A REVIEW OF EVIDENCE ON

THE JOINT RELATIONSHIP

OF ASBESTOS EXPOSURE AND SMOKING

TO RISK OF

LUNG CANCER

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EXECUTIVE SUMMARY

Evidence on the joint relationship of asbestos exposure and smoking to risk of lung cancer is reviewed. Twenty-three studies that provided relevant information were identified. These included occupational studies of miners and millers of asbestos, asbestos products workers, insulation workers, asbestos sprayers and asbestos-exposed electrochemical workers, studies of asbestosis and silicosis patients, and case-control studies conducted in railroad workers and in shipbuilding and industrial areas.

The evidence, taken as a whole, has a number of limitations, including small numbers of lung cancers in many of the studies, particularly in nonsmokers, unreliable assessment of asbestos exposure, unvalidated smoking data, frequent reliance on death certificate diagnosis, reliance on data from proxy respondents in some studies and little consideration of other lung cancer risk factors.

Despite these limitations, the data allow a number of main conclusions to be drawn:

(i) Asbestos exposure does increase risk of lung cancer in those who have never smoked.

(ii) The joint relationship of asbestos exposure and smoking to risk of lung cancer is not well explained by the additive model. The risk in smokers exposed to asbestos is, in virtually every study, more than would be expected based on the increases in risk associated with smoking only and with asbestos exposure only.

(iii) The joint relationship is well explained by the multiplicative model, i.e. the proportional increase in risk associated with asbestos exposure can be taken to be the same in smokers and in those who have never smoked.

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1. Introduction

This document describes an up-to-date review of the epidemiological evidence concerning the joint relationship of asbestos exposure and smoking to risk of lung cancer. It has been evident for many years that the incidence of lung cancer is increased as a result of smoking and as a result of asbestos exposure, but the nature of the joint relationship is not clearly defined. Suppose that the risk, relative to that in a non-smoker unexposed to asbestos, is A for an otherwise comparable non-smoker exposed to asbestos, and S for a smoker who is unexposed to asbestos, there are then various possible models to predict the risk in an asbestos exposed smoker. These include:

(i) The additive model, where the predicted risk, relative to that in the unexposed non-smoker, is 1 [the background risk] + (A-1) [the excess due to asbestos] + (S-1) [the excess due to smoking] = A + S - 1;

(ii) The multiplicative model, where the predicted risk is AS, which exceeds A + S - 1, provided A and S are each >1;

(iii) The "intermediate" model, where the risk is intermediate between that predicted by the additive and multiplicative models; and

(iv) The super multiplicative model, where the predicted risk exceeds AS.

The additive model would be consistent with asbestos and smoking affecting the same stage of a multistage model, while the multiplicative model would suggest that they affected different stages. An intermediate model would be appropriate if, say, smoking affected two stages, only one of which was affected by asbestos.

Note that the multiplicative model implies that the relative effect of asbestos exposure will be the same in smokers and non-smokers, or, equivalently, that the relative effect of smoking will be the same in those unexposed and exposed to asbestos.

A number of previous reviews of the evidence have been made, notably by Saracci[1,2], Berry et al[3], Steenland and Thun[4], Vainio and Boffetta[5], Saracci and Boffetta[6] and Erren et al[7]. None of these reach completely clear conclusions (see section 6 for further details).

This review consists of various main sections.

In section 2 the epidemiological methods that have been used for studying the joint relationship of smoking and asbestos exposure to risk of lung cancer are described in general terms.

In section 3, 23 epidemiological studies that provide relevant evidence are described, with the main data of interest tabulated.

Section 4 summarizes various features of the design of these studies, and identifies their strengths and weaknesses.

Section 5 brings together the data to answer the major questions of interest:

(i) does asbestos increase lung cancer risk in non-smokers?

(ii) are the data consistent with the additive model or is the absolute increase in risk due to asbestos exposure greater in smokers than in non-smokers? and

(iii) are the data consistent with a multiplicative model or does the relative increase in risk due to asbestos exposure differ for smokers and non-smokers?

Section 6 then provides further discussion and a summary of conclusions, followed by acknowledgements in section 7 and references in section 8.

2. Methods for studying the joint relationship of smoking and asbestos exposure to risk of lung cancer

In theory, one approach to study the joint relationship of asbestos exposure and smoking to risk of lung cancer would be to carry out a prospective study in which a large representative sample of the healthy population is interviewed to obtain details of asbestos exposure, smoking habits and relevant confounding variables and then followed-up for a number of years to identify incident and/or fatal cases of lung cancer. Though the relationship of smoking and lung cancer has been studied by a number of studies of this type, this technique has not been used to study risk related to asbestos exposure. Mainly, no doubt, this is because heavy asbestos exposure is relatively rare.

The usual approach to study health effects of asbestos is to identify particular groups likely to have asbestos exposure or to have had asbestos exposure in the past (such as asbestos miners and millers, asbestos products workers, insulation workers, shipyard workers or patients with asbestosis or silicosis) and to study their mortality. The classical occupational mortality study identifies such a population of interest and then compares its mortality over a given period with that in a standard reference population (presumed to have much lower average asbestos exposure), such as the whole country or the county, state or region in which the group is based. The period of comparison may be from the time the study starts (prospective cohort study) or may be from an earlier point of time (retrospective prospective study). Based on the number of man-years by sex, age and time period in the population of interest, and data on lung cancer rates by sex, age and time period in the reference population, one can calculate the number of lung cancer deaths (or cases) one would expect to see in the population of interest had they had the rates of the reference population. The ratio of the number of deaths observed in the population of interest to that expected is known as the standardized mortality ratio (SMR), a value of 2, for example, suggesting that the mortality in the population of interest is twice the average. Where the endpoint is cancer incidence rather than mortality, the standardized incidence ratio (SIR) is similarly calculated. Sometimes SMR and SIR values are reported multiplied by 100, but this review is consistent in not doing so.

Some studies make no attempt to estimate the asbestos exposure of individual workers, simply treating the whole population as one with undefined, but above average, exposure. Other studies do make such an attempt, however, based on their work experience. This may be relatively crude, classifying specific workers as likely to have had heavy, moderate, light or no exposure based on the type of job they carried out or, more precise, based on actual measurements of fibre levels in different areas in different time periods, linking these to the individual workers' job experience.

Where information on asbestos exposure is available, there is a choice of statistical analysis methods to use. Either one can compute separate SMRs (or SIRs) for groups of workers in different exposure categories, using the external reference standard, or not use a reference population at all, directly comparing risk in workers in different exposure categories.

Smoking data are typically not routinely available for many occupations and indeed there are many studies of asbestos exposed groups (not considered in this review) that never collect data on smoking. Where smoking data are available, e.g. from questionnaires sent to members of a workforce or by interviews conducted during medical examinations, a variety of analyses can be conducted. Not only can one compare lung cancer rates or calculate SMRs in subjects categorized jointly by smoking (and asbestos exposure if available), but one can compare observed lung cancers with those expected in a reference population with defined smoking habits. Thus comparison of observed lung cancers in non-smokers with that in a reference population of non-smokers will estimate the effect of asbestos in non-smokers, while comparison of observed lung cancers in smokers with that in a reference population of non-smokers will estimate the joint effect of asbestos exposure and smoking. One has to be careful to know what the reference population is when interpreting the meaning of the ratio of observed and expected number of lung cancers.

An alternative technique for estimating effects of asbestos exposure and smoking is the case-control study, where the relative numbers of lung cancer cases and controls in the different asbestos and smoking categories can be used to estimate relative risks in

the usual way. There are three main scenarios here. First, one might carry out a general case-control study (using either healthy population or hospital controls) with cases selected from hospitals or registers representative of a broad area. Second, one might carry out the study in an area where a history of asbestos exposure is particularly likely (e.g. in a port with shipyards). Third, one might carry out a study nested within an occupational study. One might, for example, study a large group of workers, perhaps obtaining some broad exposure data on them, then, when a number of them contract (or die from) lung cancer, carry out detailed interviews with the subject (or next-of-kin) and also with a number of healthy survivors (or decedents from other diseases unrelated to smoking or asbestos). Collecting detailed data from two or three such controls per lung cancer case, as compared to collecting such data for the whole population under study, can lead to considerable cost savings while only very slightly reducing the power to detect possible effects.

3. The 23 studies with relevant data

3.1 Introduction

Following a detailed literature search 23 studies were identified which reported epidemiological evidence relating to the joint relationship of smoking and asbestos exposure to risk of lung cancer. In the following sections, these studies are described in turn, with relevant data presented in tabular form and, where appropriate, confidence limits of relative ratios and SMRs estimated using the CIA program based on the methods described by Gardner and Altman[8]. The studies are each named by the principal author for easy reference in subsequent sections. Not included is a study by Lee et al[9] of 456 lung cancer patients which explored the relationship of smoking and asbestos exposure to location and histology of lung cancer, but not to risk of lung cancer itself.

3.2 Australia - crocidolite miners and millers (Wittenoom) - DEKLERK

Crocidolite was mined at Wittenoom in Western Australia from 1937 until 1966, and 6500 men and 410 women were known to have been employed between 1943 and 1966, a period when the mining was carried out by a single company. Deklerk et al[10-14] have presented a number of papers reporting on the mortality of the crocidolite miners. Early papers[10-12] demonstrated that risk of lung cancer was clearly associated with both level and duration of exposure to asbestos, but did not consider the role of smoking. In 1979, all the former workers who could be traced to an address were sent a questionnaire to determine their smoking history, occupational exposure already being known from employment records. Of 2928 questionnaires sent, satisfactory replies were collected from 2400 men and 149 women.

In 1991, Deklerk et al[13] reported the results of a case-control study carried out within the cohort of 2400 men. Each of the 40 men who had incident lung cancer by 1986 were matched to all other men in the cohort who were of the same age, not known to have developed asbestosis, lung cancer or malignant mesothelioma and were known to be alive in the year of diagnosis of lung cancer of the index case. Lung cancer risk in relation to asbestos exposure and ever smoking was as shown in Table 3.2.1.

The relative risk for high/low asbestos was not significantly different for never smokers and ever smokers (relative effect 0.73, 95% CI 0.11-5.80), which was noted to be not significantly different from a multiplicative model. The authors also presented the results of a conditional logistic regression analysis which included terms for cumulative asbestos exposure, time since first exposure and smoking. Compared to never smokers, relative risks were estimated as 1.30, 7.21, 13.9, 4.49, 5.76 for, respectively, ex-smokers of >10 years, 6-10 years and <6 years and current smokers of <20/day and $\geq$20/day. All increases were significant except for that in long-term ex-smokers. The authors note that "there was no significant interaction term between smoking and exposure to crocidolite ($p>0.4$ in all cases) showing that the multiplicative model fitted the data reasonably well".

In 1996, the same authors[14] repeated their case-control analyses, with updating

of mortality follow-up to 1991, so increasing the number of lung cancer cases to 71, and with consideration of histological type. The association of lung cancer with asbestos exposure was found not to significantly vary by lung cancer type, but the association of lung cancer with smoking did, being stronger for squamous cell carcinoma and small cell cancer than for adenocarcinoma and not evident for undifferentiated lung cancer. For all lung cancer types combined, results of a conditional logistic regression analysis were again presented. Here there were significant terms for duration and for intensity of exposure, for time since first exposure and for smoking category (see Table 3.2.2 below). However, again there were no significant ($p<0.20$) interaction terms between smoking and effects of asbestos exposure, consistent with a multiplicative model.

[N.B. At the time of writing a copy of a thesis by Baker published in 1985[15], describing results from this cohort of Australian crocidolite miners, was not available. The reviews by Vainio and Boffetta[5] and by Saracci and Boffetta[6] refer to the results of Deklerk et al[13] as "confirming the pattern of more than multiplicative interaction" found by Baker[15]. It seems probable that there is considerable overlap of cases between the two analyses, so the absence of Baker's thesis is of little consequence to the present review.]

TABLE 3.2.1 Lung cancer risk in relation to level of crocidolite asbestos exposure in never and ever smokers
(Miners and millers in Wittenoom, Australia[13])

Asbestos exposure	Smoking	Cases	Controls	Relative risk (95% CI)*
Low	Never	2	399	1.00 (base for never smokers)
	Ever	9	522	1.00 (base for ever smokers)
High	Never	4	357	1.90 (0.62-5.85)
	Ever	25	521	2.62 (1.18-5.79)

* matched analysis; based on the cases and controls one can calculate relative risks (95% CI) of 1.00, 3.44 (0.74-16.0), 2.24 (0.41-12.3) and 9.57 (2.25-40.7) relative to the low asbestos/never smoking group.

TABLE 3.2.2 Risk of lung cancer in relation to exposure to crocidolite asbestos and smoking history
(Miners and millers in Wittenoom, Australia[14])

Exposure/level	Relative risk (95% CI)
Crocidolite exposure:	
Duration log (days)	1.42 (1.14-1.76)
Intensity (f/ml)	1.01 (1.00-1.02)
Time since first exposure:	
0-20 y	1.00
21-25 y	0.96 (0.34-2.75)
26-30 y	0.28 (0.09-0.94)
≥31 y	0.62 (0.19-2.03)
Smoking history:	
Never smoked	1.0
Ex >10 y	2.2 (0.4-11.9)
Ex 6-10 y	12.1 (2.2-65.3)
Ex <6 y	25.1 (4.3-146.2)
Current <20/day	9.6 (2.1-43.1)
Current ≥20/day	13.1 (3.1-56.3)

3.3 Austria - asbestos cement workers (Vöcklabruck) - NEUBERGER

In 1990, Neuberger and Kundi[16] described the results of mortality follow-up until 1986 of a cohort of 2816 persons employed from 1950 to 1981 for at least three years in the oldest asbestos cement factory in the world. The factory was in Vöcklabruck in Upper Austria, where chrysotile had been used predominantly (from 1895), though crocidolite was also used in the pipe factory (from 1920 to 1977). Data on smoking habits were obtained in 1982 for living members of the cohort and, mainly from relatives, for the majority of deceased persons. Individual exposures were derived from a variety of sources including workplace history, dust concentration estimates, dust measurements, personal air samplers and membrane filter methods.

During the period 1950-1986, there were 49 deaths from lung cancer, compared with 28.50 expected based on age, sex and period specific rates for Upper Austria (SMR = 1.72, 95% CI 1.21-2.57). After adjustment for smoking habits, based on Austrian microcensus data on smoking habits and assuming that smokers have eight times the lung cancer rate of non-smokers, the SMR was recalculated as 1.04 (95% CI 0.79-1.41). An alternative analysis used data collected on average number of cigarettes smoked per day and assumed, based on results from major epidemiological studies on smoking and lung cancer, that the logarithm of the lung cancer rate was linearly related to the logarithm of the number of cigarettes smoked each day (plus one). The results, presented graphically, showed that the observed lung cancer rate was very close to the smoking-adjusted expected lung cancer rated for smokers of 0, 10, 25, 40 and 50 cigarettes/day. The paper did not give the number of lung cancer deaths by smoking group.

Overall, the results were clearly consistent with asbestos exposure having no effect on the risk of lung cancer in either ever smokers or never smokers.

3.4 Canada - chrysotile miners and millers (Quebec) - LIDDELL

In 1997, Liddell et al[17] described the results of mortality follow-up until 1992 of a cohort of 10918 men born between 1891 and 1920 and employed for at least a month in the chrysotile mines and mills in Asbestos and Thetford in Quebec. These men have been under study since 1966, lung cancer rates for 1950-1992 being compared with age-specific rates for Quebec. Smoking habits were obtained by questionnaire in 1970. Various earlier papers [18-21] have reported results relating to shorter mortality follow-up. Some of these refer to the 440 women in the cohort, though as only one lung cancer had occurred by 1975, at a time when 250 had occurred in men, these add little useful information. An earlier paper by Braun and Truan[22] presented data for miners in Asbestos only, but this related to 9 lung cancer deaths only, all in smokers.

During the complete follow-up period, 8009 deaths occurred in men, of which 657 were from lung cancer. For the period 1950-1992, the SMR for lung cancer was estimated as 1.37, based on 646 deaths. The SMR rose with increasing accumulated exposure by age 55, being 1.21, 1.46, 1.84 and 2.97 for, respectively, <300, 300 to <400, 400 to <1000 and ≥1000 million particles per cubic foot x years (mpcf.y). For the 409 deaths between 1975 and 1992, SMRs were clearly smoking relating, being 0.55, 0.72, 1.43 and 2.55 for, respectively, non-smokers of cigarettes, ex-smokers, smokers of <20 cigarettes a day and smokers of ≥20 cigarettes a day.

