ASBESTOS* (Group 1)

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

Numerous reports from several countries have described cases or series of pleural and peritoneal mesotheliomas in relation to occupational exposure to various types and mixtures of asbestos (including talc containing asbestos), although occupational exposures have not been identified in all cases[1-21]. Mesotheliomas of the tunica vaginalis testis and of the pericardium have been reported in persons occupationally exposed to asbestos[22-24].

Environmental exposure either in the houses of asbestos workers or in the neighbourhood of asbestos mines or factories has been noted in some of the cases[1,2,4-6,9,11,25,26]. It has been estimated that a third of the mesotheliomas occurring in the USA may be due to nonoccupational exposure[27]. In a study from Israel, the incidence of mesothelioma was found to be higher among those born in the USA or in Europe relative to those born in Israel[9].

In some of these case reports and in other studies, asbestos fibres were identified in the lung[5,6,11,28-32]. Amphibole fibres usually predominated, but in a few cases mainly or only chrysotile fibres were found[6,28].

The long latency required for mesothelioma to develop after asbestos exposure has been documented in a number of publications[11,13,26,28,33-37]. An increasing proportion of cases has been seen with increasing duration of exposure[36].

A number of epidemiological studies of respiratory cancer and mesothelioma have been reported in relation to exposure to unspecified or complex mixtures of asbestos in shipyard work[38-45]. The risk ratio for lung cancer has usually been moderately increased, both in these studies and in studies on various other occupational groups with similarly job-related but unspecified or complex asbestos exposures[35,46-54]. Risk ratios of about 2-5 have been reported in some studies, but the ratio was considerably higher in one rather small study[55] and did not exceed unity in another[42]. In one study, individuals suffering from asbestosis had a considerably greater risk for lung cancer, with a risk ratio of 9.0[56]. In some of the studies referred to, a number of mesotheliomas were also observed[41,42,44,47,51,53,55]. Abdominal mesotheliomas have sometimes been mistaken for pancreatic cancer[57]. Mesothelioma cases have been observed to have a relatively lower fibre content in the lungs than lung cancer cases[32].

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*Actinolite, amosite, anthophyllite, chrysotile, crocidolite, tremolite

Laryngeal cancer has been considered in two case-control studies, resulting in risk ratios of 2.4 and 2.3 that relate to shipyard work and unspecified exposure, respectively[40,58]. A cohort study of insulation workers showed a relative risk of 1.9, based on nine cases[57]. A case series indicated a high frequency of exposure to asbestos, especially in low-grade smokers[59]. A risk ratio of 3.2 for laryngeal cancer was reported among chrysotile miners in an area with generally high incidence[60], but no increased risk was seen in a cohort of workers with exposure to crocidolite[61]. Two correlation studies have also indicated a relationship between laryngeal cancer and exposure to asbestos[39,62].

Mesotheliomas related to shipyard work and other exposures, including household contact with asbestos workers, have also been subject to epidemiological studies[36,63-67], resulting in risk ratios of about 3-15 in comparison with background rates not clearly referable to asbestos exposure.

Some studies have specifically considered environmental exposures with reference to mesotheliomas[66,67]. Three correlation studies and one case-control study considering exposure to piped drinking-water[68-71] did not show consistently increased risks for any type of cancer, whereas another study[72] considering chrysotile contamination mainly from natural sources gave some indication of an increase in the incidence of peritoneal and stomach cancers in persons of each sex, although no other cancer site was consistent in this respect.

Exposure to crocidolite has been studied with regard to risk of lung cancer[61,73-76], and risk ratios of about 2-3 have been reported. Three lung cancers and two mesotheliomas occurred in 20 individuals after one year of high exposure to crocidolite; at least 17 of the cases had asbestos-induced lung changes on X-ray films[77].

One study[78] of histological types of lung cancers showed that among persons exposed to crocidolite 45.7% of cases were squamous-cell carcinomas, as compared to 35.2% among unexposed persons. In the context of unspecified and complex exposures, small-cell carcinoma was found to be relatively more prevalent than other forms[50].

Exposure to chrysotile was found in some studies to result in virtually no increase in risk ratio[60,79-81], or a slightly elevated relative risk of lung cancer[82-86]. Somewhat higher risk ratios, up to 2.5, 3.5 and 2, respectively, were obtained in one study of chrysotile miners[87] and in two independent studies from one asbestos [chrysotile] textile plant[88,89], the latter being the more comprehensive. With regard to mesotheliomas, one study suggested a particularly high risk of combined exposure to chrysotile and amphiboles (risk ratio, 61), thus almost multiplying the risk ratios (6 and 12, respectively) of exposures to chrysotile and to amphiboles alone[90]. Another study showed no mesothelioma among a large worker population with exposure to chrysotile only[91].

A slight excess of lung cancer and some mesotheliomas appeared in some groups with mixed exposures involving amosite, chrysotile and crocidolite[92-94]. Exposure predominantly to amosite, but also to chrysotile, was reported to be the probable cause of at least four of five mesotheliomas (one peritoneal) observed in a UK insulation-board factory[95]. One cohort with exposure to cummingtonite-grunerite, which is closely related to amosite, had no clear excess of lung cancer, although one case of mesothelioma was observed[96].

Exposure to tremolite and actinolite has been the subject of a few studies in investigations of vermiculite mining and milling[97,98] and environmental exposure[99]. The studies of miners indicated a risk ratio for lung cancer of up to approximately six fold. Deaths from mesothelioma were found in the occupational studies, whereas the study of environmental exposure showed no increased risk, although pleural plaques were reported. Publication of one case report of a mesothelioma after environmental exposure suggests that tremolite was of etiological importance[31].

