Cancer Causes and Control, 1997, 8, pp. 491-503

Silica, asbestos, man-made mineral fibers, and cancer*

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(Received 12 April 1996; accepted in revised form 20 June 1996)

Approximately three million workers in the United States are estimated to be exposed to silica, man-made mineral fibers, and asbestos. The lung is the primary target organ of concern. Each of these substances is composed predominantly of silicon and oxygen; asbestos and silica are crystalline, and asbestos and man-made mineral fibers are fibers. Man-made mineral fibers and asbestos are used as insulating agents, with the former having generally replaced the latter in recent years. Silica is used in foundries, pottery, and brick making, and is encountered by miners. A meta-analysis of 16 of the largest studies with well-documented silica exposure and low probability of confounding by other occupational exposures, indicates a relative risk (RR) of 1.3 (95 percent confidence interval [CI] = 1.2-1.4). Lung cancer risks are highest and most consistent for silicotics, who have received the highest doses (RR = 2.3, CI = 2.2-2.4, across 19 studies). The data for mineral fibers continue to support the International Association for Research on Cancer's 1988 judgment that mineral fibers are a possible human carcinogen (Group 2B). Recent epidemiologic studies provide little evidence for lung carcinogenicity for either glass wool or rock/slag wool. Ceramic fibers, a much less common exposure than glass wool and rock/slag wool, are of concern because of positive animal studies, but there are insufficient human data. Regarding asbestos, its carcinogenicity for the lung and mesothelium is well established. With regard to the controversy over chrysotile and mesothelioma, the data suggest chrysotile does cause mesothelioma, although it may be less potent than amphibole asbestos. *Cancer Causes and Control* 1997, 8, 491-503

Key words: Asbestos, lung cancer, mineral fibers, silica.

Introduction

The purpose of this article is to review the evidence of carcinogenicity for three common occupational exposures: silica, asbestos, and man-made mineral fibers (MMMF). All three are known or suspected carcinogens. According to the International Agency for Research on Cancer (IARC), asbestos and silica are established human lung carcinogens (Group 1), while the evidence for human lung carcinogenicity for MMMF is suggestive but inconclusive (Group 2B). Occupational lung carcinogens can be categorized broadly into four groups of inhaled materials: gases, metals, organic particles, and inorganic particles. Silica, asbestos, and MMMF are all inorganic particles that are composed largely of combinations of silicon and oxygen. Silica and asbestos are mined from the earth; man-made mineral fibers are created from glass and rock and have been used to replace asbestos in most industrialized countries. All three are among the most common occupational exposures. Silica is used in foundries, brickmaking, and sandblasting. Asbestos and MMMF are commonly used as insulators. All three are encountered in building and other construction. Asbestos and MMMF are fibers, while silica is not.

In our review, we limit ourselves to lung cancer and mesothelioma risk. For all three substances, we review

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their use and discuss exposure levels commonly encountered. We briefly review the relevant animal evidence of carcinogenicity, but most of the text is devoted to reviewing the human epidemiology, with a focus on current outstanding controversies.

Smoking is a dominant risk factor for lung cancer, and will be considered here as a possible confounding variable or with regard to possible effect modification (*i.e.*, different relative risks [RR] for exposed *cf* nonexposed for smokers and nonsmokers). Regarding confounding, a general observation needs to be made. Despite the strength of smoking as a risk factor for lung cancer (with a risk ratio on the order of 10 to 20), both theoretical and empirical studies have shown that in occupational epidemiology confounding by smoking is unlikely to explain risk ratios for exposure of 1.4 or above; when risk ratios for exposed *cf* nonexposed are elevated due to positive confounding by smoking, the effect is generally to cause a risk ratio in the range of 1.1-1.3.[1,2] Further, such confounding is largely absent when internal comparisons are made within a working population by level of exposure, because smoking habits of workers generally do not vary by level of exposure.

Regarding effect modification or interaction, there are insufficient data to characterize with confidence the nature of the interaction between smoking and exposure. Because lung cancer among nonsmokers is so rare, it is difficult to determine with any precision the lung cancer RR for nonsmokers, and hence it is difficult to distinguish it statistically from the RR for smokers. Of the substances considered here, only asbestos has reasonably sufficient data to consider effect-modification, and there are very limited data for silica.

In some instances, we have calculated summary RRs for specific agents using inverse-variance weighting and a random effects model.[3] Use of a random effects model is motivated by the fact that most of the RRs considered here show substantial heterogeneity. Such heterogeneity is expected given the widely varying exposure levels of the studies in question.

Silica

Silica is among the most common minerals on earth, making up a substantial part of the earth's crust. Silica exists in two forms, crystalline and amorphous. It is the crystalline form (also called free silica) which is of concern. There is currently no evidence that amorphous silica causes either lung fibrosis or cancer.[4,5] Crystalline silica has three principal polymorphs: quartz, tridymite, and cristobalite, with quartz being by far the most common. All have the same molecular formula, $(SiO_2)_n$. High exposures are common in foundry workers, miners, quarrymen, and sandblasters. Low exposures may occur whenever mixed dusts are breathed, but the general population is not considered to be exposed to levels sufficient to cause disease.

In the 1980s, there were an estimated 1.7 million US workers exposed to crystalline silica outside of the mining industry.[6] Some of the principal industries in which exposure occurs are masonry and stonework, concrete and gypsum, and pottery. Silica exposure is common among miners, yet is highly variable depending on the silica content of the ore.