The 1997 paper does not report results relating to the joint association of smoking and asbestos exposure with risk of lung cancer, but results based on mortality from 1976 to 1988 were reported earlier by McDonald et al[23] and are shown in Table 3.4.1. The authors calculated the "asbestos effect" as the ratio of the SMR for exposed workers (taken here as those exposed to 60 or more mpcf.y) to that for the unexposed (taken as exposed to less than 60 mpcf.y). This was 1.13 overall, highest for non-smokers of cigarettes and lowest for smokers of 20 or more cigarettes a day, though the variation by smoking habits is not significant.

Some further results related to the possible interaction of cigarette smoking and

asbestos exposure are also available. McDonald et al[20], based on mortality to 1975, reported SMRs as given in Table 3.4.2 and Table 3.4.3. The first is from standard SMR calculations, while the second is from a case-control analysis in which, for each lung cancer case, a control worker known to have survived to a greater age than that at which the case died and matched on birth year and smoking habits was randomly selected. Both analyses suggest a stronger effect of asbestos in nonsmokers, though the small numbers of deaths in nonsmokers make firm inferences impossible.

Liddell et al[21] also report results of a case-control analysis, based on deaths occurring by the end of 1975. Here the analysis was not matched for smoking habits and was based on all 223 cases and 715 referents for whom smoking histories were available. These are shown in Table 3.4.4.

Finally, Liddell et al[24] report analyses of mortality up to 1992 based on a case-control analysis of 488 lung cancer cases formerly employed at three specific workplaces and 1941 controls, up to 4 per case, sought by random selection from among survivors to a greater age, after matching on place of employment, age of starting work, smoking habits and date of birth. Detailed results showing the joint relationship of smoking and asbestos to lung cancer risk were not presented in a convenient form, but the authors commented “In the current study, the direct effects of cigarette smoking on the risks of lung cancer were effectively eliminated by the matching in the selection of referents. However, the interactions of smoking and asbestos exposure could be examined; the only two that were not trivial indicated higher lung cancer relative risks for non- and ex-smokers than for cigarette smokers”.

TABLE 3.4.1 Lung cancer SMR in relation to chrysotile asbestos exposure and smoking habits
(Miners and millers in Quebec, Canada[23])

Asbestos exposure (mpcf.y)	Smoking habits	Deaths	SMR†	Asbestos effect*
<60	Non-smokers	10	0.37	
	Ex-smokers and <20 cigs/day	44	0.97	
	≤20 cigs/day	88	2.54	
	All smokers of cigarettes	132	1.65	
≥60	Non-smokers	11	0.61	1.65
	Ex-smokers and <20 cigs/day	61	1.21	1.25
	≥20 cigs/day	85	2.29	0.90
	All smokers of cigarettes	146	1.67	1.01

† Reference = Quebec population; mortality 1976-1988
* Ratio of SMR for exposure ≥60 mpcf.y to SMR for exposure <60 mpcf.y

TABLE 3.4.2 Lung cancer SMR in relation to chrysotile asbestos dust exposure and smoking habits
(Miners and millers in Quebec, Canada[20])

Dust exposure by age 45 (mpcf.y)	Smoking habits	Deaths	SMR†
<30	Non-smokers	5	0.18
	1-25 cigs/day	73	1.14
	26-50 cigs/day	13	2.12
30-<300	Non-smokers	6	0.36
	1-25 cigs/day	64	1.35
	26-50 cigs/day	11	2.39
≥300	Non-smokers	8	1.24
	1-25 cigs/day	52	2.31
	26-50 cigs/day	10	4.50

† Reference = Quebec population; mortality 1951-1975

TABLE 3.4.3 Lung cancer risk in relation to chrysotile asbestos dust exposure in different smoking groups
(Miners and millers in Quebec, Canada[20])

Smoking habits	Dust exposure up to 9 years before death of case (mpcf.y)	Deaths†	Controls	Relative risk
Non-smokers	<30	5	10	1.00 (base)
	30-<300	5	6	1.67
	300-<1000	5	3	3.33
	≥1000	5	1	10.00
Smoking habit undifferentiated	<30	43	49	1.00 (base)
	30-<300	23	33	0.79
	300-<1000	22	17	1.47
	≥1000	12	1	13.67
Definite cigarette smokers	<30	41	49	1.00 (base)
	30-<300	45	48	1.12
	300-<1000	29	22	1.58
	≥1000	10	6	1.99

† Mortality 1951-1975

TABLE 3.4.4 Lung cancer risk in relation to chrysotile asbestos dust exposure and pack-years of smoking
(Miners and millers in Quebec, Canada[21])

Dust exposure up to 9 years before death of case (mpcf.y)	Pack-years of smoking	Deaths	Controls	Relative risk*
<100	0	6	103	0.19
	1 to <40	29	123	0.76
	40+	40	117	1.10
100-<1000	0	7	61	0.37
	1 to >40	27	93	0.93
	40+	35	79	1.42
1000+	0	10	37	0.87
	1 to >40	34	63	1.73
	40+	35	39	2.88

* Base = risk for total population

3.5 China - chrysotile asbestos products workers (Tianjin) - CHENG

Cheng and Kong[25] describe a cohort study of 662 men and 510 women working in a chrysotile asbestos products factory in Tianjin, China in 1972, with at least 1 year's asbestos exposure by that time. Exposure level of asbestos was classified as high, middle or low depending on work history, and smoking history was obtained. Mortality was followed until 1987 and compared with that in the Tianjin population, 21 deaths from lung cancer being observed as against 6.67 expected (SMR 3.15, $p<0.05$). Dose-response relationships were seen with various aspects of asbestos exposure. Table 3.5.1 shows the joint relationship of lung cancer death rate to asbestos exposure and cigarette smoking. The death rates for those unexposed to asbestos were for a control population of 3219 workers not exposed to asbestos, dust, fumes or vapour, not otherwise defined in the paper. The death rates are stated to be "standardized for age and smoking habits", although this makes little sense when the data are already subdivided by smoking habits. They are also stated to be lung cancer rates "20 or more years from onset of exposure" in relation to cigarette smoking, although they are given for unexposed and exposed populations. The numbers of deaths on which the rates are based are not given.

TABLE 3.5.1 Lung cancer risk in relation to chrysotile asbestos exposure and cigarette smoking
(Asbestos products workers in Tianjin, China[25])

Asbestos exposure	Cigarette smoking	Death rate	Mortality ratio
No	No	38.27	1.00
No	Yes	60.31	1.57
Yes	No	208.23	5.44
Yes	Yes	334.24	8.73

3.6 China - chrysotile asbestos products workers (eight factories) - HUILAN

Huilan and Zhiming[26] describe results of a study of mortality of workers in eight chrysotile asbestos factories in China during the period 1972-1986. Their mortality was compared with a control group of workers not exposed to asbestos, though it was not made clear where these workers were employed. Data were collected from a variety of sources on smoking habits and other relevant factors. There were 67 lung cancer deaths in asbestos workers during 85419 person-years of observation as against 18 in controls during 122021 person-years (RR = 5.3, $p<0.01$). A standardized relative risk was estimated as 4.2 ($p<0.01$), though it is unclear what was standardized for, and the table presenting the calculations seems incorrect, estimating the SRR as a ratio of expected deaths in asbestos workers and controls, which makes no sense. Table 3.6.1 shows the joint relationship of smoking and asbestos exposure for risk of lung cancer. It should be noted that, though the relative risks given are generally close to those calculated from the ratio of cases to person-years as compared to the group of unexposed non-smokers, this is not so for the exposed heavy smokers.

TABLE 3.6.1 Lung cancer risk in relation to chrysotile asbestos exposure and smoking habits
(Asbestos products workers in eight factories in China[26])

Asbestos exposure	Smoking habits	Cases	Person-years	RR1*	RR2*
No	No	4	42502	1.0	1.0
No	Yes	11	63714	1.8	1.8
Yes	No	15	42218	3.8	3.8
Yes	<10 cigs/day	4	3812	11.3	11.1
	1-20 cigs/day	11	8689	13.7	13.5
	>20 cigs/day	12	13432	17.8	9.5

RR1 as given in the paper; RR2 as calculated from the cases and person-years

3.7 England - asbestos factory workers (east London) - BERRY

Berry et al[3,27] have reported mortality results related to a cohort of 1834 men born between 1900 and 1930, first employed at an asbestos factory between 1933 and 1955 and who had not been employed as laggers, and 658 women first employed at the factory between 1936 and 1942.

The first paper[27] considers mortality over the period 1960 to 1970, taking into account smoking habits obtained retrospectively for 220 out of 278 decedents from medical records and in some cases from approaches to relatives, and by postal questionnaire for 1596 out of 2214 survivors. Observed numbers of lung cancer deaths, by sex, asbestos exposure and smoking habits among the deceased, were compared with expected numbers, based on national age, sex and period specific lung cancer rates, with adjustment for

1. the higher lung cancer mortality in Greater London compared to England and Wales,
2. the differing lung cancer risks in smokers, ex-smokers and non-smokers and
3. the different proportions of subjects with smoking histories amongst the survivors and the dead in any subgroup.

Table 3.7.1 shows the adjusted observed (O) and expected (E) numbers of lung cancer deaths, the ratio being an estimate of the effect of asbestos exposure. It can be seen that the evidence of an effect is limited to those with severe asbestos exposure. Table 3.7.2 gives the results of analyses carried out by the author on the subjects with severe asbestos exposure, investigating the fit of the additive and multiplicative model. Based on this analysis, the authors conclude that "for the men the excess for ex-smokers is consistent with the additive hypothesis, but the non-smokers are more in agreement with the multiplicative hypothesis. On balance the results for the men are not sufficiently clearcut for discrimination between the two hypotheses to be possible. For the women, the data clearly follow the multiplicative hypothesis, although on these data alone it might be premature to reject the additive hypothesis ($p = 0.06$). However, the relative likelihood of the two hypotheses is 6 to 1 in favour of the multiplicative".

The second paper[3] included additional data from follow-up of mortality up to

1980, and a retrospective assessment of smoking habits for those dying during the follow-up. The paper provided four main pieces of information. First, the authors compared the smoking habits obtained retrospectively after 1980 from those obtained from the subjects in 1971 when they were still alive. Whereas smoking habits were validated for most smokers, the validation rate for those who were recorded as "never smokers", either during life or at death, was found to be lower. Second, they reported (see Table 3.7.3) revised results for deaths occurring in 1960-70 among workers with severe asbestos exposure, using an adjustment method that avoided fractional observed numbers. Third, they reported the observed lung cancers occurring in 1971-80 by sex, smoking habits and asbestos exposure and compared them with expected numbers, after making allowance, in a similar way to in the previous paper, for smoking, sex, age, period and region. As shown in Table 3.7.4, the excess mortality is again seen predominantly in the workers with severe asbestos exposure.

Finally, Berry et al[3] estimated the relative risk of lung cancer associated with asbestos exposure in non-smokers (A_{NS}) and in ever smokers (A_S) in 6 "studies" - his 1960-70 data, his 1971-80 data and four major studies in US and Canada. Overall, A_{NS}/A_S was estimated as 1.8 (95% CI 1.1-2.8) indicating a simple multiplicative relationship might not hold exactly. However, the authors referred to "some uncertainty on the accuracy of this figure because of possible biases and sampling variations."

TABLE 3.7.1 Observed lung cancers by asbestos exposure and smoking compared to numbers expected for Greater London population with given smoking habits
(Asbestos factory workers in east London, England[27])

Asbestos exposure	Smoking habits	Men O†	Men E†	Men O/E	Women O†	Women E†	Women O/E
Low/moderate	Never smoked	0	0.0	-	0	0.0	-
	Ex-smokers	0	0.1	0			
	Smokers*	4.6	6.2	0.74	1	0.3	3.33
	Not known	3.4	2.0	1.70	0	0.1	0.00
Severe	Never smoked	0	0.0	-	1.7	0.2	8.50
	Ex-smokers	1.6	0.2	8.00			
	Smokers*	25.5	9.9	2.58	15.5	1.4	11.07
	Not known	10.9	2.4	4.54	2.8	0.4	7.00

† O = adjusted observed deaths from lung cancer (including pleural mesothelioma in 1960-70)
E = adjusted expected deaths (see text for details of adjustment)
* Current smokers for men; current and ex-smokers combined for women

TABLE 3.7.2 Fit of additive and multiplicative model in subjects with severe asbestos exposure
(Asbestos factory workers in east London, England[27])

Sex	Smoking habits	Observed* (adjusted)	Expected* (adj. for smoking)	Expected Additive	Expected Multiplicative
Men	Never smoked	0	0	0.9	0.1
	Ex-smokers	1.6	0.2	1.1	0.6
	Smokers	25.5	9.9	25.1	26.4
Women	Never smoked	1.7	0.2	4.7	1.9
	Smokers	15.5	1.4	12.5	15.3

* Lung cancer deaths (including pleural mesothelioma) occurring in 1960-70

TABLE 3.7.3 Observed lung cancers by sex and smoking compared to numbers expected for Greater London population with given smoking habits (Asbestos factory workers in east London, England[3])

Sex	Smoking habits	Observed deaths*	Expected (adj. for smoking)	O/E
Men	Never smoked	0	0.0	-
	Ex-smokers	2	0.3	6.7
	Smokers	27	12.0	2.2
Women	Never smoked	1	0.2	5.0
	Smoked at some time	14	1.9	7.4

* From lung cancer excluding pleural mesothelioma in 1960-70

TABLE 3.7.4 Observed lung cancers by sex, asbestos exposure and smoking compared to numbers expected for Greater London population with given smoking habits
(Asbestos factory workers in east London, England[3])

Asbestos exposure	Smoking habits	Men O†	Men E†	Men O/E	Women O†	Women E†	Women O/E
Low/moderate	Never smoked	1	0.10	10.0	0	0.04	0.0
	Ex-smokers	3	1.07	2.8	0	0.09	0.0
	Smokers	17	11.29	1.5	0	0.32	0.0
Severe	Never smoked	0	0.06	0.0	3	0.20	15.0
	Ex-smokers	8	1.25	6.4	2	0.50	4.0
	Smokers	35	14.63	2.4	10	2.02	5.0

† O = observed deaths from lung cancer excluding pleural mesothelioma in 1971-80,
E = adjusted expected deaths

3.8 England - amosite asbestos factory workers (Uxbridge) - ACHESON

Acheson et al[28] describe the mortality experience of 5969 men employed in a factory in Uxbridge where insulation board was manufactured predominantly using amosite asbestos but sometimes using chrysotile asbestos during the period 1947 to 1979. 4820 of the men had been directly employed in insulation board manufacture and 1149 had not, being brickmakers, office workers, canteen staff, cleaners, etc. Data on extent and duration of asbestos exposure was obtained from work histories and data on smoking were collected, for 2461 men who had been employed on or after 1971, when such information began to be recorded in the medical records of employees. Between 1947 and 1979, 71 deaths from lung cancer occurred compared with 38.5 from age and period specific death rates for England and Wales. 61 of these (including one pleural mesothelioma) occurred in the asbestos workers, compared to 29.1 expected, the SMR of 2.1 being significantly ($p<0.01$) elevated. In the other workers, where 10 lung cancer deaths occurred as against 9.4 expected, no significant elevation occurred. There was a clear trend in lung cancer risk with highest asbestos exposure category, the SMRs being 4.25, 2.25, 1.34 and 1.06 for, respectively, heavy, medium, low/casual and background exposure, but no relationship to duration of exposure or time since first exposure. As shown in Table 3.8.1 below, for the workers with smoking data available, among whom 26 lung cancer deaths occurred, excess mortality compared to national data was restricted to current smokers and those with high asbestos exposure.

