CADMIUM AND CADMIUM COMPOUNDS (Group 2A)

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

Exposure to cadmium (primarily as the oxide) has been associated with increased risks of prostatic and respiratory cancers[1,2]. In one follow up of an investigation of 269 cadmium-nickel battery workers (see also summary for nickel, p. 264) and 94 cadmium-copper alloy factory workers in Sweden, additional cases of nasopharyngeal, colorectal, prostatic and lung cancer were reported[3]. In another study, the mortality of 347 cadmium-copper alloy workers in the UK who were exposed to cadmium fume was compared with that of workers exposed indirectly to cadmium but also to arsenic (see p. 100). A third group of iron or brass founders was included, and the mortality rates were compared separately with statistics for the general population. Significantly increased mortality from prostatic, genito-urinary and lung cancers was seen in people working in the vicinity, but not in the cadmium workers themselves. Insufficient information was given regarding the movement of men between or out of the three adjacent plants to assess the relative contributions of arsenic, cadmium and smoking to the results (which run counter to those of most other studies)[4].

Follow-up studies of four populations of cadmium-exposed workers have been reported more recently. In the UK, excess lung cancer (16 observed, 11.3 expected) was noted among 6995 male workers employed at one of 17 plants in a group that had had 'ever medium' exposure for ten years or more; and an excess risk of prostatic cancer was seen in a group that had had 'always low' exposures for ten years or more (15 observed, 11.0 expected)[5].

Using a case-control approach for these cases of prostatic cancer and for those in two other UK cohorts (of cadmium-nickel battery and cadmium-copper alloy workers), 39 cases were reported to have an odds ratio for cadmium exposure of 1.6 for 'ever medium' compared to 'always low' exposure levels and 1.4 for 'ever high' compared to 'always low' exposures; a similar approach for nine renal cancer patients revealed no elevation of odds ratio[6]. In a cohort of 522 male Swedish cadmium workers, eight cases of lung cancer were reported, resulting in a statistically nonsignificantly elevated standardized mortality ratio (SMR) for five years' exposure and ten or more years' latency. For prostatic cancer, four cases resulted in a statistically nonsignificant excess for the same exposure and latent periods[7].

In the USA, a follow-up study of 602 white male cadmium smelter workers with at least six months of production work between 1940 and 1969 was extended to 1978. The SMR (95% confidence interval) for respiratory cancer deaths was 165 (101-254), based on 20 deaths, and that for lung cancer, 157 (93-249), based on 18 deaths. Concomitant exposure to arsenic was especially high up to 1925. Reanalysis of lung cancer mortality for workers employed before or after 1 January 1926 revealed SMRs of 714 (195-1829) for the pre-1926 group (four cases) and 229 (131-371) for the post-1926 group with two or more years employment (16 deaths). For the post-1926 group (576 workers), a significant trend was noted for cumulative cadmium exposure and lung cancer mortality. Although the data on smoking are inadequate, and arsenic exposure continued after 1926, albeit at a lower level, the authors contend that these factors do not account for the excess lung cancer rates noted in the study. The number of prostatic cancers was unchanged from the earlier study (3 observed, 2.2 expected)[8]. Further reports of a UK population of 3025 (2559 male and 466 female) cadmium-nickel battery workers showed an excess of lung cancer in groups exposed for 18 years or more[9]. The excess mortality from prostatic cancer was accounted for by the original four cases described in 1967[1].

Potential confounding factors in these studies, such as smoking and exposure to nickel and arsenic, do not appear to account for the excess of lung cancer deaths. For prostatic cancer, the risk appears to be debatable, especially when the four hypothesis-generating UK cases from 1967 are removed from the analysis.

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

Cadmium chloride, oxide, sulphate and sulphide produced local sarcomas in rats after their subcutaneous injection, and cadmium powder and cadmium sulphide produced local sarcomas in rats following their intramuscular administration. Cadmium chloride and cadmium sulphate produced testicular tumours in mice and rats after their subcutaneous administration[1,10]. In one experiment, cadmium chloride administered subcutaneously to rats produced local sarcomas, testicular tumours and a significant increase in the incidence of pancreatic islet-cell tumours[11]. Cadmium chloride produced a dose-dependent increase in the incidence of lung carcinomas in rats after exposure by inhalation[12,13] and a low incidence (5/100) of prostatic carcinomas after injection into the ventral prostate[14]. Administration of up to 50 mg/kg (ppm) cadmium chloride in the diet to rats did not increase the incidence of tumours[15]. Cadmium acetate was not carcinogenic in a mouse-lung adenoma assay[16].