Historically, silica exposure levels were calculated in terms of dust (million particles per cubic foot); actual silica exposure depended on the amount of silica in the dust. The current US Occupational Safety and Health Administration (OSHA) standard follows this tradition by setting a variable standard based on respirable dust and the percent of silica in the dust ([10 mg/m^3]/[percent crystalline silica +2]). OSHA temporarily adopted a gravimetric standard of 0.1 mg/m^3 for respirable crystalline silica from 1989-92 as part of a generic revision of many standards, but this revision was later rejected by the courts;[7] OSHA is currently attempting to resurrect this gravimetric standard for silica (personal communication, Loretta Schuman, OSHA, August 1996). Most epidemiologic studies unfortunately have not reported exposure levels. Many silica exposures have decreased markedly over time, particularly since the 1940s when silicosis was recognized as an occupational disease and dust controls were instituted in most job sites. However, very high exposures still exist in some jobs.

IARC determined in 1987 that silica was a 'probable' human carcinogen (Group 2A), based on sufficient animal evidence and limited human evidence.[4] A great deal more epidemiologic data has come out in the years since IARC's determination, and, in 1996, IARC reclassified silica as a 'definite' human carcinogen (Group 1), based on sufficient epidemiologic data with support from both sufficient animal data and data on biological mechanisms.[5]

Silica has been long known to cause progressive granulomatous and fibrotic disease in the lung in humans. It is known that silica is toxic to pulmonary macrophages which engulf the silica particles, and a variety of chemotactic and toxic substances released from lysed macrophages result in the collagen production which causes fibrosis. In rats, inhaled silica causes both fibrosis and lung cancer, while in mice, silica causes fibrosis but not lung cancer. In hamsters it causes neither.[8] Inhaled silica can cause lung cancer in rats at relatively low doses (0.74 mg/m^2 respirable silica[9]). The mechanism by which silica induces lung cancer in rats is not clear, whether directly through effects on the DNA or indirectly by promoting growth of already initiated cells.[8,10] The strong immunologic response in the lung induced by silica particles and their toxicity to macrophages releases a

Table 1. Cohort and case-control studies of lung cancer among silicotics

Author (ref.) Year	Population; control for smoking	Number of exposed cases	Lung cancer RR (CI)[a]
Westerholm[64] 1966	712 compensated silicosis 1959-77; yes	16	SMR = 4.4 (3.0-8.1)
Forastiere *et al*[65] 1986	72 cases, area of pottery industry; yes	15	OR = 3.9 (1.8-8.3) OR = 1.4 (0.7-2.8) for exposed nonsilicotics
Finkelstein *et al*[66] 1987	276 silicotics not employed in mines or foundries in Canada; no	16	SMR = 3.0 (1.7-4.9)
Zambon *et al*[67] 1987	1,313 men diagnosed 1959-63, in Italy; yes, smoking explains some of excess,	70	SMR = 2.4 (1.9-3.0)
Mastrangelo *et al*[16] 1988	309 cases, area in Italy with quarries; yes	50	OR = 1.9 (1.1-3.2) OR = 0.9 for exposed nonsilicotics
Infante-Rivard *et al*[68] 1989	1,165 silicotics compensated in Quebec, Canada, 1938-85; yes	83	SMR = 3.5 (3.1-3.9)
Tornling *et al*[69] 1990	280 silicotic ceramic workers in Sweden; no	9	SMR = 1.9 (0.9-3.6)
Ng *et al*[70] 1990	1,419 men in a silicosis registry; yes, estimated 50% of excess due to smoking	28	SMR = 2.0 (1.4-2.9)
Chiyotani *et al*[15] 1990	3,335 hospitalized pneumoconiosis patients; yes	44 4	SMR = 6.0 (5.3-6.8) SMR = 2.2 for never smokers
Amandus & Costello[14] 1991	US miners X-rayed 1951-61, 369 silicotics *cf* 9,543 nonsilicotics; yes	14	SMR = 2.0 (1.2-3.2)
Amandus *et al*[71] 1991	760 silicotics diagnosed 1930-82 in North Carolina; yes	34	SMR = 2.6 (1.8-3.6)
Hnizdo & Sluis-Cremer[72] 1991	Nested case-control study of 2,209 miners; yes	77 66	OR = 0.9 (0.5-1.6) OR = 3.9 (1.2-12.7) for silicosis of hilar gland
Chia *et al*[73] 1991	104 silicotic granite cutters 1980-84; yes		SMR = 2.0 (0.9-3.8)
Carta *et al*[74] 1991	724 silicotics diagnosed 1964-70; yes	22	SMR = 1.3 (0.8-2.0)
Chen *et al*[75] 1992	About 6,800 silicotics *via* annual exam; no	ng[b]	SMR = 1.2 (0.9-1.6)
Partanen *et al*[76] 1994	961 men diagnosed 1935-77 in Finland, consistent across industries; yes	101	SMR = 2.9 (2.4-3.5)
Merlo *et al*[77] 1995	515 silicotic patients; some, part of the excess may be due to smoking; + trend with duration	35	SMR = 3.5 (2.4-4.9)
Goldsmith *et al*[78] 1995	590 silicotics from compensation files; no	39	SMR = 1.9 (1.4-2.6)
Dong *et al*[17] 1995	1,827 silicotics in cohort, determined *via* X-ray; some, similar risk among smokers and nonsmokers	35	SMR = 2.1 (1.6-3.2)[c]