TABLE 3.8.1 Lung cancer SMR in relation to amosite asbestos exposure and smoking habits
(Factory workers in Uxbridge, England[28])

Asbestos exposure	Smoking habits	Observed deaths	Expected deaths	SMR†
Background*	Non	0	0.4	0
	Ex	0	0.5	0
	Current	0	2.1	0
Casual/low	Non	0	0.5	0
	Ex	0	0.5	0
	Current	4	2.0	2.00
Medium/heavy	Non	1	1.1	0.91
	Ex	3	0.6	5.00
	Current	18	8.4	2.14

† Reference group = England and Wales population
* Those not working in insulation board manufacture were classed as having background exposure

3.9 England - case-control study (Gateshead) - MARTISCHNIG

Martischnig et al[29] describe the results of a case-control study conducted in 1972-73 in Gateshead in North-East England involving 201 men admitted to a thoracic surgical centre with a firm diagnosis of lung cancer made by radiography, bronchoscopy or thoracotomy and 201 men, matched on age and catchment area, who were patients in general hospitals with no evidence of lung cancer. All men were interviewed to obtain a detailed occupational history and data on the greatest number of cigarettes ever smoked regularly. 58 of the men with cancer gave a history of exposure to asbestos, as compared with only 29 of the controls ($p<0.001$). None of these exposures related to working in asbestos manufacturing or in use of asbestos as a principal material in their work. Smoking was also found to be strongly associated with lung cancer, despite the control group apparently including patients with other smoking-related diseases, so distorting the relative risk estimates. Table 3.9.1 shows the joint relationship of smoking and asbestos exposure to risk of lung cancer. The authors note that "although these figures were consistent with a constant risk from asbestos exposure (independent of smoking level), they were also consistent with some element of synergism".

TABLE 3.9.1 Risk of lung cancer in relation to asbestos exposure and smoking habits (Case-control study in Gateshead, England[29])

Asbestos exposure	Smoking habits (cigs/day)	Cases	Controls	Relative risk* (95% CI)
No	0-14	28	52	1.00
	15-24	66	77	1.59 (0.91-2.80)
	25+	49	43	2.12 (1.14-3.92)
Yes	0-14	7	12	1.08 (0.38-3.06)
	15-24	25	10	4.64 (1.95-11.0)
	25+	26	7	6.90 (2.66-17.9)

* Calculated from numbers of cases and controls

3.10 Finland - asbestos sprayers and asbestosis and silicosis patients - OKSA

Oksa et al[30] identified three cohorts for mortality follow-up:

(i) 129 men and 4 women who had worked as asbestos sprayers some time between 1955 and 1976. The sprayers were identified in 1987 at which time 60 living members reported data on smoking habits and duration of exposure during a health examination.

(ii) 118 men and 10 women identified as having diagnosed asbestosis. Smoking habits and exposure data were reported during clinical examinations in 1977-1985.

(iii) 163 men and 7 women identified as having silicosis. Smoking habits and exposure were available for all of these subjects, as for the asbestosis group.

Follow-up for cancer was carried out starting in 1967 or the date of first employment as an asbestos sprayer or the first health examination since 1977 for the asbestosis and silicosis and ending in 1994 or at death or emigration if earlier. Cancer incidence and mortality were compared with national age, sex and period specific rates for Finland. The main results of the study for men are summarized in Table 3.10.1. It can be seen that incidence of lung cancer was higher than expected in all groups, particularly so for asbestos sprayers and asbestosis patients. The paper notes that elevated risk was clearly elevated for all the main histological types of lung cancer - squamous cell, small cell and adenocarcinoma. None of the 58 lung cancers were seen in non-smokers.

Later Oksa et al[31] reported further results for 78 men and 5 women in the asbestosis group, who had attended for radiography at least twice. 24 of the men were classified as having progressive small opacity profusion, the remainder being classified as having asbestosis without progression. The SIR for lung cancer was estimated as 37 (95% CI 18-66) for the progressors and 4.3 (1.4-9.9) for the non-progressors. As would be expected from the previous paper, all the lung cancers occurred in current or ex-smokers. After adjustment for age at the beginning of radiographic follow-up, occupation, exposure time, ILO minor category at the beginning of the follow-up, and time lag between diagnosis of asbestosis and beginning of the follow-up, only small

opacity progression (OR = 9.6, 95% CI 2.53-36.8) and current smoking (8.3, 2.15-32.2) were found to significantly predict lung cancer risk. The effect of possible interactions between current smoking and other variables was apparently not tested.

TABLE 3.10.1 Lung cancer SMR in relation to smoking habits in three groups exposed to asbestos
(Finnish asbestos sprayers and asbestosis and silicosis patients[30])

	Asbestos sprayers			Asbestosis patients			Silicosis patients		
Smoking habits	n	SIR*	95% CI	n	SIR*	95% CI	n	SIR*	95% CI
Incidence									
All subjects	10	17	8.2-31	33	10	6.9-14	15	2.7	1.5-4.5
Non-smokers	0	(0.1)	0.0-57	0	(0.6)	0.0-6.2	0	(1.1)	0.0-3.5
Ex-smokers	1	8.8	0.2-49	14	6.8	3.7-11	6	2.0	0.7-4.4
Smokers	2	13	1.5-46	19	30	18-47	9	6.1	2.8-11
Smoking unknown	7	28	11-58	-	-	-	-	-	-
Mortality									
All subjects	8	17	7.2-33	25	8.0	5.2-12	10	1.9	0.9-3.5

* SIR for incidence, SMR for mortality. Bracketed numbers are expected numbers. Reference group = Finnish population

3.11 Finland - anthophyllite asbestos miners (North Savo) - MEURMAN

Two anthophyllite asbestos mines were in operation in North Savo, Finland between 1918 and 1975. Meurman et al have published three papers[32-34] describing the mortality of the workers there. The first [32] concerned 1092 workers employed for at least 3 months between 1936 and 1967. These workers were compared with the same number of inhabitants of Maaninka, an agricultural area 60 km from the mines containing no mines or other industrial plants, matching being on date of birth, sex, vital status as at 1967 and date of death if dead. Of the 248 deaths in each population, there were 21 from lung cancer in the mineworkers and 13 from lung cancer in the matched controls. This compared with an expected number of 12.6, based on national age-specific data for Finland on the proportion of total deaths that were from lung cancer. For asbestos employees with more than 10 years of exposure, 8 lung cancer deaths occurred as against 2.4 expected. Smoking habits were collected from cases and controls living in 1967, but were not known for decedents. On the basis of published data on the relationship between lung cancer and number of cigarettes smoked, the relative frequency of smoking in living cases and controls, and assuming a multiplicative relationship between asbestos and smoking, the authors estimated that the risk, relative to a non-smoker without exposure to asbestos, is 1.4 for a non-smoking asbestos worker, 12 for a smoker without exposure to asbestos and 17 for an asbestos worker who smokes. However, it should be emphasized that these estimates are not based on actual data on risk of lung cancer according to smoking habits and asbestos exposure, and are based on the very assumptions that one wishes to verify.

The second paper[33] also concerned the mortality of workers employed between 1936 and 1967 but incorporated data collected on smoking habits from interviews of survivors in 1967 and involved mortality follow-up to 1977. There were 23 further lung cancer deaths in workers occurring in 1967-1977, as against 9.4 expected from proportional mortality data for Finland. 17 of these occurred in those with heavy asbestos exposure, as against 5.1 expected. Based on the 1967-77 data, assuming that the smoking habits of those living in 1967 are representative of the whole population of employees and that there is a multiplicative relationship between cigarette smoking and asbestos exposure as regards risk of lung cancer, the authors estimated relative risks of

1, 1.6, 12 and 19 for, respectively, unexposed non-smokers, asbestos exposed non-smokers, unexposed smokers and exposed smokers. However, again these risks are theoretical, and not actual. The only actual information regarding smoking habits presented in the paper showed that 22 of the 23 lung cancer cases were smokers, no data being given on the joint relationship of smoking and extent of asbestos exposure to risk of lung cancer.

The most informative paper as regards the joint effect of smoking and asbestos exposure was the latest one, published in 1994[34]. This describes a study of cancer incidence of 736 male and 167 female workers employed for at least 3 months between 1953 (after nationwide cancer registration began in Finland) and 1967. Between 1953 and 1991 incident lung cancer was recorded in 76 male and 1 female worker. Compared with age specific incidence rates in the administrative unit of Finland where the mines were located, the SIR was estimated as 2.88 (95% CI 2.27-3.60) for males and 2.22 (0.06-12.4) for females. In males, the increased incidence was evident both in those with heavy exposure (55 cases, SIR 3.15, 95% CI 2.37-4.09) and those with moderate exposure (21 cases, SIR 2.35, 95% CI 1.45-3.58). Heavy exposure was defined as actually working in the mine or the mill, moderate exposure as the rest of the personnel. As noted above, data on smoking habits were collected in 1967 for almost all workers alive at the time. Risk in relation to smoking habits among the 598 men with smoking data, 398 with heavy exposure, is summarized in Table 3.11.1. As can be seen, risk was similarly smoking-related in both asbestos exposure categories.

TABLE 3.11.1 Lung cancer SIR in relation to anthophyllite asbestos exposure and smoking habits
(Finnish miners[34])

Exposure	Smoking habits	Cases	SIR (95% CI)*
Moderate	No	1	0.58 (0.01-3.21)
	1-15	4	2.65 (0.45-4.21)
	16+	8	4.49 (1.94-8.84)
Heavy	No	1	0.48 (0.01-2.64)
	1-15	20	2.79 (1.70-4.30)
	16+	21	4.91 (3.04-7.50)
Total	Total	55	2.79 (2.10-3.63)

* Reference group = administrative unit of Finland where mines based

3.12 Italy - chrysotile asbestos miners and millers (Balangero) - RUBINO

The Balangero mine and mill near Turin has been producing pure chrysotile asbestos since 1916. Rubino et al[35] describe a study of the mortality of 952 male asbestos workers first employed between 1930 and 1965. Between 1946 and 1975, 11 of the workers were recorded as having died of lung cancer on their death certificate, a number similar to that expected, 10.4, based on age and period specific rates for the Italian population. A case-control study was also conducted from within the study population, involving 12 cases diagnosed from the most reliable available source as having lung cancer and 5 controls for each case matched on year of birth and alive at the time of death of the case. Data on smoking habits and on cumulative dust exposure were obtained, and are summarized in Table 3.12.1. Risk was non-significantly higher in those with 101+ fibres/year exposure than in those with lower exposure (RR = 2.89, 95% CI 0.58-14.4). All 12 lung cancer cases were smokers.

An earlier study of Balangero workers was carried out by Ghezzi et al[36] on miners employed between 1932 and 1970. Lung cancer rates in the miners were no higher than in male inhabitants of two neighbouring villages. Smoking habits were not studied.

TABLE 3.12.1 Lung cancer cases and controls by chrysotile asbestos dust exposure and smoking habits
(Miners and millers in Balangero, Italy[35])

Dust exposure (fibres/year)	Smoking habits	Lung cancer cases	Controls
≤100	Non-smokers	0	6
	Unknown	0	3
	Smokers	2	13
101+	Non-smokers	0	7
	Unknown	0	3
	Smokers	10	28
Total	Total	12	60

3.13 Italy - case-control study (Lombardy) - PASTORINO

Pastorino et al[37] describe the results of a study of lung cancer carried out in 1976-79 in a highly industrialized region of Lombardy in Northern Italy, involving 204 men with a confirmed diagnosis of lung cancer and 351 age-matched male population controls. Information was obtained on their occupational and smoking history, from next-of-kin for over half the cases and about 10% of the controls and from direct interviews of the subject otherwise. Exposure to asbestos (and other chemicals) was inferred as being probable, possible or not occurring, based on the occupational history, no direct questions being asked about specific exposures. Table 3.13.1 summarizes relevant results from the study. The authors note that the results, which show clear evidence of an effect for both asbestos and smoking, are generally "comparable with what one would expect under a multiplicative model".

TABLE 3.13.1 Risk of lung cancer in relation to smoking habits and exposure to asbestos and polycyclic aromatic hydrocarbons (case-control study in Lombardy, Italy[37])

PAH exposure	Asbestos exposure	Smoking habits (cigs/day)	Cases	Controls	Relative risk (95% CI)*
No	No	0-9	7	69	1.00 (base for no PAH data)
		10-19	17	42	3.99 (1.53-10.4)
		20+	49	77	6.27 (2.66-14.8)
	Yes	0-9	2	7	2.82 (0.49-16.3)
		10-19	9	13	6.82 (2.16-21.6)
		20+	22	18	12.0 (4.45-32.6)
Yes	No	0-9	4	31	1.00 (base for PAH data)
		10-19	12	17	5.47 (1.53-19.6)
		20+	30	30	7.75 (2.43-24.7)
	Yes	0-9	2	7	2.21 (0.34-14.6)
		10-19	7	2	27.1 (4.12-179)
		20+	15	9	12.9 (3.42-48.8)
Both	No	0-9	11	100	1.00 (base for overall data)
(adjusted		10+	108	166	5.95 (3.05-11.6)
for PAH)	Yes	0-9	4	14	2.52 (0.70-9.10)
		10+	53	42	11.5 (5.47-24.3)

* Calculated from numbers of cases and controls

3.14 Italy - case-control study (Trieste) - BOVENZI

Bovenzi et al[38] describe the results of a study conducted in Trieste, a coastal area of North Eastern Italy where metallurgical and mechanical industries, docks and shipyards are located. The study involved 756 men who died of lung cancer in 1979-81 or 1985-86 and a similar number of men, matched on age and period of death, who died of causes other than chronic lung disease and various smoking-related cancers. (Note that a large proportion of the control men died of vascular disease, so this will somewhat bias the smoking relative risk estimates.) Data on occupational history, smoking and area of residence were collected from interviews of next-of-kin. Asbestos exposure was assessed from the work history as definite, possible or absent. Table 3.14.1 shows the joint relationship of lung cancer risk to smoking and asbestos exposure, the authors noting that the joint effect was "near multiplicative" though this does not seem to have been formally tested. Additional analyses showed that the risks of squamous cell carcinoma, small cell carcinoma and adenocarcinoma were each significantly increased by about 2-fold in relation to definite asbestos exposure, but the joint relationship with smoking and asbestos was not shown by histological type.

TABLE 3.14.1 Risk of lung cancer in relation to smoking habits and exposure to asbestos (case-control study in Trieste, Italy[38]

Asbestos exposure	Smoking habits (cigs/day)*	Cases	Controls	Relative risk (95% CI)**
None	Never	10	103	1.0
	1-19	66	122	5.57 (2.73-11.4)
	20-39	99	88	11.6 (5.70-23.6)
	40+	80	39	21.1 (9.94-44.9)
Possible	Never	4	26	1.58 (0.46-5.46)
	1-19	41	46	9.18 (4.23-19.9)
	20-39	38	30	13.0 (5.82-29.2)
	40+	31	13	24.6 (9.82-61.4)
Definite	Never	4	19	2.17 (0.62-7.63)
	1-19	40	37	11.1 (5.06-24.5)
	20-39	63	27	24.0 (10.9-53.0)
	40+	40	11	37.5 (14.8-95.0)

* Lifetime average ** CI calculated from numbers of cases and controls

3.15 Japan - case-control study (Yokosuka) - MINOWA

Minowa et al[39] describe the results of a case-control study of lung cancer carried out in Yokosuka, the location of a pre-war Japanese naval factory and present site of a US naval base. 116 men who had died of lung cancer in Yokosuka Kyosai hospital between 1978 and 1982 and for whom the address of the family was known were identified and were individually matched on date of birth with fatal cases without cancer, pneumoconiosis, accident or suicide. Successful interviews with relatives, using a detailed questionnaire which included detailed data on smoking and occupation were obtained for 96 cases and 86 controls. The occupational history was used to classify subjects as having exposure, suspected exposure or no exposure. Table 3.15.1 summarizes some relevant results that are available from the study. There is a clear association of risk with smoking and a weak but statistically significant association with asbestos exposure. Unfortunately numbers of cases and controls are not given for the analyses of the joint effects, and it is not even clear from the data presented whether the relative risk for asbestos exposed non-smokers or long-term quitters is zero or infinite. The authors also calculate that the relative risks for the 3 levels of exposure are 1.00, 1.56 and 2.41 ($p<0.05$) afer adjustment for smoking and the relative risk for smoking or short-term quitting is 6.01 ($p<0.05$) after adjustment for asbestos. Associations with smoking and with asbestos are noted to be stronger for the Kreyberg I histological type of lung cancer (predominantly squamous cell carcinoma) than for the Kreyberg II type (predominantly adenocarcinoma).

