., Bodor, F. & Ficsór, E. (1980) Urinary bladder cancer induced by chronic arsenic poisoning (Hung.). *Orv. Hetil., 121*, 1009-1011

[16]Chen, C.-J., Chuang, Y.-C., Lin, T.-M. & Wu, H.-Y. (1985) Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. *Cancer Res., 45*, 5895-5899

[17]Chen, C.-J., Chuang, Y.-C., You, S.-L., Lin, T.-M. & Wu, H.-Y. (1986) A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. *Br. J. Cancer, 53*, 399-405

[18]Falk, H., Herbert, J.T., Edmonds, L., Heath, C.W., Jr, Thomas, L.B. & Popper, H. (1981) Review of four cases of childhood hepatic angiosarcoma — elevated environmental arsenic exposure in one case. *Cancer, 47*, 382-391

[19]Brown, L.M., Pottern, L.M. & Blot, W.J. (1984) Lung cancer in relation to environmental pollutants emitted from industrial sources. *Environ. Res., 34*, 250-261

[20]Pershagen, G. (1985) Lung cancer mortality among men living near an arsenic-emitting smelter. *Am. J. Epidemiol., 122*, 684-694

[21]Matanoski, G.M., Landau, E., Tonascia, J., Lazar, C., Elliott, E.A., McEnroe, W. & King, K. (1981) Cancer mortality in an industrial area of Baltimore. *Environ. Res., 25*, 8-28

[22]Matanoski, G.M., Landau, E., Tonascia, J. & Elliott, E.A. (1983) Epidemiologic approach to arsenic pollution. *J. Univ. occup. environ. Health, 5 (Suppl.)*, 117-124

[23]Greaves, W.W., Rom, W.N., Lyon, J.L., Varley, G., Wright, D.D. & Chiu, G. (1981) Relationship between lung cancer and distance of residence from nonferrous smelter stack effluent. *Am. J. ind. Med., 2*, 15-23

[24]Rom, W.N., Varley, G., Lyon, J.L. & Shopkow, S. (1982) Lung cancer mortality among residents living near the El Paso smelter. *Br. J. ind. Med., 39*, 269-272

[25]Higgins, I., Welch, K., Oh, M., Bond, G. & Hurwitz, P. (1981) Influence of arsenic exposure and smoking on lung cancer among smelter workers: a pilot study. *Am. J. ind. Med., 2*, 33-41

[26]Lubin, J.H., Pottern, L.M., Blot, W.J., Tokudome, S., Stone, B.J. & Fraumeni, J.R., Jr (1981) Respiratory cancer among copper smelter workers: recent mortality statistics. *J. occup. Med., 23*, 779-784

[27]Welch, K., Higgins, I., Oh, M. & Burchfiel, C. (1982) Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. *Arch. environ. Health, 37*, 325-335

[28]Lee-Feldstein, A. (1983) Arsenic and respiratory cancer in humans: follow-up of copper smelter employees in Montana. *J. natl Cancer Inst., 70*, 601-609

[29]Lee-Feldstein, A. (1986) Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. *J. occup. Med., 28*, 296-302

[30]Enterline, P.E. & Marsh, G.M. (1980) Mortality studies of smelter workers. *Am. J. ind. Med., 1*, 251-259

[31]Enterline, P.E. & Marsh, G.M. (1982) Cancer among workers exposed to arsenic and other substances in a copper smelter. *Am. J. Epidemiol., 116*, 895-911

[32]Wall, S. (1980) Survival and mortality pattern among Swedish smelter workers. *Int. J. Epidemiol., 9*, 73-87

[33]Pinto, S.S., Henderson, V. & Enterline, P.E. (1978) Mortality experience of arsenic-exposed workers. *Arch. environ. Health, 33*, 325-331

[34]Brown, C.C. & Chu, K.C. (1983) Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. *J. natl Cancer Inst., 70*, 455-463