[a] CI = 95% confidence interval; SMR = standardized mortality ratio; OR = odds ratio from case-control studies.
[b] ng = not given.
[c] CI calculated from data in paper.

number of substances (*e.g.*, lysosomal enzymes) which may promote not only fibrosis but also cancer.[8] Silica can cause chromosomal aberrations and transformation *in vitro* in mammalian cells.[10] There is recent evidence that lung tumors in rats arise in areas adjacent to areas of fibrosis, that silica can bind directly with DNA, and some suggestion that a particular cytokine (transforming growth factor β1) may play a role in carcinogenesis.[10]

There have been a large number of epidemiologic investigations; Goldsmith and McDonald have written two recent reviews,[11,12] as has IARC.[5] A general summary of the evidence is that the studies of silica-exposed workers suggest an increased lung cancer risk but they are not consistent, and exposure-response analyses also are not consistent. The evidence for a lung cancer association is stronger for the many studies of workers with silicosis.

Most of these have shown elevated lung cancer risk, often statistically significant and often beyond the range of excess risk which might be caused by confounding by smoking or other occupational exposures.

Cohort and case-control studies of silicotics are shown in Table 1. (Omitted from this table are studies in mines and foundries which might involve confounding exposures, autopsy and proportional mortality studies, and data from presentations or proceedings). The summary RR for these 19 studies is 2.3 (95 percent confidence interval [CI] = 2.2-2.6). Other investigators conducting a meta-analysis on the same issue found a summary RR of 2.2 (CI = 2.1-2.4).[13] Concerns have been expressed that this elevated risk was a product of selection bias, because a number of cohorts were based on worker's compensation data of ill patients who smoked heavily. These concerns have been dissipated because there are now a number of studies of silicotics ascertained *via* sources other than compensation records and because the risk has been shown to exist after control for smoking.[14-17] The data suggest that either the relatively high doses of silica which are required to cause silicosis in turn result in lung cancer, or that some aspect of the fibrotic disease itself accounts for the observed excess lung cancer risk. Generally, the data are insufficient to determine which is the case. Regarding effect modification by smoking, the data suggest that nonsmoking silicotics and smoking silicotics share similar increased risks of lung cancer, although the data are limited by the small number of cases among nonsmokers.[14-17]

Table 2 lists the larger studies of silica-exposed workers with reasonably well-documented exposure, and without known confounding exposures to lung carcinogens (*e.g.*, arsenic and radon among miners). The studies in Table 2 suggest a moderate excess, with a combined RR of 1.3 (CI = 1.2-1.4). The combined RR of 1.3 with a narrow CI suggests the observed excess risk is not due to chance, but such a relatively low excess risk possibly could be due to confounding by smoking. However, this argument is less plausible because a number of studies have controlled for smoking either directly or indirectly.

Despite some inconsistency, the weight of the evidence supports the thesis that silica is a human lung carcinogen. Those with the highest exposure (silicotics) show the highest risks, and silica-exposed cohorts in general exhibit a moderate increased risk. A number of suggestions have been made about why some silica exposures might be more carcinogenic than others. For example, Shoemaker *et al* [18] have shown that freshly cleaved, inhaled quartz results in higher cytotoxicity and inflammatory responses in rat lungs, suggesting that freshly produced quartz dust might be more carcinogenic. McDonald[13] has theorized that cristobalite and tridymite, known to be more fibrogenic than quartz, also may be more carcinogenic.

Man-made mineral fibers

Man-made mineral fibers (MMMF), also called man-made vitreous fibers, can be classified into three broad categories: glass wool; rock or slag wool (sometimes call mineral wool); and refractory ceramic fibers (RCF). Discussion of their production and use can be found in Ohberg[19] and IARC.[20] Glass wool and rock/slag wool are made up of silicon, calcium, and aluminum oxides (SiO_2, CaO, Al_2O_3), in that order, with silicon dioxide making up over 50 percent of the mix. Ceramic fibers usually are made up of 50 percent SiO_2 and 50 percent Al_2O_3, and are characterized by their stability at high temperatures. The fibers generally are considered respirable only if less than three microns in diameter, and those of concern (like asbestos) are generally those longer than five microns and with a 3:1 ratio of length to width.

Glass wool, or fiber glass, is made from molten glass which is blown or spun into long fibers. Sometimes, glass wool also is extruded through a nozzle into continuous filaments, which are longer and wider than the original fibers. Glass continuous filaments are generally too wide to be respirable, although a small fraction of these fibers are under three microns in width.

Rock wool is made from molten igneous rock, while slag wool is made from molten slag from smelters (*e.g.*, copper smelters). Slag in some instances has been contaminated with metals known to be lung carcinogens, such as arsenic, particularly in early production years.