TABLE 3.15.1 Lung cancer risk in relation to asbestos exposure and smoking habits (Case-control study in Yokosuka, Japan[39])

Asbestos exposure	Smoking habits	Cases	Controls	Relative risk* (95% CI)
Any	Non-smokers	3	15	1.00 (base)
	Ex-smokers	15	12	7.69 (1.8-32.9)
	Smokers	78	59	6.52 (1.8-23.6)
Not exposed	Any	32	43	1.00 (base)
Suspected		26	21	1.66 (0.8-3.5)
Exposed		38	22	2.54 (1.27-5.09)
Not exposed	Non-smokers + Quit 10+ years			1.00 (base)
	Smokers + Quit <10 years			3.38
Suspected	Non-smokers + Quit 10+ years			2.33
	Smokers + Quit <10 years			4.84
Exposed	Non-smokers + Quit 10+ years			-
	Smokers + Quit <10 years			8.28

* Adjusted for age, CI estimated from numbers; dash indicates "not applicable because of zero division in odds ratio calculation"

3.16 Norway - case-control study (Telemark and Vestfold) - KJUUS

Kjuus et al[40] describe results of a study, conducted in 1979-1983 in two Norwegian county hospitals (Telemark and Vestfold) in industrial and shipbuilding areas, involving 176 male incident lung cancer cases and 136 age-matched controls without COPD, other diseases which would have precluded employment in heavy industry, obvious mental impairment or poor general health. As described more fully in another paper[41], subjects were interviewed in detail concerning occupational exposures, including asbestos, smoking habits, and other relevant variables. Asbestos exposure was graded into four categories, 0 = no exposure, 1 = uncertain, indirect or light/sporadic, 2 = moderate for less than 10 years or heavy for less than 1 year, and 3 = moderate for 10 years or more and heavy for one year or more. After adjustment for smoking (0-9, 10-19, 20+ cigs/day) and urban/rural status, relative risks of lung cancer by level of asbestos exposure were 1.0, 1.4 (95% CI 0.8-2.3), 2.8 (1.2-6.7) and 4.3 (1.5-12.0). Associations were evident for squamous cell, small cell and adenocarcinoma. Table 3.16.1 shows how the relative risk of lung cancer varied by asbestos exposure and smoking. The authors note that the interaction observed between asbestos and smoking conformed more closely to a multiplicative model than to an additive one. They also presented a table giving risks of lung cancer jointly by cigarette smoking in five levels (0-4, 5-9, 10-19, 20-29, 30+) and the four individual grades of exposure. However, these are clearly risks fitted by a multiplicative model and not actual risks observed. In the model risk is increased by factors 1.0, 2.9, 9.1, 16.5 and 90.3 for the five smoking categories and by 1.0, 1.2, 2.7 and 4.1 for the four asbestos groups, giving a predicted 370.2-fold increase for the combination of the two highest categories.

TABLE 3.16.1 Lung cancer risk in relation to asbestos exposure and smoking habits (Case-control study in Telemark and Vestfold, Norway[40])

Asbestos exposure	Smoking (cigs/day)	Cases	Controls	Relative risk (95% CI)*
0-1	0-9	29	96	1.0
	10-19	68	55	4.1 (2.4-7.1)
	20+	35	8	14.5 (6.1-34.7)
2-3	0-9	8	11	2.4 (0.9-6.6)
	10-19	27	5	17.9 (6.3-50.6)
	20+	9	1	29.8 (3.6-245)

*CI estimated from numbers of cases and controls

3.17 Norway - workers in an electrochemical plant (Telemark) - HILT

In a nitric acid production plant within an electrochemical industrial complex in Telemark county in southern Norway, asbestos has been extensively used since 1928 as a joining material in granite towers where nitric acid was synthesized, and as a gasket material in various processes. Hilt et al[42] studied the mortality, over the period from 1953 to 1980, of a cohort of men regularly exposed to asbestos at the plant between 1928 and 1961. Information on extent of asbestos exposure was inferred from type of job and information on smoking was obtained from various sources. Between 1953 and 1980 there were 17 deaths from cancer of the lung or pleura, 4 of which were from malignant mesothelioma. The 17 deaths could be compared with 3.8 expected based on age, sex and period specific mortality rates for Norway. The SMR, 4.5 for the total cohort, was higher for heavily exposed men, 8.9, than for lightly exposed men, 2.4. Hilt et al[42] compared age-adjusted lung cancer rates by smoking habits for the period 1966-1977 for the 214 cohort members alive at the start of the period with corresponding data from a Norwegian general population sample. The results, shown in Table 3.17.1 show that in smokers, lung cancer rates were over 4 times higher in the cohort than in the population sample. No deaths were seen in the 33 nonsmokers in the cohort.

TABLE 3.17.1 Age-adjusted lung cancer rates by smoking habits in asbestos-exposed workers and in a general population sample[42]

Sample	Smoking habits	Sample size	Deaths	Lung cancer rate	Relative risk* (95% CI)
Population	Never smoked	2707	7	1.9	1.00
	Ever smoked	9272	111	11.1	5.84 (2.72-12.5)
Asbestos-exposed	Never smoked	33	0	0.0	0.00
workers	Ever smoked	182	9	47.8	25.2 (9.37-67.6)

* Calculated from lung cancer rates and numbers of deaths

3.18 Northern Ireland - insulation workers (Belfast) - ELMES

Elmes and Simpson[43] identified 170 men in Belfast employed as insulators and pipe coverers in 1940 and followed all but five of them up for mortality over the period 1940-1966. Causes of death were based on death certificates except where definitive alternative evidence was available from medical records. Twenty-eight deaths from respiratory cancer (lung, larynx and pleura) were observed as compared with 1.639 expected from age and period specific mortality of other men in Northern Ireland. Smoking habits were known for all but 46 of the men and Table 3.18.1 shows the observed relationship of smoking to mortality from respiratory cancer. It can be seen that there were no deaths observed in nonsmokers, with mortality similarly elevated in the other smoking groups.

Taking those whose smoking habits were known and comparing them with people surveyed in Inner Belfast by Wicken[44] it was evident that the insulators were heavy smokers. The authors estimated that the expected frequency of lung cancer for the insulators, on the basis of their increased smoking alone, should be 1.26 times that for Inner Belfast. Based on data from the same survey on lung cancer mortality by smoking habits, and on the smoking habit distribution of the insulation workers, it can be estimated that only 0.5% of the 28 lung cancers, or 0.15 deaths would have been expected in nonsmokers.

TABLE 3.18.1 Observed lung cancers by smoking habit compared to numbers expected for Inner Belfast population with given smoking habits (insulation workers, Northern Ireland[43])

Smoking habits	At risk	Observed deaths	Expected deaths	O/E
Nonsmokers	5	0	-	-
Less than 20 cigs/day (including pipe and ex smokers)	62	10	0.67	14
More than 20 cigs/day	52	9	0.53	17
Not known	46	9	0.462	19.5

3.19 USA - asbestos cement product workers (New Orleans) - HUGHES

Hughes and Weill[45] describe mortality findings from a prospective study of all workers in two New Orleans asbestos cement manufacturing plants in 1969. Over a period of about one year, an interview and pulmonary function tests were administered and chest X-ray films taken. 839 with adequate data were followed up until 1983, during which 29 deaths from lung cancer occurred, all among the 77% of the workers who reported current or former cigarette smoking. When follow-up was limited to the period starting at least 20 years from hire and at least six months after the chest X-ray film, 26 lung cancers were observed as against 15.4 expected from rates for Louisiana (SMR = 1.69, $p < 0.01$). Lung cancer risk was not raised in those with no X-ray abnormalities in 1969, and was only clearly elevated in those with small opacities, profusion $\geq$ 1/0, where nine lung cancers were seen compared to 2.1 expected (SMR = 4.29, $p < 0.001$). Lung cancer risk was not consistently related to cumulative asbestos exposure in the workers without X-ray abnormalities. Among ever smokers, the relative risk of lung cancer for those with small opacities $\geq$ 1/0 compared with other workers was estimated as 2.88, after adjustment for pack-years, age and exposure to asbestos.

3.20 USA - amosite asbestos factory workers (New Jersey) - SELIKOFF 1

Selikoff et al[46-50] have, on a number of occasions, reported results from a study of 933 amosite asbestos factory workers in Paterson, New Jersey, who, in 1941 to 1945, started work, the plant closing down in 1954. At 20 years from onset of employment, 582 were known to be alive and to have had asbestos work experience only at the factory. Smoking habits were ascertained at the 20 year point and observation was then maintained prospectively until 1977. The earlier reports[46-49], based on mortality follow-up for a shorter period of time, all noted a substantially higher risk of lung cancer in the workers as compared to that in US white males, but did not report results for smoking. Attention will therefore be restricted to the latest report[50].

One feature of the study was that diagnosis as recorded on death certificates was checked using all relevant clinical and pathological material. As a result 60 lung cancer deaths were discovered in 1961 to 1977, as against 52 on the death certificates. Observed mortality was compared with expected mortality calculated in four ways:

1. Based on age and period specific rates for New Jersey white males without regard for smoking habits;
2. Based on the age and period specific mortality of amosite asbestos factory workers who never smoked regularly, the calculations being made both for rates calculated using death certificates and those using best evidence;
3. Based on the age, smoking and period specific mortality of white men in the American Cancer Society (ACS) Cancer Prevention Study I[51];
4. Based on the age and period specific mortality of white men in the ACS study who never smoked regularly.

Three points should be noted with regard to these calculations:

(i) For 1, 3 and 4, death certificate data were used for the observed mortality, as the reference rates (New Jersey or ACS) were also based on death certificate data;

(ii) For 3 and 4 ACS data were only available for 1963-66 and 1967-71, rates for other periods being estimated by extrapolation based on changes in rates for US white males;

(iii) The ACS rates were for men who were not farmers with at most a high school

education and with a history of occupational exposure to dust, fumes, chemicals, gases or radiation.

Table 3.20.1 compares observed and expected lung cancer deaths by smoking habits and overall. Of the 60 lung cancer deaths according to best evidence, 55 occurred in those with a history of cigarette smoking and only 3 in those who never smoked regularly. The rates in the workers with a history of cigarette smoking were 3.3 times higher than in workers who never smoked regularly and about 80 times higher than in ACS men who never smoked regularly.

TABLE 3.20.1 Observed lung cancers by smoking habits compared to numbers expected for various reference populations
(Amosite asbestos factory workers in New Jersey[50])

Smoking habits	Basis of diagnosis*	Observed deaths	Expected deaths based on New Jersey men	Never smoking workers	ACS men, same smoking history	ACS never smoking men
Ever smoked cigarettes	DC	45		28.8	9.6	0.7
	BE	55		16.5		
Never smoked regularly	DC	5		5.0	0.2	0.2
	BE	3		3.0		
Pipe and/or cigar only	DC	2		3.0	0.2	0.2
	BE	2		1.8		
Smoking history unknown	DC	0		0.5	0.1	0.0
	BE	0		0.3		
Total	DC	52	10.1	37.3	10.1	1.1
	BE	60		21.6		

* DC = based on death certificates BE = based on best evidence

3.21 USA - insulation workers (New York and New Jersey) - SELIKOFF 2

Selikoff, Hammond and others, on numerous occasions,[46-49,52-54] have reported on the mortality of male insulation workers in New York and New Jersey. The first report, in 1964,[46] concerned those 632 men who entered the trade before 1943 and who had 20 years' exposure history, mortality being traced to 1962. During this period, 45 deaths from lung cancer occurred as against 6.6 expected on the basis of age and period specific rates for US white men. Smoking habits were not available for those who had died, but an interview of 320 of the 377 survivors showed that "a substantial proportion" of men had never smoked. In any case, they noted that even had all the workers smoked, this could not explain why lung cancer rates were 6.8 times higher than in white men in the general population.

Further papers concerned the 370 insulation workers who had been a member of the relevant union in 1942, had joined by 1962 and who were still living in 1963. 181 of these were current cigarette smokers, 102 were ex cigarette smokers, 39 had not smoked cigarettes but had smoked pipes and/or cigars and 48 had never smoked. Table 3.21.1, taken from a report in 1975[47] based on mortality from 1963 to 1973, compares observed and expected lung cancer mortality by smoking group.

In another paper, in 1977,[48] mortality from 1943 to 1974 is considered. For the period 1943-1962, comparable to that cited in the 1964 report, it is stated that 42 lung cancer deaths had occurred as against 6.02, it being unclear why the numbers are slightly lower than those reported earlier. For the whole period 1943-1974, 89 lung cancer deaths had occurred as against 12.2 expected, implying no more deaths had occurred since 1962 than shown in Table 3.21.1. Other papers too[49, 52-54] give similar information, with differences due to the follow-up date used.

It should be noted that the study described in the next section includes the workers considered here as part of a nationwide investigation of the mortality of insulation workers.

TABLE 3.21.1 Lung cancer SMR by smoking habits

(Insulation workers in New York and New Jersey[47])

Smoking habits	Observed deaths	Expected deaths	SMR[†]
Never smoked cigarettes	2	1.58	1.27
Pipe/cigar only	2	0.74	2.70
Never smoked	0	0.84	0.00
Ever smoked cigarettes	45	4.07	11.06
Current smokers	32	2.48	12.09
Ex smokers	13	1.59	8.18
Total	47	5.65	8.32

[†] Reference group = US white men

3.22 USA and Canada - insulation workers (Nationwide) - HAMMOND

In 1973 Hammond and Selikoff[54] described how, in 1967, they had started a study involving all 17,800 members of the insulation workers union in the United States and Canada (including those in New York and New Jersey considered in section 3.17). 11,656 completed a questionnaire providing, among other details, information concerning smoking habits. By 1971, 213 of the 17,800 men had died of lung cancer. Table 3.22.1 shows how the observed deaths compared with those expected based on the age-specific lung cancer rates of US white males.

In 1975, Selikoff and Hammond[47] reported results of extended follow-up to 1972, presenting results broken down additionally according to duration from onset of work (Table 3.22.2).

In 1977, Selikoff[48], based on mortality follow-up in 1975, noted that there were by then 427 lung cancer deaths in the insulation workers, as against 92.28 expected, but although they noted that deaths/1000 man years were far higher in men with a history of cigarette smoking (3.50) than in those with no history (0.33), they did not report expected deaths by smoking habits.

Finally, in 1979, Hammond et al[55] reported results of follow-up to 1976. There were some important differences between the methods used in this paper and that used in the previous papers. Firstly, although they noted that 2,271 deaths from all causes had occurred in the total population of 17,800 men identified in 1967, detailed analysis was limited to the 12,051 men who had survived at least 20 years after occupational exposure to asbestos dust, 1,946 of whom had died by 1976. Smoking history was available for 8,220 of these men. Second, they used the best available evidence (BE) to reallocate, where appropriate, diagnosis of cause of death as based on death certificates (DC). This increased the number of lung cancer deaths occurring in workers with 20+ years exposure from 397 to 450. Third, they extended their calculations of expected deaths by not only basing them, as before, on age and period specific rates for US white men, but also by basing them on age, period and smoking specific rates for white men in the ACS Cancer Prevention Study, who were not farmers, had no more than high school education

and had a history of occupational exposure to dust, fumes, vapours, gases, chemicals or radiation. As this study followed men only until 1972, death rates for 1972-76 were extrapolated using a factor based on official mortality statistics. The smoking habits of the ACS "control" group were based on questionnaires completed at a similar time to when the insulation workers completed their questionnaires.

As shown in Table 3.22.3, lung cancer death rates were four to five times higher in the insulation workers than would be expected, based on rates for either the ACS control group or US white males.

Table 3.22.4 compares observed lung cancer rates (based on death certificates) with those expected based on rates for never smokers in the ACS control group.

Table 3.22.5 presents the results of an analysis comparing lung cancer death rates (standardized to the age-distribution of the man-years of all the asbestos workers) by smoking habit and by exposure to asbestos. The rates for exposed to asbestos are for the insulation workers, those for unexposed to asbestos are for the ACS control group. This table is perhaps the most widely cited when referring to the joint association of lung cancer risk to asbestos exposure and smoking. The data can be seen to fit well to a multiplicative model.