[35]Brown, C.C. & Chu, K.C. (1983) A new method for the analysis of cohort studies: implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. *Environ. Health Perspect., 50*, 293-308

[36]Wicks, M.J., Archer, V.E., Auerbach, O. & Kuschner, M. (1981) Arsenic exposure in a copper smelter as related to histological type of lung cancer. *Am. J. ind. Med., 2*, 25-31

[37]Pershagen, G., Wall, S., Taube, A. & Linnman, L. (1981) On the interaction between occupational arsenic exposure and smoking and its relationship to lung cancer. *Scand. J. Work Environ. Health, 7*, 302-309

[38]Wester, P.O., Brune, D. & Nordberg, G. (1981) Arsenic and selenium in lung, liver, and kidney tissue from dead smelter workers. *Br. J. ind. Med., 38*, 179-184

[39]Gerhardsson, L., Brune, D., Nordberg, I.G.F. & Wester, P.O. (1985) Protective effect of selenium on lung cancer in smelter workers. *Br. J. ind. Med., 42*, 617-626

[40]Wingren, G. & Axelson, O. (1985) Mortality pattern in a glass producing area in SE Sweden. *Br. J. ind. Med., 42*, 411-414

[41]Buiatti, E., Kriebel, D., Geddes, M., Santucci, M. & Pucci, N. (1985) A case control study of lung cancer in Florence, Italy. I. Occupational risk factors. *J. Epidemiol. Commun. Health, 39*, 244-250

[42]Lüchtrath, H. (1983) The consequences of chronic arsenic poisoning among Moselle wine growers. Pathoanatomical investigations of post-mortem examinations between 1960 and 1977. *J. Cancer Res. clin. Oncol., 105*, 173-182

[43]Thiers, H., Colomb, D., Moulin, G. & Colin, L. (1967) Arsenical skin cancer in vineyards in the Beaujolais (Fr.). *Ann. Dermatol., 94*, 133-158

[44]Horiguchi, S. (1979) A case of lung cancer due to exposure to arsenical compounds in an insecticides factory. (Studies on lead arsenate poisoning. Part 4). *Osaka City med. J., 25*, 45-51

[45]Leyh, F. & Rothlaender, J.P. (1985) Multiple bowenoid keratoses due to arsenic (Ger.). *Dermatosen, 33*, 99-101

[46]Mabuchi, K., Lilienfeld, A.M. & Snell, L.M. (1980) Cancer and occupational exposure to arsenic: a study of pesticide workers. *Prev. Med., 9*, 51-77

[47]Rudnay, P. & Börzsönyi, M. (1981) The tumorigenic effect of treatment with arsenic trioxide (Hung.). *Magyar Onkol., 25*, 73-77

[48]Ishinishi, N., Yamamoto, A., Hisanaga, A. & Inamasu, T. (1983) Tumorigenicity of arsenic trioxide to the lung in Syrian golden hamsters by intermittent instillations. *Cancer Lett., 21*, 141-147

[49]Pershagen, G., Nordberg, G. & Björklund, N.-E. (1984) Carcinomas of the respiratory tract in hamsters given arsenic trioxide and/or benzo[*a*]pyrene by the pulmonary route. *Environ. Res., 34*, 227-241

[50]Katsnelson, B.A., Neizvestnova, Y.M. & Blokhin, V.A. (1986) Stomach carcinogenesis induction by chronic treatment with arsenic (Russ.). *Vopr. Onkol., 32*, 68-73

[51]Pershagen, G. & Björklund, N.-E. (1985) On the pulmonary tumorigenicity of arsenic trisulfide and calcium arsenate in hamsters. *Cancer Lett., 27*, 99-104

[52]Shirachi, D.Y., Johansen, M.G., McGowan, J.P. & Tu, S.-H. (1983) Tumorigenic effect of sodium arsenite in rat kidney. *Proc. West. pharmacol. Soc., 26*, 413-415

[53]*IARC Monographs, Suppl. 6*, 71-76, 1987