RCFs are produced primarily by the blowing and spinning of furnace-melted siliceous kaolin [$(Al_2Si_2)O_5(OH)_4$] clay or blends of kaolin, silica, and zircon. They also are produced using continuous filamentation and whisker-making technologies for specialty applications.[20]

IARC has determined that glass wool, rock/slag wool, and ceramic fibers are 'possible' human carcinogens (Group 2B).[20] Evidence for glass filaments was considered inadequate. The overall categorization of possibly carcinogenic was based on a combination of animal and human evidence. Animal evidence was considered sufficient for carcinogenicity for glass wool and ceramic fibers, limited for rock wool, and inadequate for slag wool and glass filaments. Human evidence was considered limited for rock/slag wool, and inadequate for glass wool, glass filaments, and ceramic fibers.

Estimated worldwide production of MMMF in 1985 exceeded six million tons, which surpassed the peak production of asbestos (five million tons) recorded in the 1970s.[20]

Production of MMMF in the US mostly dates from World War I, when rock and slag wool began to be produced in substantial quantities. Glass wool production began in the 1930s, while ceramic fibers were first produced in the 1940s.[20] The US currently accounts for

Table 2. Cohort and case-control studies of lung cancer among silica-exposed workers

Author (ref.) Year	Population; control for smoking	Number of exposed cases	Lung cancer SMR, PMR, PCMR or OR (CI)[a]
Davis *et al*[79] 1983	969 dead granite workers, no trend with estimated dust exposure; no	62	PMR 1.3 (1.0-1.6)
Steenland & Beaumont[80] 1986	1,905 dead granite cutters with high levels of silica exposure and silicosis before 1950; no	97	PMR = 1.2 (1.0-1.5) PCMR = 1.1 (0.9-1.3)
Neuberger *et al*[81] 1986	1,630 Austrians exposed to nonfibrous dust, no change in SMR after excluding foundries; no	175	SMR = 1.5 (1.2-1.7)
Costello & Graham[82] 1988	5,414 granite workers employed 1950-82, high exposures, especially for shed workers; no	118 98	SMR = 1.2 (1.0-1.4) SMR = 1.3, shed workers
Guenel *et al*[83] 1989	2,071 Danish stone workers with high historical rates of silicosis; no	44	SMR = 2.0 (1.5-2.7)
Siemiatycki *et al*[84] 1990	Cases restricted to nonadenocarcinoma (no risk for adenocarcinoma, *n* = 37); yes	161 75	OR = 1.3 (1.0-1.8) OR = 1.7 for 20+ exp.
Winter *et al*[85] 1990	3,669 pottery workers aged < 60, surveyed for dust and smoking in 1970-71, positive dose-response; yes	30	SMR = 1.3 (1.0-1.7)
Mehnert *et al*[86] 1990	2,483 slate quarry workers, positive trends with duration and exposure level; no	27	SMR = 1.1 (0.7-1.6)
Merlo *et al*[87] 1991	1,022 brick workers, high historical silica exposure and silicosis excess, yes	28	SMR = 1.5 (1.0-2.1)
Hnizdo & Sluis-Cremer[72] 1991	Case-control study among 2,209 gold miners, positive dose response, low radon exposure; yes	77	OR = 2.0 (1.1-3.3)
McLaughlin *et al*[88] 1992	Case-control studies (*n* = 316) among pottery workers, tungsten miners, and iron miners, OR's for high silica *cf* none; yes	7 25 5	OR = 2.1 (0.7-7.0)[b] OR = 0.5 (0.3-1.0) OR = 0.7 (0.2-2.3)
Checkoway *et al*[89] 1993	2,570 diatomaceous earth miners with high past exposures, positive dose-response; no	59	SMR = 1.4 (1.1-1.8)
Koskela *et al*[90] 1994	1,026 granite workers; no, but smoking habits probably similar to referents	43	SRR = 1.7 (1.2-2.3)
Steenland & Brown[91] 1995	3,328 gold miners, high historical exposures, no dose-response, low radon/arsenic; yes	115	SMR = 1.1 (0.9-1.4)
Cocco *et al*[92] 1995	2,603 miners in lead/zinc mine with low radon and high silica; some	29	SMR = 0.8 (0.5-1.2)
Dong *et al*[17] 1995	6,266 refractory brick makers; excess confined to silicotics (smokers and nonsmokers) in cohort (*n* = 1,827); some		

[a] SMR = standardized mortality ratio; SRR = standardized rate ratio; OR = odds ratio; PMR = proportional mortality ratio; PCMR = proportional cancer mortality ratio; CI = 95 percent confidence interval.
[b] CIs calculated from data in paper. Tin miner data omitted because of arsenic confounding.
[c] CI calculated from data in paper.

more than half of worldwide production. Eighty percent of MMMF production in the US is glass wool, with 40 glass fiber plants, 12 ceramic fiber plants, one rock wool plant, and 19 slag wool plants.[21] In 1986, there were 37 rock/slag wool plants and 37 bier-glass plants in Europe.[20] Based on surveys for epidemiologic studies, which have covered much of the plants producing glass wool or rock wool, there are approximately 40,000 to 50,000 workers currently exposed during production of MMMF in the US. The US National Institute for Occupational Safety and Health (NIOSH) estimates[22] that approximately 500,000 workers are exposed during use, primarily in construction. Exposure levels have been measured in the US in the 1970s as part of epidemiologic studies, and investigators have estimated past levels which were considerably higher (for example, in later years, binders or oil was added to suppress dust). Marsh *et al*[23] have estimated that in their large US cohort of glass and rock/slag wool workers, the average exposure level across all years to fibers less than three microns in diameter was 0.04 fibers/cc for glass wool workers, and 0.35 fibers/cc for rock/slag wool workers. Exposures were comparable

in Europe and Canada, the sites of other cohort studies. Current levels in production are probably in the range of 0.01-0.10 fibers/cc for small diameter fibers, mostly at the lower end of the range.[24] Somewhat higher levels occur when the product is applied (*e.g.*, blowing insulation into houses).[20]