TABLE 3.22.1 Lung cancer SMR in relation to asbestos exposure and smoking habits (US insulation workers[54])

Smoking habits	Number of men	Observed deaths	Expected deaths	SMR*
Never smoked cigarettes	2066	2	5.98	0.33
Ever smoked cigarettes	9590	134	25.09	5.34
Not known	6144	77	13.35	5.77
Total	17800	213	44.24	4.80

* Reference group = US white males, follow-up to 1971

TABLE 3.22.2 Lung cancer SMR* in relation to duration of asbestos exposure and smoking habits
(US insulation workers[47])

Smoking habits	Duration < 20 yrs			Duration 20+ years			Total		
	O	E	SMR	O	E	SMR	O	E	SMR
Never smoked cigarettes	0	0.87	0.0	2	6.64	0.3	2	7.51	0.3
Ever smoked cigarettes	13	4.95	2.6	166	26.65	6.2	179	31.60	5.7
Not known	15	2.59	5.8	79	14.17	5.6	94	16.76	5.6
Total	28	8.41	3.4	247	47.46	5.2	275	55.87	4.9

* Reference group = US white males, follow-up to 1972

TABLE 3.22.3 Lung cancer SMR by source of diagnosis using two different reference groups
(US insulation workers with 20+ years exposure[55])

Source of diagnosis*	Reference group	Observed deaths†	Expected deaths**	SMR
DC	ACS "controls"	397	81.7	4.86
	USA		93.7	4.24
BE	ACS "controls"	450	81.7	5.51
	USA		93.7	4.80

* DC = death certificate, BE = best evidence
† Follow-up to 1976
** Expected deaths are based on death certificates

TABLE 3.22.4 Observed lung cancers* by smoking habit compared to numbers expected for never smokers in ACS "control" group
(US insulation workers with 20+ years exposure[55])

Smoking habits	Observed	Expected	Ratio
Ever smoked cigarettes	268	4.7	57.63
Current 20+ cigs/day	152	1.7	87.36
Current < 20 cigs/day	31	0.6	50.82
Ex-cigarettes	83	2.3	36.56
Pipe/cigar only	4	0.6	7.02
Never smoked regularly	4	0.7	5.33
Total	276	6.0	46.23

* Follow-up to 1976

TABLE 3.22.5 Lung cancer rates* by asbestos exposure and cigarette smoking
(US insulation workers[55])

Group	Asbestos exposure	Cigarette smoking	Death rate†	Mortality ratio
ACS "controls"	No	Never	11.3	1.00
		Ever	122.6	10.85
Insulation workers with 20+ years exposure	Yes	Never	58.4	5.17
		Ever	601.6	53.24

* Follow-up to 1976
† Per 100,000 man-years age standardized

3.23 USA - railroad workers - GARSHICK

Garshick et al[56] describe results from a case-control study conducted among the US Railroad Retirement Board (RRB) population of approximately 650,000 active and retired male US railroad workers with 10 years or more railroad service born in or after 1900. All cases and controls had died in 1981 and 1982, with 1256 decedents from lung cancer individually matched to two decedents not from cancer, suicide, accidents or unknown causes with similar date of birth and date of death. Data on smoking habits, available for 1081 cases, were obtained from the next of kin. Data on occupational exposures to diesel exhaust and asbestos were obtained from job codes available from the RRB and an industrial hygiene survey. Table 3.23.1 shows the results of a multivariate conditional logistic regression analysis studying the simultaneous effects of diesel exhaust, asbestos and cigarette smoking on the incidence of lung cancer. In both those aged < 65 and those aged 65+ the odds ratios were significantly increased in cigarette smokers, but no significant association was seen with asbestos exposure. A positive relationship with diesel exposure was only seen in the younger men. The analysis assumes a multiplicative relationship between lung cancer risk and the three types of exposure. The authors note that there was no significant interaction between diesel exposure and cigarette smoking, but do not refer to any analysis testing the adequacy of the multiplicative relationship between asbestos exposure and cigarette smoking.

TABLE 3.23.1 Results of regression analysis relating risk of lung cancer in different age-groups to exposure to diesel, asbestos and smoking (US railroad workers[56])

Exposure category	Age < 65 Odds ratio (95% CI)	Age 65+ Odds ratio (95% CI)
Diesel-years*	1.41 (1.06-1.88)	0.91 (0.71-1.17)
Asbestos; Yes/No	1.20 (0.87-1.65)	0.98 (0.81-1.20)
≤ 50 pack years**	3.29 (1.57-6.93)	4.38 (2.90-6.60)
> 50 pack years**	5.68 (2.73-11.80)	9.14 (6.11-13.70)
Pack-years missing**	3.97 (1.86-8.51)	3.87 (2.56-5.84)

* Odds ratio is per 20 years exposure
** Reference category is zero pack-years (never smokers)

3.24 USA - shipyard workers (Georgia, Virginia, Florida, Maine) - BLOT

Atlases of US cancer mortality for 1950-1969[57] have revealed clusters of elevated mortality among white males along the Gulf and Southeast Atlantic coasts. Shipbuilding underwent massive expansion in the US during World War II and became the largest single manufacturing industry in the country[58]. Because of the known exposure to asbestos in shipbuilding, the National Cancer Institute conducted 3 large case-control studies of lung cancer in men in areas along the Atlantic coast where the shipbuilding industry had been prominent. These studies were conducted in 1970-1976 in coastal Georgia[59], in 1976 in coastal Virginia[60] and in 1976-1978 in Northeast Florida[61]. The study in Georgia involved 525 hospitalized and decedent lung cancer cases and 659 hospitalized and decedent controls, the study in Virginia involved 336 decedent lung cancer cases and 361 decedent controls, and the study in Florida involved 321 hospitalized and decedent lung cancer cases and 434 hospitalized decedent controls. Controls were always diagnosed to have (or to have died from) diseases other than lung cancer and COPD, other specific diseases being excluded in some studies. In the Georgia and Florida studies controls for hospitalized cases were matched 2:1 on age, race, hospital and county of residence. Controls for diseased cases were matched 1:1 using similar criteria. In the Virginia study personal interviews were carried out with hospital patients, while next-of-kin interviews were conducted for decedents. Detailed questions were asked about employment history and cigarette smoking. After adjustment for smoking, and other variables (which differ by study), the relative risk associated with ever having been employed in shipbuilding was estimated as 1.6 (95% CI 1.1-2.3) for Georgia and 1.4 (95% CI 0.9-2.1) for Florida. For Virginia, the relative risk associated with shipyard work initiated before 1950 was 1.7 (95% CI 1.2-1.4). Table 3.24.1 shows the results by smoking habit and shipyard working.

In a review paper, Blot and Fraumeni[58] present combined results from these three studies and also a much smaller study in Bath, Maine involving a total sample of only 64 cases and controls combined. This paper reports that the relative risks associated with shipbuilding employment adjusted for cigarette smoking are, as above, 1.6 for Georgia and 1.4 for Florida, but are 1.5 for Virginia and 1.7 for Maine. For the four areas combined, the summary estimate was 1.44 (95% CI 1.17-1.78). As shown in Table

3.24.2 the authors also presented summary relative risks, without confidence intervals, jointly by shipyard employment and cigarette smoking status. The authors note that "in the combined data set, the increased risk of lung cancer among shipyard workers was seen in nearly all cigarette smoking categories. There was a twofold increased risk among non-smokers, but the largest absolute excess occurred among heavy smokers". They go on to comment that "a synergistic relation with smoking is characteristic of asbestos-induced lung cancer" citing Saracci[1].

TABLE 3.24.1 Risk of lung cancer by State in relation to employment in shipbuilding and smoking habits
(Case-control studies in Georgia, Virginia and Florida[59-61])

State	Ever employed in shipbuilding	Smoking category	Cases	Controls	Relative risk (95% CI)*
Georgia	No	Never, <½ packs/day, ex 10+ yrs	50	203	1.00
		½ to 1½ packs/day, unknown	217	220	4.00(2.79-5.75)
		2+ packs/day	96	50	7.80(4.92-12.4)
	Yes	Never, <½ packs/day, ex 10+ yrs	11	35	1.28(0.61-2.69)
		½ to 1½ packs/day, unknown	70	42	6.77(4.14-11.1)
		2+ packs/day	14	3	18.9(5.24-68.5)
Virginia	No	Never, <½ packs/day, ex 10+ yrs	38	103	1.00
		½ to 1½ packs/day, unknown	123	126	2.65(1.69-4.14)
		2+ packs/day	63	37	4.62(2.66-8.00)
	Yes	Never, <½ packs/day, ex 10+ yrs	25	36	1.88(1.00-3.54)
		½ to 1½ packs/day, unknown	49	32	4.15(2.32-7.42)
		2+ packs/day	21	7	8.13(3.20-20.7)
Florida	No	Never, <½ packs/day, ex 10+ yrs	17	110	1.00
		½ to 1½ packs/day, unknown	117	132	5.74(3.25-10.1)
		2+ packs/day	91	92	6.40(3.56-11.5)
	Yes	Never, <½ packs/day, ex 10+ yrs	5	18	1.80(0.59-5.48)
		½ to 1½ packs/day, unknown	33	37	5.77(2.88-11.5)
		2+ packs/day	32	17	12.2(5.59-26.5)

* Estimated from numbers of cases and controls

TABLE 3.24.2 Risk of lung cancer in relation to employment in shipbuilding and current smoking habits
(Combined results from four case-control studies[58])

Employment in shipyards	Current smoking habits		Relative risk
No	Non-smoker		1.0
	Former smoker		3.7
	Light	(<½ pack/day)	4.8
	Moderate	(½ to 1½ packs/day)	7.2
	Heavy	(2+ packs/day)	10.3
Yes	Non-smoker		2.2
	Former smoker		3.0
	Light	(<½ pack/day)	5.2
	Moderate	(½ to 1½ packs/day)	10.2
	Heavy	(2+ packs/day)	21.7

4. A summary of features of the 23 studies

Table 4.1 lists the 23 studies, showing the study population, location, design, period of mortality follow-up (or of hospitalization or death for case-control studies) and the date smoking habits were obtained. Each study is also associated with the name of the first author of the publication (or principal publication) reporting the results.

Of the 23 studies, 12 were conducted in Europe (UK 4, Italy 3, Finland 2, Norway 2 and Austria 1), seven were conducted in North America (USA 5, Canada 1, and both USA and Canada 1), three in Asia (China 2, Japan 1) and one in Australia.

Four of the studies were conducted in miners (and millers), two of chrysotile, one of crocidolite and one of anthophyllite asbestos. Seven studies were conducted in asbestos products workers, two of chrysotile, two of amosite, one of chrysotile and crocidolite and two not referring to the type of asbestos used. One study was conducted in workers in a nitric acid production plant. One study was conducted in asbestos sprayers, and also in asbestosis and silicosis patients. Three studies were conducted in insulation workers, an occupation involving asbestos exposure. The remaining seven studies were case-control studies, four conducted in shipbuilding areas, one in railroad workers, one in an industrial area and one in a shipbuilding and industrial area.

Of the 16 occupational cohort studies, four started follow-up in the 1940s, four in the 1950s, five in the 1960s and three in the 1970s. Length of mortality follow-up ranged from 9 to 42 years, being 20 years or more in over 60% of the studies. For many of the studies with follow-up starting early, smoking habits were not obtained until later into the study, so limiting the numbers of lung cancers for which analysis by smoking habit could be attempted.

Table 4.2 gives details concerning the lung cancer deaths and cases. Of the 16 occupational cohort studies, 14 reported results for mortality from lung cancer, based on death certificates only in eight and on death certificates and additional medical records in six. The other two occupational cohort studies both reported results for cancer incidence, based on national cancer registration data. Of the seven case-control studies,

two were of hospital patients, three of decedent cases and two used both hospital patients and decedents. All the case-control studies but one used hospital patients as controls for hospital cases and decedent controls for decedent cases. These case-control studies differed in the exclusions used for the controls. Two studies excluded cancers, accidents and suicides, two excluded COPD, one excluded COPD and cancers (with a few exceptions) and one had no exclusions (apart, of course, for lung cancer). One case-control study used general population controls.

The number of lung cancers for which smoking habits were available varied markedly from study to study, ranging from about 750 to 1100 in three studies, around 200-300 in five studies, between 50 and 100 in seven studies and less than 50 in eight studies. The case-control studies included the three studies with over 750 lung cancers and three of the studies with around 200-300 lung cancers. These studies would not have involved very many cases with severe asbestos exposure. The study of chrysotile miners and millers in Quebec (LIDDELL) and the USA/Canada study of insulation workers (HAMMOND) would have involved the most cases with severe asbestos exposure. Many of the studies, because of their small number of cases, would have provided relatively little information on the risk of asbestos exposure in non-smokers.

Table 4.3 give details on the source of the asbestos exposure and smoking data. For the four studies of insulation workers, no attempt was made to compare risks by level of asbestos exposure with the study, the risk of the whole study population being compared to that of an external standard, evidence of exposure essentially being inferred from the nature of the occupation (though SELIKOFF 1 and SELIKOFF 2 did have some data on work history and fibre counts). Comparison was also only made with an external standard in the study of asbestos sprayers and asbestosis and silicosis patients (OKSA). All the other studies presented within-study comparisons of risk by exposure level. In nine of the remaining 18 studies, exposure categories were based on work history including dust measurements, the other nine being based on work history only. The occupational studies generally obtained their data through employment records, supplemented with industrial hygiene data where available, while the case-control studies generally relied on data reported by patients, or, in three studies, proxies. Most of the 18

studies reporting risk by exposure level only used quite broad categories (e.g. heavy, medium, light) though a few used more defined categories. Three of the studies simply classified subjects as asbestos exposed or not, with one study classifying subjects by ever having worked in shipbuilding.

Data on smoking were obtained by questionnaire in ten studies and by interview in 12 studies, with one study using various unspecified sources. Some of the interviews were carried out during medical examinations. Eight (possibly nine) of the studies involved proxy interviews to obtain data for at least some of the subjects.

Table 4.4 gives details of those potential confounding variables taken into account, either in the design stage by matching of cases and controls or in the analysis stage by statistical adjustment, or by being taken into account in the SMR calculations. It can be seen that, though care has generally been taken to take age into account in design or analysis, other environmental variables have generally not been considered. Exceptions are PASTORINO, where data were presented subdivided by exposure to polycyclic aromatic hydrocarbons, GARSHICK, where a term for diesel exposure was included in the regression analysis, and the SELIKOFF 1 and HAMMOND analyses which endeavoured to make the study and reference group more comparable by calculating expected values based on US white men who were not farmers, had no more than high school education and had a history of occupational exposure to dust, fumes, vapours, gases, chemicals or radiation.

Effects of asbestos exposure are clearly difficult to study and a number of the studies represent years of work by dedicated researchers. That said, there are a number of limitations affecting many or all of the studies, including:

(i) Reliance on death certificate data, known to be inaccurate[62]. However, for studies comparing observed deaths to those expected using an external reference, this is inevitable, as the reference data are themselves based on death certification;

(ii) Difficulties in assessment of asbestos exposure. Even where dust measurements are available, these are never complete, making it difficult to know levels of exposure associated with specific jobs at specific times. Assessment of asbestos

exposure is often no more than an educated guess;

(iii) Inaccuracies in statements on smoking habits[63], with none of the studies using cotinine measurements to validate self-reported non-smoking status;

(iv) Failure to take into account the many other environmental factors known to be associated with risk of lung cancer;

(v) Reliance on data obtained from proxy respondents in a number of studies; and

(vi) Small numbers of lung cancers, particularly in never smokers, in many of the studies.

There are three limitations that seem likely to have the most serious effect on conclusions. First, the possibility that some of the self- (or proxy-) reported never smokers may actually be current or ex-smokers may affect estimates of the effect of asbestos exposure in never smokers. Second, the small number of lung cancer cases in some studies means that estimated lung cancer rates will be unreliable, particularly in never smokers. Third, the failure, in analysis, to account for potential confounding by other lung carcinogens means that one cannot necessarily be sure whether increases seen in the asbestos exposed groups actually result totally from asbestos exposure or could have arisen partly from occupational exposure to other lung carcinogens with which asbestos exposure may be associated. For example, some of the groups of miners might have had higher radon exposure than average, railroad workers may have increased exposure to coal dust and diesel, while shipyard work may involve exposure to agents other than just asbestos. Also a number of the groups studied may have undergone more X-rays than is normal for the general population. The likely effect of any confounding will clearly vary depending on the study population.

TABLE 4.1 The 23 studies

Study author*	Study population	Location	Design	Mortality follow-up**	Date smoking habits obtained
DEKLERK	Crocidolite miners and millers	Wittenoom, Australia	Occupational (with nested case-control)	1979-91	1979
NEUBERGER	Asbestos cement products workers	Vöcklabruck, Austria	Occupational	1950-87	1982†
LIDDELL	Chrysotile miners and millers	Quebec, Canada	Occupational (with nested case-control)	1950-92	1970
CHENG	Chrysotile asbestos products workers	Tianjin, China	Occupational	1972-87	1972
HUILAN	Chrysotile asbestos products workers	8 factories, China	Occupational	1972-86	1972
BERRY	Asbestos factory workers	E. London, England	Occupational	1960-80	1971
ACHESON	Amosite asbestos factory workers	Uxbridge, England	Occupational	1947-79	1971
MARTISCHNIG	Hospital patients in shipbuilding area	Gateshead, England	Case-control	1972-73	1972-73†
OKSA	Asbestos sprayers, asbestosis and silicosis patients	Finland	Cohort of identified groups	1967-94	1987 (sprayers), 1977-85 (patients)
MEURMAN	Anthophyllite miners	N. Savo, Finland	Occupational, (with nested case-control)	1953-91	1967
RUBINO	Chrysotile miners and millers	Balangero, Italy	Occupational (with nested case-control)	1946-75	≃1976†
PASTORINO	Hospital patients and general population in industrial areas	Lombardy, Italy	Case-control	1976-79	>1979†
BOVENZI	Decedents in industrial and shipbuilding area	Trieste, Italy	Case-control	1979-81, 1985-86	>1979†
MINOWA	Decedents in shipbuilding area	Yokosuka, Japan	Case-control	1978-82	>1982†

TABLE 4.1 The 23 studies
(contd.)