C. Other relevant data

People exposed occupationally to cadmium (in an alkaline-battery factory and in the manufacture of cadmium pigments) did not exhibit increased frequencies of chromosomal aberrations in their peripheral lymphocytes. These findings contrast markedly with the positive results obtained on workers exposed in zinc smelting plants and on people environmentally intoxicated by cadmium; these people were also exposed to other compounds. In one study, sister chromatid exchanges were not induced in people exposed to cadmium in the environment[17].

Cadmium compounds did not produce dominant lethal effects in mice or rats nor did they increase the frequencies of chromosomal aberrations or micronuclei in mice treated *in vivo*. Cadmium compounds induced aneuploidy in hamsters but not in mice treated *in vivo*. They did not induce sister chromatid exchanges in human cells *in vitro*, and studies of chromosomal aberrations gave inconclusive results. They induced transformation of cultured rodent cells in several test systems and induced chromosomal aberrations but not sister chromatid exchanges in rodent cells *in vitro*. Cadmium compounds induced DNA single-strand breaks in human and rodent cells, and there is conflicting evidence that they produced mutation in rodent cells *in vitro*. Cadmium compounds did not induce aneuploidy or somatic or sex-linked recessive lethal mutations in *Drosophila*. They induced mitotic recombination in yeast, but they did not induce mutation in yeast or bacteria, nor did they induce prophage in bacteria[17].

References

[1]*IARC Monographs, 11*, 39-74, 1976

[2]Piscator, M. (1981) Role of cadmium in carcinogenesis with special reference to cancer of the prostate. *Environ. Health Perspect., 40*, 107-120

[3]Kjellström, T., Friberg, L. & Rahnster, B. (1979) Mortality and cancer morbidity among cadmium-exposed workers. *Environ. Health Perspect., 28*, 199-204

[4]Holden, H. (1980) *Further mortality studies on workers exposed to cadmium fume.* In: *Seminar on Occupational Exposure to Cadmium, March 1980*, London, Cadmium Association

[5]Kazantzis, G. & Armstrong, B.G. (1983) *A mortality study of cadmium workers in seventeen plants in England.* In: Wilson, D. & Volpe, R.A., eds, *Proceedings of the Fourth International Cadmium Conference, Munich, 1982*, London, Cadmium Association, pp. 139-142

[6]Armstrong, B.G. & Kazantzis, G. (1985) Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: a case control study. *Br. J. ind. Med., 42*, 540-545

[7]Elinder, C.G., Kjellström, T., Hogstedt, C., Andersson, K. & Spång, G. (1985) Cancer mortality of cadmium workers. *Br. J. ind. Med., 42*, 651-655

[8]Thun, M.J., Schnorr, T.M., Smith, A.B., Halperin, W.E. & Lemen, R.A. (1985) Mortality among a cohort of US cadmium production workers — an update. *J. natl Cancer Inst., 74*, 325-333

[9]Sorahan, T. (1983) *A further mortality study of nickel-cadmium battery workers.* In: Wilson, D. & Volpe, R.A., eds, *Proceedings of the Fourth International Cadmium Conference, Munich, 1982*, London, Cadmium Association, pp. 143-148

[10]Reddy, J., Svoboda, D., Azarnoff, D. & Dawar, R. (1973) Cadmium-induced Leydig cell tumors of rat testis: morphologic and cytochemical study. *J. natl Cancer Inst., 51*, 891-903

[11]Poirier, L.A., Kasprzak, K.S., Hoover, K.L. & Wenk, M.L. (1983) Effects of calcium and magnesium acetates on the carcinogenicity of cadmium chloride in Wistar rats. *Cancer Res., 43*, 4575-4581

[12]Takenaka, S., Oldiges, H., König, H., Hochrainer, D. & Oberdörster, G. (1983) Carcinogenicity of cadmium chloride aerosols in W rats. *J. natl Cancer Inst., 70*, 367-373

[13]Oldiges, H., Hochrainer, D., Takenaka, S., Oberdörster, G. & König, H. (1984) Lung carcinomas in rats after low level cadmium inhalation. *Toxicol. environ. Chem., 9*, 41-51

[14]Hoffmann, L., Putzke, H.-P., Kampehl, H.-J., Russbült, R., Gase, P., Simonn, C., Erdmann, T. & Huckstorf, C. (1985) Carcinogenic effects of cadmium on the prostate of the rat. *J. Cancer Res. clin. Oncol., 109*, 193-199

[15]Löser, E. (1980) A 2 year oral carcinogenicity study with cadmium on rats. *Cancer Lett., 9*, 191-198

[16]Shimkin, M.B., Stoner, G.D. & Theiss, J.C. (1978) Lung tumor response in mice to metals and metal salts. *Adv. exp. Med. Biol., 91*, 85-91

[17]*IARC Monographs, Suppl. 6*, 132-135, 1987