There are no OSHA standards for exposure specifically for these fibers. By comparison, the OSHA standard for asbestos fibers (greater than five microns, 3:1 length-width ratio) was 5.0 fiber/cc, with subsequent reduction to 2.0 fibers/cc in 1976, to 0.2 fibers/cc in 1986, and recently 0.1 fibers/cc in 1994. European countries generally also do not have standards specifically for MMMF, although standards governing total dust and quartz would apply. Sweden has a limit of two fibers/ml over a working day for glass fibers.[20]

Animal data on carcinogenicity have been recently reviewed by Ellouk and Jaurand[25] and by Infante *et al.*[26] There have been a large number of animal studies, which are difficult to summarize, partly because they have used different doses over different time periods, and used different fiber sizes (respirable fibers in rodents need to be under two microns in diameter – some inhalation studies have used primarily nonrespirable fibers). Fibers have been tested in rats and hamsters *via* inhalation, intratracheal instillation, intrapleural and intraperitoneal inoculation – although not all of these methods were used in each species.

Inhalation exposures to RCFs have been found to induce lung tumors and mesotheliomas and both rats and hamsters. For other MMMFs, inhalation studies have been negative in hamsters, although asbestos used as a positive control was also negative. Inhalation studies of glass wool in rats were largely negative as well, although a weak but statistically significant positive response has been observed for glass wool in rats when all studies are combined (2.2 percent tumor incidence, compared with 0.7 percent in controls, and 17.2 percent in asbestos-dosed positive controls). Infante *et al* [26] have argued that results for glass-wool inhalation studies in rats should be viewed as positive because in several studies with different exposure levels, a positive response has been observed in the highest dose group, although this finding has not been consistent.

Intratracheal instillations in rats or rodents have been few and largely negative, with the exception of glass filaments, but again, positive asbestos controls were also negative. Intrapleural and intraperitoneal inoculation studies in rats have been largely positive in causing sarcomas and mesotheliomas for RCFs, glass wool and rock wool (but not slag wool), and for asbestos used as a positive control. Such studies were not performed in hamsters.

Overall, the animal data for MMMF are inconsistent. While RCFs appear to induce carcinogenic responses in inhalation studies, glass wool and rock/slag wool are either not carcinogenic or weakly carcinogenic in inhalation studies. However, glass wool has shown a lung cancer response in some rat inhalation studies at higher doses, and questions about the adequacy of some of the inhalation experiments remain. Positive results for sarcomas and mesotheliomas have been observed for all fibers except slag wool when minerals were administered to rats *via* inoculation.

It should be noted that one issue regarding MMMF is their bio-persistence, which appears to be relatively low in humans.[27] Autopsy data on a large number of decedents who had been exposed to glass wool (n = 585) or rock/slag wool (n = 11) from the large US study of MMMF-exposed workers, with a matched group of nonexposed men, did not show any differences in the number of fibers in the lung between exposed and nonexposed men. Although well-designed studies are lacking, it appears that MMMF are cleared relatively rapidly from the lung, in contrast to other dusts, such as silica and asbestos. However, this does not necessarily argue against the possibility that MMMF are lung carcinogens, as they might do their damage rapidly.

The principal human studies of MMMF are listed in Table 3. A number of small and early studies are omitted for simplicity and because they offer only limited information (few cases, short latency). Studies of construction or other workers with only 'potential' exposure to MMMF also have been omitted. Only the most recent updates of any study, and only mortality results (no incidence), are considered. There are two large cohort studies of rock/slag wool and glass wool workers from the US[23] and Europe,[28] and one small one from Canada.[29] The rock/slag wool component of the Marsh *et al* [23] study has been updated with an extra four years of follow-up (through 1989) and more detailed exposure information in a recent publication,[30] and similar updates of the fiber glass workers underway. In addition, there are four case-control studies of these workers, three of which are nested within the US cohort study, and the other[31] nested within another cohort of slag wool workers. There is only one cohort study for occupational exposure to RCFs.[32] A recent review of the epidemiology of MMMF-exposed workers has been published by Lee *et al*;[33] these authors concluded that occupational exposure to fiber glass "did not appear to increase the risk of respiratory cancer."