Study author*	Study population	Location	Design	Mortality follow-up**	Date smoking habits obtained
KJUUS	Hospital patients in industrial and shipbuilding areas	Telemark and Vestfold, Norway	Case-control	1979-83	1979-83†
HILT	Workers in nitric acid production plant	Telemark, Norway	Occupational	1953-80	?
ELMES	Insulation workers	Belfast, N. Ireland	Occupational	1940-66	?
HUGHES	Asbestos cement product workers	New Orleans, USA	Occupational	1969-83	1969
SELIKOFF 1	Amosite asbestos factory workers	New Jersey, USA	Occupational	1961-77	1961
SELIKOFF 2	Insulation workers	New York and New Jersey,USA	Occupational	1943-74	1962
HAMMOND	Insulation workers	USA and Canada	Occupational	1967-76	1967
GARSHICK	Decedent railroad workers	USA	Case-control	1981-82	>1982†
BLOT	Hospital patients and decedents in shipbuilding areas	4 states, USA	Case-control	1970-78	1970-78†

* First author of paper or of main paper where multiple publications; see sections 3.2-3.24 for fuller details of the studies
** Or period of hospitalization or death for case-control studies
† Data obtained after death or diagnosis

TABLE 4.2 Lung cancer deaths and cases

Study author	Deaths or cases	Source of diagnosis	Number of deaths/cases	
			Total	With smoking data
DEKLERK	Deaths	Death certificates	71	40
NEUBERGER	Deaths	Death certificates and medical records	50	≤50
LIDDELL	Deaths	Death certificates	657	299
CHENG	Deaths	Death certificates (?)	21	≤21
HUILAN	Deaths	Death certificates and medical records	67	57
BERRY	Deaths	Death certificates	123	79
ACHESON	Deaths	Death certificates	71	26
MARTISCHNIG	Cases	Firm diagnosis by radiography, bronchoscopy or thoracotomy	201	201
OKSA	Cases	Cancer registration	58	51
MEURMAN	Cases	Cancer registration	77	55
RUBINO	Deaths	Death certificates and medical records	12	12
PASTORINO	Cases	Hospital diagnosis and review of medical records	204	176
BOVENZI	Deaths	Autopsy records	756	756
MINOWA	Deaths	Confirmed by cytology, surgical specimens or autopsy	96	96
KJUUS	Cases	Hospital diagnosis	176	176
HILT	Deaths	Death certificates	13	9
ELMES	Deaths	Death certificates and medical records	28	19
HUGHES	Deaths	Death certificates	29	29
SELIKOFF 1	Deaths	Death certificates and medical records	60	60
SELIKOFF 2	Deaths	Death certificates and medical records	89	47
HAMMOND	Deaths	Death certificates and medical records	450	276
GARSHICK	Deaths	Death certificates	1256	1081
BLOT	Deaths and cases	Death certificates and hospital diagnosis	≃1100*	≃1100*

* There were a total of 1072 cases in 3 of the sub-studies; with a combined total of 64 cases and controls in the fourth sub-study

TABLE 4.3 Source of asbestos and smoking data

Study author	Source of asbestos exposure	Risk related to exposure*	Source of smoking data
DEKLERK	Work history and dust measurements	Measured	Questionnaire to workers
NEUBERGER	Work history and dust measurements	Broad	Questionnaire to living workers or proxies for decedents
LIDDELL	Work history and dust measurements	Measured	Questionnaire to living workers or proxies for decedents
CHENG	Work history and dust measurements	Broad	Questionnaire to workers (?)
HUILAN	Work history and dust measurements	Yes/No	Questionnaire to workers (?)
BERRY	Work history (?)	Broad	Questionnaire or interview with workers
ACHESON	Work history and dust measurements	Broad	Medical interview with workers
MARTISCHNIG	Questionnaire re work history and asbestos exposure; fibre counts in lung tissue of cases	Yes/No	Medical interview with patients
OKSA	Medical interview with subjects	External	Medical interview with subjects
MEURMAN	Work history	Broad	Questionnaire to workers
RUBINO	Work history and dust measurements	Measured	Interviews with living workers or proxies for decedents
PASTORINO	Interview of subjects and proxies re work history	Yes/No	Interview with subjects or proxies
BOVENZI	Interview of proxies re work history	Broad	Interview with proxies
MINOWA	Interview of proxies re work history	Broad	Interview with proxies
KJUUS	Interview with patients re asbestos exposure	Broad	Interview with patients
HILT	Work history	Broad	Various unspecified sources
ELMES	Inferred from nature of population studied	External	Interview with living workers and search of hospital and work records for decedents
HUGHES	Work history and dust measurements	Measured	Interview with workers
SELIKOFF 1	Inferred from nature of population studied	External	Questionnaire to workers
SELIKOFF 2	Inferred from nature of population studied	External	Interview with workers
HAMMOND	Inferred from nature of population studied	External	Questionnaire to workers

TABLE 4.3 Source of asbestos and smoking data
(cont'd)

Study author	Source of asbestos exposure	Risk related to exposure*	Source of smoking data
GARSHICK	Work history	Yes/No	Questionnaire to proxies
BLOT	Interview with patients or proxies re work history	Yes/No**	Interview with patients or proxies

* Results presented by either measured category of asbestos exposure, broad category (e.g. heavy, medium, light), or simply by whether exposure occurred or not (yes/no). In 5 studies, risk was not related to level of exposure within the study population, risk for the whole population being compared to an external population

** Yes/No for BLOT refers to ever employed in shipbuilding

TABLE 4.4 Potential confounding variables taken into account by matching, confounding adjustment or in the SMR calculations

	Variables taken into account in		
Study author	Matching	Adjustment	SMR calculations
DEKLERK	Age	None	-
NEUBERGER	-	None	Age, period, region
LIDDELL	Date of birth, age of starting work, period of employment	None	Age, period, region
CHENG	-	Age	Age, period, region
HUILAN	-	Not stated	-
BERRY	-	None	Age, period, region, availability of smoking data
ACHESON	-	None	Age, period, country
MARTISCHNIG	Age, catchment area	None	-
OKSA	-	None	Age, period, country
MEURMAN	Date of birth, vital status, date of death	None	Age, period, region
RUBINO	Date of birth	None	-
PASTORINO	Age	PAH*	-
BOVENZI	Age, date of death	None	-
MINOWA	Date of birth	Age	-
KJUUS	Age	None	-
HILT	-	Age	-
ELMES	-	None	Age, period, country
HUGHES	-	None	Age, period, region
SELIKOFF 1	-	None	Age, period, country**
SELIKOFF 2	-	None	Age, period, country
HAMMOND	-	None	Age, period, country**
GARSHICK	Date of birth, date of death	Age, diesel-years	-
BLOT	Age, race, hospital, county of residence	None	-

* Exposure to polycyclic aromatic hydrocarbons at work

** Comparisons were made with a group of white men who were not farmers, had no more than high school education and had a history of occupational exposure to dust, fumes, vapours, gases, chemicals or radiation

5. Summary of results

5.1 Overall effects of asbestos exposure

From the material presented in section 3 it is clear that asbestos exposure is associated with a markedly increased risk of lung cancer. Of the 23 studies, statistically significant excesses of lung cancer risk were noted in 20. The only exceptions were:

(i) the GARSHICK study of asbestos exposure in railroad workers,

(ii) the NEUBERGER study of asbestos cement workers, both of which showed little or no relationship, and

(iii) the RUBINO study of Italian chrysotile miners and millers, which reported a relative risk of 2.89 in those with 101+ fibres/year exposure compared to those with lower exposure, which was not significant (95% CI 0.58-14.4), the study only involving 12 lung cancers.

High relative risks were seen, exceeding 5.0 in a number of studies; HUILAN 5.3, OKSA 17 for asbestos sprayers and 10 for asbestosis patients, ELMES 16.8, SELIKOFF 1 5.1, SELIKOFF 2 7.0 and HAMMOND 5.5.

5.2 Effects of asbestos exposure in never smokers

The relationship of asbestos exposure to lung cancer risk in never smokers has been assessed using three main types of comparison:

(i) Direct comparison within study of lung cancer rates in never smokers categorized by different levels of asbestos exposure,

(ii) Comparison of lung cancer rates in never smoking asbestos exposed workers with those in a reference population of never smokers, and

(iii) Comparison of lung cancer rates in never smoking asbestos-exposed workers with those in a total reference population (of ever and never smokers combined).

The first two types of comparison give a direct estimate of the relative increase in risk associated with asbestos exposure in never smokers. However, the third does not. An SMR of, for example, 0.5 for never smoking asbestos-exposed workers might actually indicate a positive effect of asbestos if never smokers generally have much lower risk than average. To use data of the third type to generate an estimate of the effect of

asbestos exposure in never smokers one needs to have an estimate, for the reference population, of Z, the ratio of the risk of never smokers to the risk of the whole population. Based on 40 years follow-up of men in the British Doctors Study[64], it can be calculated that Z = 0.15. If this were appropriate in our example, the SMR of 0.5 would indicate a 0.5/0.15 = 3.3-fold increase in risk associated with asbestos exposure in never smokers.

Table 5.1 summarizes data from the 23 studies related to effects of asbestos exposure in never smokers. For each study it shows the comparison made, the number of lung cancers involved, the source of the data (table number in section 3) and an estimate (or, in the case of four studies, more than one estimate) of the relative risk associated with asbestos exposure, with 95% CI. Estimates based on converting simple SMRs to never smoking SMRs using Z = 0.15 are shown in square brackets. Confidence limits are estimated using the CIA program[8].

It is important to note that the three studies with the largest number of lung cancers shown in Table 5.1, MARTISCHNIG, KJUUS and BLOT, do not provide data specifically for never smokers, the results relating to a group which included also light smokers and/or long-term ex-smokers. It is also possible that some of the never smokers in other studies may include pipe or cigar smokers (questions in some studies relating only to cigarette smoking) and misclassified cigarette smokers.

It is also important to note that, for quite a number of these studies, the number of lung cancers observed in never smokers is very low indeed, zero in five studies and less than five in at least a further seven.

Of the 23 studies in Table 1, two do not allow testing of whether asbestos exposure increases risk of lung cancer in non-smokers, one (RUBINO) because no lung cancers occurred in non-smokers and comparisons were only made within study, the other (MINOWA) because of inadequate reporting of the results. The other 21 can be divided into three groups:

(i) Six studies which showed a statistically significant increase in risk with relative

risks associated with asbestos exposure (in at least one analysis) of 25.0 (SELIKOFF 1), 11.5 (BERRY), 8.44 (SELIKOFF 2), 5.71 (HAMMOND), 4.07 (LIDDELL) and 3.78 (HUILAN);

(ii) Six studies which reported at least a moderate increase in risk which was not statistically significant or where significance could not be tested. Relative risks for these studies were 5.44 (CHENG), 2.52 (PASTORINO), 2.41 (KJUUS), 1.90 (DEKLERK), 1.83 (BOVENZI) and 1.28, 1.80 and 1.88 (BLOT - 3 US states);

(iii) Three studies (NEUBERGER, MARTISCHNIG and GARSHICK) which showed little or no evidence of an effect of asbestos. NEUBERGER and GARSHICK were the only studies that found no evidence on effect of asbestos for smokers and non-smokers combined.

(iv) Six studies which provided very little information at all. These were ACHESON, MEURMAN, OKSA, HILT, ELMES and HUGHES.

Taken as a whole, the evidence demonstrates that asbestos exposure does increase risk in never smokers, though the extent of the increase seen in the different studies will depend on the difference in exposure between the test and comparison group.

5.3 Are the data consistent with an additive model?

There are clear overall effects of asbestos exposure on the risk of lung cancer in the studies considered in section 5.1. The evidence of an effect of asbestos exposure is of course much more extensive than this (analyses in this report being limited only to those studies providing evidence on the joint relationship of smoking and asbestos exposure to risk of lung cancer), recent meta-analyses of data from 69 asbestos-exposed occupational cohorts[65] confirming the clear relationship. Because the vast majority of the lung cancer cases occurred in smokers, it is therefore also clear that asbestos exposure increases lung cancer risk in smokers. This has been accepted for many years, and data relevant to this question are not summarized here.

Of more interest is the nature of the joint relationship of asbestos exposure and smoking to risk of lung cancer. The key data relevant to this comparison are presented in Table 5.2. Note that data from five studies are omitted:

(i) NEUBERGER, because the results were only presented graphically and the study showed no evidence of an asbestos effect anyway,

(ii) MINOWA, because risk estimates were not available for exposed non-smokers,

(iii) ELMES, because there were only five never smokers in the study, none of whom died of lung cancer,

(iv) HUGHES, because there were no deaths from lung cancer in never smokers and expected deaths are not available by smoking habits, and

(v) GARSHICK, because their analysis assumed a multiplicative relationship and data on risk jointly by asbestos exposure and smoking were not presented.

Under the additive model, the sum of the risks in the unexposed group (A^-S^-) and the group jointly exposed to asbestos and smoking (A^+S^+) should equal the sum of the risks in the group exposed to asbestos only (A^+S^-) and the group exposed to smoking only (A^-S^+). Table 5.3 tests this hypothesis, by comparing these two sums. For the case-control and cohort analyses, the calculations are based on risks relative to the A^-S^- group except for RUBINO where, due to zeros, risks are expressed relative to the A^-S^+ group. For the other analyses, calculations are based on SMRs (or SIRs) relative to a common reference population. Where results were only given for asbestos-exposed populations (OKSA, SELIKOFF 1, SELIKOFF 2), it was assumed that the SMR for the unexposed group was 0.15 and the SMR for the group exposed to smoking only was 1.07, based on the British Doctors data[64]. Where expected values were expressed relative to a never smoking reference, these were divided by 0.15 before computing the SMR. Where they were expressed relative to a smoking reference, these were divided by 1.07 before computing the SMR.

While some of these corrections are relatively crude, the overall impression from Table 5.3 is so clear that this limitation is not important. It is abundantly clear that the additive model does not fit the data. In 24 of the 25 estimates, the risk in the jointly exposed group is higher than one would expect on the basis of the risks in the singly exposed groups. Formal statistical significance testing has not been attempted. However, it is evident at a glance that a number of the studies show highly significant discrepancies from the additive model. The most notable example is HAMMOND,

where the increase in risk due to asbestos in smokers is quite reliably estimated as about 40 times the baseline risk. Had the increase in never smokers been 40 times the baseline risk, one would have expected to see about 60 lung cancer deaths in the never smoking asbestos workers - in fact, only 8 were seen, a discrepancy which is very highly significant indeed. Other studies showing results that seem quite clearly non-additive include PASTORINO, KJUUS, HILT, OKSA and SELIKOFF 2.

5.4 Are the data consistent with a multiplicative model?

Let Q_1 be the product of the risks for A^-S^- and A^+S^+ and let Q_2 be the product of the risks for A^+S^- and A^-S^+. If $U = Q_1/Q_2 = 1$ the data are consistent with a multiplicative model. For a super multiplicative model, one would expect $U>1$, while for an intermediate model one would expect $U<1$. U can also be thought of as the relative increase in risk due to asbestos in ever smokers divided by the relative increase in risk due to asbestos in never smokers.

For case-control studies the variance of log U can be approximately estimated from the sum of the reciprocals of the numbers of cases and controls in each of the four exposure groups, while for cohort studies or occupational studies using SMR/SIR analysis the variance can be approximately estimated from the sum of the reciprocals of the numbers of cases in the four groups. In both situations it is then straightforward to estimate 95% confidence intervals (CI) for U assuming log U is normally distributed. Where numbers of cases were only available for the A^+S^- and A^+S^+ groups, 95% CI for U can be estimated using the CIA program[8].