Cancers other than of the lung or mesothelioma have been considered in many studies[1,17,35,39,41-44,48,51,55,60-62,68-70,72-74,76,83,87,89,92,93,96,97,99-108]. Some indicated an approximately two-fold risk with regard to gastrointestinal cancer in connection with shipyard work[41,43], and some increased risk was also seen in association with exposure to both chrysotile and crocidolite[103], to crocidolite[61,74] or to chrysotile[87]. Cancer of the colon and rectum was associated with asbestos exposure during chrysotile production, with an approximately two-fold risk[87]; a similar excess was found for unspecified asbestos exposure[104]. Some excess of ovarian cancer has been reported in two studies[73,76] but not in another[92]; exposure to crocidolite was probably more predominant in the studies that showed excesses. Bile-duct cancer appeared in excess in one study based on record-linking[105], and large-cell lymphomas of the gastrointestinal tract and oral cavity appeared to be strongly related to asbestos exposure in one small study covering 28 cases and 28 controls, giving a risk ratio of 8; however, ten cases and one control also had a history of malaria[106]. An excess of lymphopoietic and haematopoietic malignancies has been reported in plumbers, pipe-fitters, sheet-metal workers and others with asbestos exposure[17,54,107,108].

The relationship between asbestos exposure and smoking indicates a synergistic effect of smoking with regard to lung cancer[1]. Further evaluations indicate that this synergistic effect is close to a multiplicative model[52,109]. As noted previously[1], the risk of mesothelioma appears to be independent of smoking[47,66], and a significantly decreasing trend in risk was observed with the amount smoked in one study[65].

The studies of the carcinogenic effect of asbestos exposure, including evidence reviewed earlier[1], show that occupational exposure to chrysotile, amosite and anthophyllite asbestos and to mixtures containing crocidolite results in an increased risk of lung cancer, as does exposure to minerals containing tremolite and actinolite and to tremolitic material mixed with anthophyllite and small amounts of chrysotile. Mesotheliomas have been observed after occupational exposure to crocidolite, amosite, tremolitic material and chrysotile asbestos. Gastrointestinal cancers occurred at an increased incidence in groups occupationally exposed to crocidolite, amosite, chrysotile or mixed fibres containing crocidolite, although not all studies are consistent in this respect. An excess of laryngeal cancer has also been observed in some groups of exposed workers. No clear excess of cancer has been associated with the presence of asbestos fibres in drinking-water. Mesotheliomas have occurred in individuals living in the neighbourhood of asbestos factories and mines and in people living with asbestos workers.

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

Asbestos has been tested for carcinogenicity by inhalation in rats, by intrapleural administration in rats and hamsters, by intraperitoneal injection in mice, rats and hamsters and by oral administration in rats and hamsters. Chrysotile, crocidolite, amosite, anthophyllite and tremolite produced mesotheliomas and lung carcinomas in rats after inhalation[1,110,111] and mesotheliomas following intrapleural administration[1,112]. Chrysotile, crocidolite, amosite and anthophyllite induced mesotheliomas in hamsters following intrapleural administration[1]. Intraperitoneal administration of chrysotile, crocidolite and amosite induced peritoneal tumours, including mesotheliomas, in mice[1,113] and rats[1,111,114]. Given by the same route, crocidolite produced abdominal tumours in hamsters[115], and tremolite and actinolite produced abdominal tumours in rats[110,116-118]. A statistically significant increase in the incidence of malignant tumours was observed in rats given filter material containing chrysotile orally[1]. In more recent studies, tumour incidence was not increased by oral administration of amosite or tremolite in rats[119], of amosite in hamsters[120,121] or of chrysotile in hamsters[121]. In two studies in rats, oral administration of chrysotile produced a low incidence of benign adenomatous polyps of the large intestine in males (9/250 *versus* 3/254 pooled controls)[122] and of mesenteric haemangiomas (4/22 *versus* 0/47 controls)[123]. Synergistic effects were observed following intratracheal administration of chrysotile and benzo[*a*]pyrene to rats and hamsters[1] and of intratracheal administration of chrysotile and subcutaneous or oral administration of *N*-nitrosodiethylamine to hamsters[124].

C. Other relevant data

Insulation workers exposed to asbestos 'displayed a marginal increase' in the incidence of sister chromatid exchanges in lymphocytes in one study[125].

Chrysotile did not induce micronuclei in bone-marrow cells of mice or chromosomal aberrations in bone-marrow cells of rhesus monkeys treated *in vivo*. In cultured human cells, conflicting results were reported for the induction of chromosomal aberrations and negative results for the induction of sister chromatid exchanges by chrysotile and crocidolite; amosite and crocidolite did not induce DNA strand breaks, and crocidolite was not mutagenic. Amosite, anthophyllite, chrysotile and crocidolite induced transformation of Syrian hamster embryo cells, chrysotile and crocidolite transformed BALB/c 3T3 mouse cells, and chrysotile transformed rat mesothelial cells. Neither amosite nor crocidolite transformed CH3 10T1/2 cells. In cultured rodent cells, amosite, anthophyllite, chrysotile and crocidolite induced chromosomal aberrations, and amosite, chrysotile and crocidolite induced sister chromatid exchanges; chrysotile and crocidolite induced aneuploidy and micronuclei. Chrysotile induced unscheduled DNA synthesis in rat hepatocytes. Amosite, chrysotile and crocidolite were inactive or weakly active in inducing mutation in rodent cells *in vitro*; none was mutagenic to bacteria[125].

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