Table 3 shows that the two large cohort studies of rock and glass wools have very similar overall results for lung cancer; no excess for glass filament, a slight excess for glass wool, and a more pronounced excess for rock/slag wool. A few mesotheliomas have been seen in these cohorts but they do not appear excessive; rather, they conform to what one would expect for any large cohort of industrial workers. The lung cancer results in Table 3

Table 3. Cohort and case-control studies of MMMF-exposed workers

Author (ref.) Year	Population; control for smoking	Fiber	Number of exposed cases	Lung cancer SMR or OR (CI)[a]
Cohort studies				
Marsh *et al*[23] 1990	16,661 male workers in 17 US plants; no trend by duration or time from first employment; local comparison rates; average intensity of exposure 0.05, 0.01, 0.35 for glass wool, filament and rock/slag respectively; 1 yr. minimum employment 1940-63, 1985 follow-up (rock/slag lung SMR = 1.30 with 1989 follow-up); no	All Glass wool Filament Rock/slag	474 99 84 73	1.13 (1.03-1.23) 1.12 (1.00-1.24) 0.98 (0.78-1.22) 1.36 (1.06-1.71)
Boffetta *et al*[28] 1990	22,002 workers in 14 European plants; positive trend for rock/slag wool with time since-first-employment, and with duration when short-term workers (< 1 yr.) excluded; local comparison rates; 1990 follow-up; multivariate internal analyses found no significant trends with duration or time-since-first-employment; no	All Glass wool Filament Rock/slag	344 157 25 162	1.23 (1.10-1.36) 1.12 (0.95-1.31) 1.07 (0.69-1.57) 1.39 (1.18-1.62)
Shannon *et al*[29] 1987	2,557 workers in one Canadian plant; local rates; levels < 0.1 f/ml in 1970s; no trends with duration or time-since-first employment; employment 1955-77, followed through 1984; no	Glass wool	19	1.99 (1.20-3.11)
Lockey *et al*[32] 1993	868 workers in two plants in New York and Indiana (USA); levels from 0.01 to 5.0 fib/ml; study limited by small number of deaths and short follow-up of the cohort; no	Ceramic fibers	4	1.14 (0.31-2.91)
Case-control studies				
Enterline *et al*[35] 1987	Nested case-control study of US cohort of 16,661 workers; 1982 follow-up; logistic regression analysis by estimated cumulative exposure (fib/ml-month) at end of follow-up may have overestimated controls' exposure; yes	Glass wool Rock/slag	211 38	Negative trend Significant positive trend
Wong *et al*[31] 1991	Nested in nine plant cohort of 4,841 workers; 1989 follow-up; matched dead controls, analysis by cumulative exposure; 4/9 plants in Marsh study; exposure estimates based on two 1970 surveys, assumed constant over time; yes	Slag wool	55	No significant trends
Chiazze *et al*[36] 1993	Nested in one plant in US cohort of 16,661 workers; 1982 follow-up; controls matched on birth year and survival past case; analysis by cumulative exposure; inclusion of age and date of hire in analysis may have resulted in over-matching; yes	Glass wool	162	Medium *cf* low OR = 1.43 (0.90-2.27) High *cf* low OR = 0.95 (0.56-1.60)
Marsh *et al*[30] 1996	Nested within five plants in cohort study of 3,035 workers; new hires included; 1989 follow-up; mean exposure 0.24 f/cc, mean cumulative exposure 19.8 fib/cc-months, median 7.0; yes	Rock/slag	76	No dose-response trends

[a] SMR = standardized mortality ratio; OR = odds ratio; CI = 95% confidence interval.

conform to what might be expected based on average levels of exposure (see comment to the Marsh *et al*[23] study); few glass filament fibers are respirable, and rock/slag wool exposures have been higher than glass wool exposures. Arguing against a true association, however, are the lack of trends with duration and time-since-first-employment (some univariate trends are apparent in the European results for rock/slag wool workers using external comparisons, but are weakened in multivariate analyses using internal referents). Further, the RRs observed here, especially for glass wool workers, are slight and attain statistical significance primarily because the number of lung cancers is large. The relatively small RRs mean that confounding by cigarette smoking could still explain most if not all of the excesses.

The one cohort study of workers exposed to RCFs[32] has failed to demonstrate an excess of lung cancer. However, due to the study size and relatively young age of the cohort, this study probably should be viewed as inconclusive rather than negative.

Four nested case-control studies have been conducted and are listed in Table 3. Three of the four are nested within plants in the large US cohort, while the Wong *et al*[31] study also includes other slag wool plants. However, all four were done independently and exposure estimates are also independent. These case-control studies were designed to control for cigarette smoking and to analyze the data by cumulative exposure to fibers in order to determine if an exposure-response trend is present. Such a design is, in theory, preferable to the cohort studies which do not control for smoking and often have only duration of exposure to use in analyses of exposure-response. However, the difficulty of obtaining good historical estimates of smoking by decedents from next-of-kin (often limited to ever *cf* never-smoked), and the loss of approximately 30 to 40 percent of cases whose next-of-kin cannot be found, may result in estimates 'controlled' for smoking which are even less precise than estimates based on cohort data.[34] Further, estimates of exposure-response based on estimated cumulative exposure are only as good as the job-exposure matrices which are constructed over all production years at a given plant or plants. Since actual exposure measurements are available only in the 1970s, the critical element in the cumulative exposure estimates is the attempt to estimate past exposures in the 1930s-60s. These are the exposures which are of the most etiologic importance, as sufficient potential latency will have occurred for these exposures to have had an effect. Yet, these are precisely the exposures which are most difficult to estimate accurately.

The four case-control studies have been generally negative, although Enterline *et al*[35] found a positive exposure-response for glass wool, and Chiazze *et al*[36] found some increase in the middle category for glass wool. As stated above, imprecise exposure estimates for the past can lead to misclassification and may tend to dampen exposure-response trends. For example, in the Wong *et al* study, exposures for specific jobs measured in the 1970s apparently were considered constant across time, although they almost certainly were higher in the past. However, detailed consideration of the quality of historical exposure estimates in the case-control studies is beyond the scope of this paper and is often not possible based on the sparse data presented in the cited publications.