Table 5.4 presents, for each of the studies concerned, Q_1, Q_2, U and the 95% CI for U. For five studies, two sets of estimates are shown:

(a) using data for all four exposure groups - internal comparison, and

(b) using data only for A^+S^- and A^+S^+ assuming the SMR in A^-S^- is 0.15 and that in A^-S^+ is 1.07 - external comparison.

It can be seen that there is no obvious tendency for U to be consistently greater or less than 1.0. Restricting attention to estimates based on data for all four exposure

groups for the five studies where two estimates are shown and excluding estimates of U that are undefined or infinite (which were based on very few cases), a fixed-effects meta-analysis[66] of the 16 estimates gave an overall estimate 0.90 (95% CI 0.67-1.20) with no evidence of heterogeneity. The only statistically significant estimates of U are for SELIKOFF 1 and for LIDDELL (second estimate). Both these estimates assume smoking relative risks for non asbestos exposed populations based on the British Doctors' study, which may not necessarily be applicable to the study population concerned.

To test the validity of the multiplicative model further, formal statistical analysis was carried out using the General Linear Interactive Modelling program GLIM[67] for studies with data for all four exposure groups. For case-control studies a linear logistic (or logit) model with binomial error was used, while for cohort and occupational studies a loglinear model with Poisson error was used. For studies where data were only available for the asbestos exposed groups (A^+S^- and A^+S^+), fitted values were estimated assuming the smoking effect in these two groups was the same as that in the standard population selected.

Table 5.5 shows the fitted values of the estimated risks associated with asbestos only, with smoking only and with both exposures combined.

It is apparent that the estimated risks for asbestos exposure are very variable, being generally smaller in the case-control studies than in the other studies. With the exception of MEURMAN and GARSHICK (Age 65+), where the estimates are just less than 1, all the estimates are greater than 1 confirming the clear evidence that asbestos exposure increases the risk of lung cancer. The variation in the estimates no doubt reflects the difference in extent and type of asbestos exposure for the different populations studied.

All the estimated risks for smoking only are positive, reflecting the known relationship of smoking to lung cancer. The variation in risks reflect not only sampling variation, but also variation in the definition of smoking used in the different studies and in the average amount and duration smoked by the different populations.

The estimated risks for joint exposure, which are the product of the estimates for asbestos only and for smoking only, also show considerable variability ranging from about 4 in LIDDELL and in BERRY (1971-80, men) to over 50 in HAMMOND, SELIKOFF 2 and OKSA (asbestos sprayers and asbestosis patients).

Table 5.6 compares the observed number of cases with those fitted by the model and gives the estimated deviance from the model for each study, a statistic which is approximately distributed as chisquared on 1 degree of freedom (though the approximation may be poor where fitted values are small).

The results confirm the fact that generally the fit to the multiplicative model is excellent. Only for SELIKOFF 1 is the deviance statistically significant, as judged by a deviance exceeding 3.84. Note that the fitted values are contingent on the assumed smoking relative risk estimate of 7.13 from the British Doctors Study[64]. Were a lower value assumed, as found in a number of the other studies in Table 5.5, the fit to the model would improve. For example, with a smoking risk of 4.00 the fitted numbers would be 1.79 and 48.21 and the deviance would reduce to 5.97 (or to 4.26 with a correction for continuity). Apart from this study, only MARTISCHNIG is close to showing any notable deviation from the model.

Brief comments should be made about two other analyses not included in Tables 5.5 and 5.6. For CHENG, insufficient data were given to allow formal testing, but U was so close to 1 (= 0.49) and the total number of cases so low (= 21) that the multiplicative model clearly fitted well.

Berry et al[3] also presented results of analyses based on a comparison of observed and expected numbers of lung cancer deaths for smokers (O = 75, E = 31.03) and never smokers (O = 4, E = 0.55). Here the data are for men and women combined and for the whole population, with the smoking-adjusted expected values standardized for sex and degree of exposure. Although the relative effect of asbestos exposure was less in smokers (2.4) than in never smokers (7.3), the estimate of U, 0.33, was not statistically significant, with the 95% CI estimated as 0.13-1.25.

Considering the data as a whole, the fit to the multiplicative model is clearly good.

5.5 Attributable risks

Assuming a multiplicative model is appropriate, one can estimate attributable risks associated with background exposure, asbestos only, smoking only and their joint effect. If R_A is the asbestos relative risk, R_S is the smoking relative risk, and N_O, N_A, N_S and N_{AS} are the observed numbers of lung cancer cases (or deaths) in the four groups, the attribution is calculated as follows:

		Numbers of cases attributed to			
Exposure	Cases	Background	Asbestos only	Smoking only	Joint effect
A^-S^-	N_O	N_O	-	-	-
A^+S^-	N_A	$\frac{N_A}{R_A}$	$\frac{N_A(R_A-1)}{R_A}$	-	-
A^-S^+	N_S	$\frac{N_S}{R_S}$	-	$\frac{N_S(R_S-1)}{R_S}$	-
A^+S^+	N_{AS}	$\frac{N_{AS}}{R_AR_S}$	$\frac{N_{AS}(R_A-1)}{R_AR_S}$	$\frac{N_{AS}(R_S-1)}{R_AR_S}$	$\frac{N_{AS}(R_AR_S-R_A-R_S+1)}{R_AR_S}$

The attributable deaths can be expressed as percentages. Thus, for those exposed to both agents, the numbers of cases attributed in row 4 of the above table can be expressed as a percentage of N_{AS}. For the whole population, one can sum the attributed numbers in each column down the four rows and express them as a percentage of the total cases ($N_O + N_A + N_S + N_{AS}$). One can also express them as percentages of asbestos exposed cases ($N_A + N_{AS}$). Relevant data are given in Table 5.7.

For those exposed to both agents, it can be seen that there is considerable variation between study in the estimated attributable percentages. For the third group of studies, where the estimated effect of asbestos was relatively high, the percentages attributed to background are low (averaging 2.7%) and those attributable to the joint effect are high (averaging 69.3%), with percentages attributed to smoking only (averaging 16.8%) only slightly higher than those attributed to asbestos only (averaging

11.2%). For the first two groups of studies, where the estimated effect of asbestos was relatively low, the percentages attributed to background are higher (averaging 10.4% for case-control studies and 11.4% for cohort/occupational studies with data for all four groups) and those attributed to the joint effect are lower (38.4% and 36.2%). The percentages attributed to smoking only (41.1% and 31.9%) are again higher than those attributed to asbestos only (10.0% and 20.5%). Even within the studies, there is considerable variation between the estimates (which is why it seemed more appropriate to give simple means not weighted on study size) however, and it is clear that using the averages may be over simple - the percentages will depend on *inter alia* the definitions and the nature of the two exposures.

Table 5.7 also includes estimates for the whole population studied. These are more difficult to interpret as they depend on the distribution of the population by exposure, e.g. if asbestos exposure is rare, percentages are likely to be small. However, the results show a similar pattern to those given for those exposed to both agents, with percentages attributed to the joint exposure much higher in the third group of studies (68.0%) than in the other two (15.4% or 20.9%).

TABLE 5.1 Effects of asbestos exposure in never smokers

Study author		Test group/ comparison group	Source of data	No. of lung cancers	Relative risk (95% CI)*	Notes
DEKLERK		High/low exposure	3.2.1	6	1.90(0.62-5.85)	
NEUBERGER		Study group/reference	3.3 (text)	?	≃1.00	b
LIDDELL	(a)	60+/≤60 mpcf.y	3.4.1	21	1.65(0.64-4.33)	a
	(b)	60+ mpcf.y/reference	3.4.1	11	[4.07(2.03-7.29)]	e
CHENG		Exposed/unexposed	3.5.1	?	5.44	b
HUILAN		Exposed/unexposed	3.6.1	19	3.78(1.25-11.4)	
BERRY	(a)	Study group/never smoking reference 1960-70	3.7.3	1	5.00(0.13-27.9)	
	(b)	Severe/low or moderate exposure reference 1971-80	3.7.4	4	1.62(0.13-85.1)	a
	(c)	Severe exposure/never smoking reference 1971-80	3.7.4	3	11.5(2.38-33.7)	
ACHESON	(a)	Medium or heavy/background exposure	3.8.1	1	∞	a,c
	(b)	Medium or heavy/reference	3.8.1	1	[6.06(0.15-33.8)]	e
MARTISCHNIG		Exposed/unexposed	3.9.1	35	1.08(0.38-3.06)	d
OKSA		Study group/reference	3.10.1	0	[0.00]	e
MEURMAN	(a)	Heavy/moderate	3.11.1	2	0.83(0.01-64.6)	a
	(b)	Heavy/reference	3.11.1	1	[3.21(0.08-17.8)]	e
RUBINO		101+/≤100 f/y	3.12.1	0	Undefined	f
PASTORINO		Exposed/unexposed	3.13.1	15	2.52(0.70-9.10)	i,q
BOVENZI		Exposed/unexposed	3.14.1	18	1.83(0.68-4.95)	
MINOWA		Exposed/unexposed	3.15.1	≤3	Undefined	g,h
KJUUS		Moderate or heavy/none or light exposure	3.16.1	37	2.41(0.89-6.55)	i
HILT		Study group/never smoking ref	3.17.1	0	[0.00]	p
ELMES		Study group/reference	3.18.1	0	[0.00]	j
HUGHES		Study group/reference	3.19 (text)	0	[0.00]	k
SELIKOFF 1		Study group/never smoking ref	3.20.1	5	25.0(8.12-58.3)	
SELIKOFF 2		Study group/reference	3.21.1	2	[8.44(1.02-30.5)]	e
HAMMOND		Study group/never smoking ref	3.22.4	4	5.71(1.56-14.6)	

TABLE 5.1 Effects of asbestos exposure in never smokers (cont'd)

Study author	Test group/ comparison group	Source of data	No. of lung cancers	Relative risk (95% CI)*	Notes
GARSHICK	Exposed/unexposed	3.23.1	?	1.20(0.87-1.65) 0.98(0.81-1.20)	l
BLOT	Never/ever employed in ship-building	3.24.1	61 63 22	1.28(0.61-2.69) 1.88(1.00-3.54) 1.80(0.59-5.48)	m,n

* Square brackets indicate reference population for smokers and never smokers combined, with need for adjustment of SMR by 1/0.15

Key to notes

a Calculated from ratio of SMRs (or SIRs)

b CI cannot be calculated

c 1 death v 1.1 expected in test group, 0 v 0.4 expected in comparison group

d Not never smokers, but smokers of 0-14 cigs/day

e Expected values multiplied by 0.15 to account for inappropriate reference group

f No lung cancers in non-smokers

g Relative risk either zero or infinite, but unclear which. Only 3 cases at most

h Never smokers include quitters for 10+ years

i Not never smokers, but smokers of 0-9 cigs/day

j No deaths in never smokers in study group; only 5 men at risk; expected not given but would be very low for reference non-smokers

k Expected number not available

l Estimates are for age <65 and age 65+ respectively and are from regression analysis which assumes that the effect of asbestos is independent of smoking

m Estimates are for Georgia, Virginia and Florida respectively

n Never smokers include quitters for 10+ years and smokers of less than ½ pack/day

p No deaths in never smokers in study group; only 33 men at risk; were the lung cancer rate the same as in the reference population of never smokers only about 0.06 deaths would have been expected

q Adjusted for PAH exposure

TABLE 5.2 A summary of data relating to the joint relationship of asbestos exposure and smoking to risk of lung cancer

Study (source table number)	Data	Exposure* A^-S^-	A^+S^-	A^-S^+	A^+S^+
Case-control analyses (within study)					
DEKLERK	Cases	2	4	9	25
(3.2.1)	Controls	399	357	522	521
	RR	1.00	2.24	3.44	9.57
MARTISCHNIG	Cases	28	7	115	51
(3.9.1)	Controls	52	12	120	17
	RR	1.00	1.08	1.78	5.57
RUBINO	Cases	0	0	2	10
(3.12.1)	Controls	6	7	13	28
	RR	0.00	0.00	1.00**	2.32
PASTORINO	Cases	7	2	66	31
(3.13.1)- no PAH	Controls	69	7	119	31
	RR	1.00	2.82	5.47	9.86
- PAH	Cases	4	2	42	22
	Controls	31	7	47	11
	RR	1.00	2.21	6.93	15.50
BOVENZI	Cases	10	8	245	253
(3.14.1)	Controls	103	45	249	164
	RR	1.00	1.83	10.13	15.89
KJUUS	Cases	29	8	103	36
(3.16.1)	Controls	96	11	63	6
	RR	1.00	2.41	5.41	19.86
BLOT	Cases	50	11	313	84
(Georgia,	Controls	203	35	270	45
3.24.1)	RR	1.00	1.28	4.71	7.58
BLOT	Cases	38	25	186	70
(Virginia,	Controls	103	36	163	39
3.24.1)	RR	1.00	1.88	3.09	4.87
BLOT	Cases	17	5	208	65
(Florida,	Controls	110	18	224	54
3.24.1)	RR	1.00	1.80	6.01	7.79

TABLE 5.2 (cont'd) A summary of data relating to the joint relationship of asbestos exposure and smoking to risk of lung cancer

Study (source table number)	Data	Exposure* A^-S^-	A^+S^-	A^-S^+	A^+S^+
Cohort analysis (within study)					
CHENG (3.5.1)	Cases†	-	-	-	-
	Man-years†	-	-	-	-
	RR	1.00	1.57	5.44	8.73
HUILAN (3.6.1)	Cases	4	15	11	27
	Man-years	42502	42218	63714	25933
	RR	1.00	3.78	1.83	11.06
SMR/SIR analysis (external comparison with overall reference population; data available by asbestos exposure					
LIDDELL (3.4.1)	O	10	11	132	146
	E	27.03	18.03	80.00	87.43
	SMR	0.37	0.61	1.65	1.67
ACHESON (3.8.1)	O	0	1	0	21
	E	0.40	1.10	2.60	9.00
	SMR	0	0.91	0	2.33
MEURMAN (3.11.1)	O	1	1	12	41
	E	1.72	2.08	3.29	11.45
	SIR	0.58	0.48	3.65	3.58
SMR/SIR analysis (external comparison with overall reference population; data not available by asbestos exposure					
OKSA (Asbestos sprayers, 3.10.1)	O		0		3
	E		0.10		0.267
	SIR		0		11.22
OKSA (Asbestosis patients, 3.10.1)	O		0		33
	E		0.60		2.692
	SIR		0		12.26
OKSA (Silicosis patients, 3.10.1)	O		0		15
	E		1.10		4.475
	SIR		0		3.35
SELIKOFF 2 (3.21.1)	O		2		45
	E		1.58		4.07
	SIR		1.27		11.06

TABLE 5.2 (cont'd 2) A summary of data relating to the joint relationship of asbestos exposure and smoking to risk of lung cancer

Study (source table number)	Data	Exposure* A^-S^-	A^+S^-	A^-S^+	A^+S^+
SMR analysis (external comparison with reference population for given smoking habit; data available by asbestos exposure					
BERRY(1971-80, men, 3.7.4)	O	1	0	20	43
	E	0.10	0.06	12.36	15.88
BERRY(1971-80, women, 3.7.4)	O	0	3	0	12
	E	0.04	0.20	0.41	2.52
SMR analysis (external population with reference population for given smoking habit; data not available by asbestos					
BERRY(1960-70, men + women, 3.7.3)	O		1		43
	E		0.20		14.20
SELIKOFF 1 (3.20.1)	O		5		45
	E		0.20		9.60
Cohort analysis (comparison with large defined control group, data available by asbestos exposure)					
HILT (3.17.1)	Cases	7	0	111	9
	Death rate	1.90	0.00	11.10	47.80
	RR	1.00	0.00	5.84	25.2
HAMMOND (3.22.5)	Cases††	-	8	-	268
	Death rate	11.30	58.40	122.60	601.60
	RR	1.00	5.17	10.85	53.24

* A^+, A^- relates to asbestos exposure with test and comparison groups as defined in Table 5.1. S^+, S^- relates usually to ever smokers and never smokers. For MARTISCHNIG, KJUUS, PASTORINO and BLOT S^- includes light smokers and/or long-term ex-smokers - see notes to Table 5.1