We are left then with some excesses in the most recent updates of large cohort studies of workers exposed to glass and rock/slag wool. However, these results tend to be discounted by the results of nested case-control studies of glass and rock/slag wool workers, which use internal comparisons, exposure-response analyses, and attempt to control for smoking. The animal data discussed above do not help resolve the issue, as they may be interpreted as either generally negative or weakly positive, except for RCFs. The rather unsatisfactory situation remains of neither offering a completely clean bill of health to MMMF regarding lung cancer, nor being able to affirm that they are carcinogenic in humans. The data, to date, continue to support IARC's 1988 judgment that MMMF are 'possibly' carcinogenic in humans.

Asbestos

While the use of asbestos has been increasingly restricted as its dangers have become well recognized, NIOSH estimates that approximately 700,000 US workers were exposed to asbestos in the 1980s, primarily maintenance and construction workers exposed to asbestos insulation, and mechanics exposed to asbestos in brake linings.[6] Nicholson *et al*[37] estimated that from 1940-79, 27.5 million US workers were potentially exposed, of whom 18.8 million had exposure in excess of the equivalent of two months in primary manufacturing of asbestos. Twenty-one million exposed workers were estimated to be alive in 1980, and approximately 6,000 incident annual US lung cancer cases in the 1990s are estimated to be attributable to asbestos. Although asbestos consumption has declined in North America and Europe, sales in other countries (*e.g.*, southeast Asia, South America, and eastern Europe) have increased primarily due to the use of asbestos-based construction materials.[38]

Asbestos refers to a variety of hydroxylated silicate minerals. Asbestos minerals are divided into two broad groups, serpentine and amphibole. Serpentine asbestos is called chrysotile, while the amphibole family includes crocidolite, anthophyllite, amosite, actinolite, and tremolite. These minerals are said to exist in an asbestiform or fibrous 'habit' when the mineral has grown in one dimension to form long thin crystals. For the purpose of

Table 4. Summary of lung cancer findings from selected epidemiologic studies of mining and industrial cohorts exposed to asbestos

Author (ref.) Year	Fiber type[a]	Industry	Cohort size	Number of exposed cases	SMR[b] (95%CI)	Exposure-response?
Piolatto *et al*[93] 1990	CHR, BAL	Mining	1,058	22	1.1 (0.7-1.7)	No
McDonald *et al*[94] 1993	CHR	Mining	11,379	34	1.4 (1.2-1.5)	Yes
Armstrong *et al*[95] 1988	CROC	Mining	6,916	91	2.6 (2.2-3.6)	Yes
Sluis-Cremer *et al*[96] 1990	AMOS, CROC	Mining	7,317	35	1.7 (1.3-2.2)	Yes
McDonald *et al*[97] 1986	TREM	Mining	406	21	2.5 (1.6-3.8)	Yes
Finkelstein[98] 1984	CHR, CROC	Cement	535	26	4.8[c] (4.4-5.3)	Yes
Albin *et al*[99] 1990	CHR, AMOS	Cement	1,929	46	1.7 (1.2-2.4)	No
Botta *et al*[100] 1991	CHR, CROC	Cement	3,367	110	2.7 (2.2-3.3)	—
Hughes *et al*[55] 1987	Plant 1: CHR, AM, CROC	Cement	2,565	48	1.2 (0.9-1.3)	Yes
	Plant 2: CHR, CROC		4,366	107	1.4 (1.2-1.7)	Yes
Gardner *et al*[101] 1986	CHR	Cement	2,167	35	1.0 (0.6-1.3)	No
Thomas *et al*[102] 1982	CHR, CROC	Cement	1,970	30	0.9 (0.7-1.4)	—
Raffin *et al*[103] 1993	CHR, AMOS, CROC	Cement	8,580	104	1.8 (1.5-2.0)	—
Neuberger & Kundi[104] 1990	CHR, AMOS, CROC	Cement	2,816	49	1.0 (0.8-1.4)	—
McDonald *et al*[105] 1984	CHR, ANTH, CROC	Friction products	3,641	73	1.5[c] (0.8-1.4)	No
Newhouse *et al*[106] 1989	CHR, CROC	Friction products	13,450	254	1.0[d] (0.9-1.2)	—
Peto *et al*[107] 1985	CHR, CROC	Textiles	3,211	132	1.3 (1.1-1.5)	Yes
Newhouse *et al*[108] 1985	CHR, AMOS, CROC	Textiles	3,000	158	3.0 (2.6-3.3)	Yes
Dement *et al*[109] 1994	CHR	Textiles	3,022	126	1.8 (1.5-2.1)	Yes
Cheng & Kong[110] 1992	CHR	Textiles, friction products, & cement	1,172	21	3.2 (2.0-4.8)	Yes
McDonald *et al*[111] 1983	CHR, AMOS, CROC	Textiles	4,137	53	1.1[c] (0.8-1.3)	Yes
Selikoff *et al*[48] 1979		Insulation	17,800	429	4.1 (3.9-5.0)	Yes
Seidman *et al*[112] 1986	AMOS	Insulation	820	102	5.0 (4.1-6.0)	Yes
Henderson & Enterline[113] 1979	CHR, AMOS, CROC	Insulation	1,075	63	2.7 (2.1-3.5)	Yes

[a] The abbreviations for fiber types used are: CHR = chrysotile; AMOS = amosite; CROC = crocidolite; BAL = balengorite; TREM = tremolite; and ANTH = anthophyllite.
[b] SMR = standardized mortality ratio; CI = 95% confidence interval.
[c] SMR for workers after 20 years since first exposure.
[d] SMRs for cancers of the lung and pleura combined.

regulation, OSHA has restricted its definition of asbestos to asbestiform fibers greater than five microns with aspect (length to width) ratios of at least 3:1. The OSHA standard for asbestos recently has been revised to 0.1 fibers/ml.[39]

Among the substances reviewed in this paper, asbestos was the earliest and is the most widely recognized carcinogenic hazard. The IARC has classified asbestos as being carcinogenic to humans based on both sufficient toxicologic and epidemiologic evidence.[40] The dangers of asbestos first became known in the 1940s, largely from animal studies and case-reports, but were not recognized widely except perhaps within the industries producing asbestos.[41]

Numerous studies have demonstrated that asbestos has the potential to induce lung tumors and mesotheliomas in experimental animals. Chrysotile, amosite, anthophyllite, and crocidolite have been shown to produce mesotheliomas in rats after intrapleural inoculation.[42] The same five asbestos types all produced lung tumors in rats in long-term inhalation studies, and all but the Rhodesian chrysotile sample produced mesotheliomas.[43] Therefore, one can conclude that all types of asbestos have the potential to cause respiratory cancer in animal models.

The earliest reports of an increased risk of lung cancer among asbestos workers can be traced to the 1940s,[44] although asbestosis has been recognized as a disease associated with asbestos exposure since the beginning of the 20th century.[45] The first major human studies showing a lung cancer effect were published in England in 1955[46] and in the US in 1964.[47] Table 4 presents the findings from the larger cohort studies (restricted to only on the most recent update). An excess of mortality from lung cancer and evidence for an exposure-response relationship has been observed in most but not all of the studies. There appear to be important differences in risk between workers in different industries with the lowest risks being evident among workers in the cement and friction products industries, and the highest risks being evident among workers in mining and the textile industries. The explanation for these differences is unknown but could be related to differences in levels of exposure and/or the distribution of fiber dimensions. There are no clear patterns of differences in risk for the various asbestos fiber types.

The observed excesses of lung cancer did not appear to be explained by differences in cigarette smoking habits in the studies that controlled for tobacco consumption.[48-50] Early studies suggested that there was an interaction between cigarette smoking and asbestos which was multiplicative.[51] Recent reviews of this issue suggest that the interaction between smoking and asbestos may be greater than additive but somewhat less than multiplicative (*i.e.*, the RR for asbestos among smokers is less than the RR among nonsmokers).[52,53]

For asbestos, like silica, the argument can be made that lung cancer may not occur without preceding fibrosis. This hypothesis is difficult to assess epidemiologically because: (i) those with fibrosis are those who also had higher doses, and higher doses would be expected to cause more lung cancer; (ii) few studies have good data on the three variables necessary to test this hypothesis, *i.e.*, dose, radiographic changes, and smoking;[54] and (iii) fibrosis may be present but not detectable on X-ray. Three recent studies within asbestos-exposed cohorts, all with reasonably good data on these three variables, suggest that only those with observable radiographic changes develop lung cancer.[55-57] However, another recent population-based study (without data on dose) suggests the opposite.[58] All four of these studies have some limitations. At this point, the human epidemiology is too sparse to draw firm conclusions.

Mesothelioma of the pleura and peritoneum has been reported in a large number of case reports and formal epidemiologic studies of asbestos-exposed workers. There is little doubt that these findings are attributable to asbestos exposure, given the fact that there are very few other causes of this disease. There has been considerable recent debate concerning the extent to which mesothelioma is related to chrysotile asbestos exposure. It has been hypothesized that the mesothelioma observed among workers exposed to chrysotile asbestos may be explained by the relatively low concentrations of tremolite fibers in commercial chrysotile asbestos fibers and that chrysotile asbestos may be less potent than amphiboles in the induction of asbestosis and lung cancer. This hypothesis has been dubbed the 'amphibole hypothesis.' [59,60] This issue was reviewed most recently by Stayner *et al* [61] who suggested that chrysotile may be less potent for inducing mesothelioma than other forms of asbestos, but that there is strong toxicologic and epidemiologic evidence that workers exposed to chrysotile asbestos are at increased risk for mesothelioma as well as lung cancer.

Peto *et al* [62] recently conducted an analysis of trends in mesothelioma rates in Great Britain. The results from this analysis suggest that the epidemic of mesothelioma among males from occupational exposure to asbestos has not yet peaked and predicts that it will not peak until the year 2020. The risk appeared to be the greatest among workers in the construction trades based on death certificates. Among those born in the 1940s, it was estimated that mesothelioma may account for one percent of all deaths. The number of deaths due to mesothelioma in the US still appears to be rising.[63] Of course, for every case of mesothelioma it should be expected that there are additional cases of lung cancer and asbestosis. Hence, these findings in Great Britain and the US indicate that a very substantial public health burden from historical exposures to asbestos may continue well into the future, despite recent efforts to reduce or eliminate exposures to asbestos.

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