** Base for comparison is A^-S^+. Base is A^-S^- for other case-control studies

† Cases and man-years not available for CHENG

†† Number of cases not known for ACS control group, but will be large

TABLE 5.3 Validity of additive model

Study	Sum of risks for[a] A^-S^- and A^+S^+	Sum of risks for[a] A^-S^+ and A^+S^-	Difference
DEKLERK	10.57	5.68	4.90
MARTISCHNIG	6.57	2.86	3.71
RUBINO*	2.32	1.00	1.32
PASTORINO (no PAH)	10.86	8.28	2.57
PASTORINO (PAH)	16.50	9.14	7.36
BOVENZI	16.89	11.97	4.92
KJUUS	20.86	7.82	13.04
BLOT (Georgia)	8.58	5.98	2.60
BLOT (Virginia)	5.87	4.98	0.89
BLOT (Florida)	8.79	7.81	0.98
CHENG	9.73	7.02	2.72
HUILAN	12.06	5.61	6.45
LIDDELL	2.04	2.26	-0.22
ACHESON	2.33	0.91	1.42
MEURMAN	4.16	4.13	0.03
OKSA (Asbestos sprayers)**	11.37	1.07	10.30
OKSA (Asbestosis patients)**	12.41	1.07	11.34
OKSA (Silicosis patients)**	3.50	1.07	2.43
SELIKOFF 2**	11.21	2.34	8.87
BERRY (Men+women,1960-70)†,**	3.39	1.82	1.57†,**
BERRY (Men, 1971-80)†	4.40	1.73	2.67
BERRY (Women, 1971-80)†	5.10	2.25	2.85
SELIKOFF 1†,**	5.17	4.82	0.35
HILT	26.16	5.84	20.32
HAMMOND	54.24	16.02	38.22

[a] Based on RRs for first 12 studies and last 2 studies and on SMRs for remainder

* Risk relative to A^-S^+

** Assuming SMR in A^-S^- is 0.15 and in A^-S^+ is 1.07

† Dividing smoking specific expected values by 0.15 for S^- and 1.07 for S^+ to make them comparable to the same reference population

TABLE 5.4 Validity of multiplicative model

Study*		Product of risks for[a] A^-S^- and A^+S^+	Product of risks for[a] A^-S^+ and A^+S^-	Ratio = U (95% CI)
DEKLERK		9.57	7.69	1.25 (0.19-8.08)
MARTISCHNIG		5.57	1.92	2.89 (0.87-9.62)
RUBINO		0.00	0.00	Undefined
PASTORINO (no PAH)		9.86	15.40	0.64 (0.10-4.06)
PASTORINO (PAH)		15.50	15.32	1.01 (0.13-7.94)
BOVENZI		15.89	18.54	0.86 (0.31-2.39)
KJUUS		19.86	13.03	1.52 (0.39-5.93)
BLOT (Georgia)		7.58	6.01	1.26 (0.54-2.93)
BLOT (Virginia)		4.87	5.82	0.84 (0.39-1.81)
BLOT (Florida)		7.79	10.82	0.72 (0.22-2.36)
CHENG		8.73	8.57	0.98 (Not estimable)
HUILAN		11.06	6.93	1.60 (0.43-5.90)
LIDDELL	(a)	0.62	1.01	0.61 (0.25-1.49)
	(b)**	0.25	0.65	0.38 (0.21-0.79)
ACHESON	(a)	0.00	0.00	Undefined
	(b)**	0.35	0.97	0.36 (0.06-14.7)
MEURMAN	(a)	2.08	1.75	1.19 (0.07-20.4)
	(b)**	0.54	0.51	1.05 (0.18-46.4)
OKSA (Asbestos sprayers)**		1.68	0.00	∞
OKSA (Asbestosis patients)**		1.84	0.00	∞
OKSA (Silicosis patients)**		0.50	0.00	∞
SELIKOFF 2**		1.66	1.35	1.22 (0.32-10.4)
BERRY (Men+women,1960-70)		0.49	0.80	0.61 (0.10-25.7)
BERRY (Men)[†]	(a)	4.35	0.00	∞
	(b)**	0.43	0.00	∞
BERRY (Women)[†]	(a)	0.00	0.00	Undefined
	(b)**	0.76	2.41	0.32 (0.09-1.75)
SELIKOFF 1**,[†]		0.75	4.01	0.19 (0.07-0.61)

TABLE 5.4 Validity of multiplicative model (cont'd)

Study*	Product of risks for[a] A^-S^- and A^+S^+	Product of risks for[a] A^-S^+ and A^+S^-	Ratio = U (95% CI)
HILT	25.20	0.00	∞
HAMMOND	53.24	56.07	0.95 (0.47-2.21)
Meta-analysis ††		Fixed effects Heterogeneity	0.90 (0.67-1.20) χ^2 = 14.89 on 15 d.f.

[a] Based on RRs for first 12 studies and last 2 studies and on SMRs or SIRs for remainder

* For LIDDELL, ACHESON, MEURMAN and BERRY the first estimate (a) uses the data for all four groups, A^-S^-, A^+S^-, A^-S^+ and A^+S^+, while the second estimate (b) uses only the data for the A^+S^- and A^+S^+ groups.

** Assuming SMR in A^-S^- is 0.15 and in A^-S^+ is 1.07

† Dividing smoking specific expected values by 0.15 for S^- and 1.07 for S^+ to make them comparable to same reference population

†† See text for description of studies included in meta-analysis

TABLE 5.5 Multiplicative model - fitted risks

Study	Risk for asbestos only	Risk for smoking only†	Risk for joint exposure
Case-control studies			
DEKLERK	2.68	4.00	10.75
MARTISCHNIG	2.40	2.21	5.29
RUBINO	2.32	∞	∞
PASTORINO (no PAH)	1.88	5.03	9.46
PASTORINO (PAH)	2.23	6.95	15.52
BOVENZI	1.58	9.50	15.05
KJUUS	3.04	5.77	17.54
BLOT (Georgia)	1.53	4.90	7.49
BLOT (Virginia)	1.67	2.93	4.89
BLOT (Florida)	1.35	5.63	7.58
GARSHICK (Age <65)*	1.20	5.68	6.82
GARSHICK (Age 65+)*	0.98	9.14	8.96
Cohort and occupational studies with data for all four groups			
LIDDELL	1.05	3.54	3.71
HUILAN	5.33	2.65	14.13
BERRY (1971-80,men)	1.61	2.33	3.76
BERRY (1971-80,women)	∞	2.26	∞
ACHESON	∞	2.57	∞
MEURMAN	0.97	6.87	6.69
HILT	4.17	6.08	25.36
Other studies			
BERRY (1960-70)	3.06	[7.13]	21.80
OKSA (Asbestos sprayers)	9.96	[7.13]	71.04
OKSA (Asbestosis patients)	11.11	[7.13]	79.20
OKSA (Silicosis patients)	3.03	[7.13]	21.60
SELIKOFF 1	5.10	[7.13]	36.39
SELIKOFF 2	10.24	[7.13]	73.01
HAMMOND	4.91	[10.85]	53.37

† Square bracketed numbers are risks from external population

* >50 pack-years smoking, fitted risks are as given by Garshick *et al*[56]

TABLE 5.6 Testing fit of multiplicative model - comparison of observed and fitted cases

Study	Cases	Exposure A^-S^-	A^+S^-	A^-S^+	A^+S^+	Deviance*
Case-control studies						
DEKLERK	Observed	2	4	9	25	
	Fitted	1.765	4.235	9.235	24.765	0.05
MARTISCHNIG	Observed	28	7	115	51	
	Fitted	25.075	9.925	117.925	48.075	3.08
RUBINO	Observed	0	0	2	10	
	Fitted	0.000	0.000	2.000	10.000	0.00
PASTORINO (no PAH)	Observed	7	2	66	31	
	Fitted	7.470	1.530	65.530	31.470	0.21
PASTORINO (PAH)	Observed	4	2	42	22	
	Fitted	3.990	2.010	42.010	21.990	0.00
BOVENZI	Observed	10	8	245	253	
	Fitted	10.561	7.439	244.439	253.56	0.08
KJUUS	Observed	29	8	103	36	
	Fitted	28.099	8.901	103.901	35.099	0.38
BLOT (Georgia)	Observed	50	11	313	84	
	Fitted	48.715	12.285	314.285	82.715	0.30
BLOT (Virginia)	Observed	38	25	186	70	
	Fitted	39.153	23.847	184.847	71.153	0.21
BLOT (Florida)	Observed	17	5	208	65	
	Fitted	17.853	4.147	207.147	65.853	0.28
All case-control studies combined	Observed	185	72	1289	647	
	Fitted	182.681	74.319	1291.319	644.68	4.59
Cohort and occupational studies with data for all four groups						
LIDDELL	Observed	10	11	132	146	
	Fitted	12.36	8.64	129.60	148.40	1.16
HUILAN	Observed	4	15	11	27	
	Fitted	3.02	15.98	11.98	26.02	0.47
BERRY (1971-80, men)	Observed	1	0	20	43	
	Fitted	0.51	0.49	20.49	42.51	1.37
BERRY (1971-80, women)	Observed	0	3	0	12	
	Fitted	0.00	3.00	0.00	12.00	0.00

TABLE 5.6 (cont'd) Testing fit of multiplicative model - comparison of observed and fitted cases

Study	Cases	Exposure A^-S^-	A^+S^-	A^-S^+	A^+S^+	Deviance
ACHESON	Observed	0	1	0	21	
	Fitted	0.0	1.00	0.00	21.00	0.00
MEURMAN	Observed	1	1	12	41	
	Fitted	0.92	1.08	12.08	40.92	0.01
HILT	Observed	7	0	111	9	
	Fitted	6.74	0.26	111.26	8.74	0.54
All cohort etc. studies combined	Observed	23	31	286	299	
	Fitted	23.55	30.45	285.41	299.59	3.56
Other studies**						
BERRY (1960-70)	Observed		1		43	
	Fitted		0.61		43.39	0.25
OKSA (Asbestos sprayers)	Observed		0		3	
	Fitted		0.15		2.85	0.16
OKSA (Asbestosis patients)	Observed		0		33	
	Fitted		1.00		32.00	1.03
OKSA (Silicosis patients)	Observed		0		15	
	Fitted		0.50		14.50	0.52
SELIKOFF 1	Observed		5		45	
	Fitted		1.02		48.98	15.85
SELIKOFF 2	Observed		2		45	
	Fitted		2.43		44.57	0.08
HAMMOND	Observed		8		268	
	Fitted		7.61		268.39	0.02
All other studies combined	Observed		16		452	
	Fitted		13.32		454.68	17.91

* Estimated by logistic model for case-control studies, by loglinear model for cohort, etc. studies and by $\Sigma(\text{Observed-Fitted})^2/\text{Fitted}$ for other studies. The deviance is an approximate chisquared statistic. However, the approximation will be poor for studies with small fitted values.

** Estimated assuming smoking risk of 10.85 for HAMMOND and 7.13 for the remaining other studies.

TABLE 5.7(a) Attributable risks from smoking and asbestos exposure among those exposed to both agents

		% attributable to			
Study	Cases	Background	Asbestos only	Smoking only	Both factors
Case-control					
DEKLERK	25	9.3	15.7	27.9	47.1
MARTISCHNIG	51	18.9	26.4	22.8	31.9
RUBINO	10	0	0	43.1	56.9
PASTORINO (no PAH)	31	10.6	9.3	42.6	37.5
PASTORINO (PAH)	22	6.4	8.0	38.3	47.3
BOVENZI	253	6.6	3.9	56.5	33.0
KJUUS	36	5.7	11.6	27.2	55.5
BLOT (Georgia)	84	13.3	7.0	52.1	27.5
BLOT (Virginia)	70	20.4	13.7	39.4	26.4
BLOT (Florida)	65	13.2	4.6	60.7	21.1
Mean (10 studies)		10.4	10.0	41.1	38.4
Cohort and occupational with data for all 4 groups					
LIDDELL	146	27.0	1.3	68.5	3.2
HUILAN	27	7.1	30.7	11.7	50.6
BERRY(1971-80,men)	43	26.6	16.3	35.3	21.7
BERRY(1971-80,women)	12	0	44.2	0	55.8
ACHESON	21	0	39.0	0	61.0
MEURMAN	41	14.9	-0.4	87.7	-2.3
HILT	9	3.9	12.5	20.0	63.5
Mean (7 studies)		11.4	20.5	31.9	36.2
Other studies with data only for asbestos exposed populations*					
BERRY (1960-70)	43	4.6	9.4	28.1	57.9
OKSA (asbestos sprayers)	3	1.4	12.6	8.6	77.4
OKSA(asbestosis patients)	33	1.3	12.8	7.7	78.2
OKSA(silicosis patients)	15	4.6	9.4	28.4	57.6
SELIKOFF 1	45	3.0	12.3	18.3	66.4
SELIKOFF 2	45	1.4	12.6	8.4	77.6
HAMMOND	268	2.4	9.4	17.9	70.2
Mean (7 studies)		2.7	11.2	16.8	69.3

* Assuming a smoking relative risk of 7.13 for BERRY (1960-70), OKSA, SELIKOFF 1 and SELIKOFF 2 and of 10.85 for HAMMOND

TABLE 5.7(b) Attributable risks from smoking and asbestos exposure among the whole population

		% attributable to			
Study	Cases	Background	Asbestos only	Smoking only	Both factors
Case-control					
DEKLERK	40	20.2	16.1	34.3	29.4
MARTISCHNIG	201	46.1	8.7	37.1	8.1
RUBINO	12	0	0	52.6	47.4
PASTORINO (no PAH)	106	23.1	3.6	62.4	11.0
PASTORINO (PAH)	70	17.7	4.1	63.4	14.9
BOVENZI	516	11.2	2.5	70.2	16.2
KJUUS	176	29.3	5.4	53.9	11.3
BLOT (Georgia)	458	28.9	2.1	64.0	5.1
BLOT (Virginia)	319	41.0	6.1	47.1	5.8
BLOT (Florida)	295	22.5	1.4	71.5	4.7
Mean (10 studies)		24.0	5.0	55.7	15.4
Cohort and occupational with data for all 4 groups					
LIDDELL	299	32.5	0.8	65.2	1.6
HUILAN	57	22.6	35.9	17.5	24.0
BERRY(1971-80,men)	64	32.9	11.0	41.6	14.6
BERRY(1971-80,women)	15	0	55.3	0	44.7
ACHESON	22	0	41.7	0	58.3
MEURMAN	55	18.0	-0.3	84,1	-1.7
HILT	127	20.2	0.9	74.4	4.5
Mean (7 studies)		18.0	20.8	40.4	20.9
Other studies with data only for asbestos exposed populations*					
BERRY (1960-70)	44	5.2	10.7	27.5	56.5
OKSA (asbestos sprayers)	3	1.4	12.6	8.6	77.4
OKSA(asbestosis patients)	33	1.3	12.8	7.7	78.2
OKSA(silicosis patients)	15	4.6	9.4	28.4	57.6
SELIKOFF 1	50	4.7	19.1	16.5	59.8
SELIKOFF 2	47	1.7	16.0	8.0	74.3
HAMMOND	276	1.9	7.3	18.5	72.3
Mean (7 studies)		3.0	12.6	16.5	68.0

* Assuming a smoking relative risk of 7.13 for BERRY (1960-70), OKSA, SELIKOFF 1 and SELIKOFF 2 and of 10.85 for HAMMOND

6. Discussion and conclusions

In 1977 Saracci[1] analysed the epidemiological evidence then available relating to the interaction between asbestos and smoking. The abstract of this paper referred to "three simple models for the asbestos-smoking interaction on human lung cancer production." "In the first model the excess incidence of lung cancer independently due to asbestos and to smoking adds together when both agents are present (additive model). In the second the addition of each one of the two agents produces an effect (increase in lung cancer incidence) which is proportional to the effect of the other (multiplicative model). In the third, asbestos can only increase lung cancer incidence in the presence of smoking." They noted that "as previously found by other investigators, the additive model appears the least plausible in the light of the data from two published epidemiological studies." They attempted "a discrimination between the other two models" "through a detailed analysis of the five published epidemiological studies today available which provide information on occupational asbestos exposure, smoking habits and lung cancer risk," and concluded that "although the data do not allow a definitive discrimination, the multiplicative model appears to be more plausible, being also consistent with a multistage carcinogenic mechanism and with evidence from animal (rat) experiments." They noted that "it is relevant both for biology and for public health that in this model asbestos and smoking are regarded as independently capable of producing lung cancer in humans and that they act synergistically when exposure to both occurs."

In 1985, in a paper reporting updated results from their own study of factory workers in east London, Berry et al[3] reviewed data from several studies, concluding that "although overall non-smokers have a relative risk of lung cancer due to asbestos that is 1.8 times that of smokers, there is some uncertainty on the accuracy of this figure because of possible biases and sampling variation."

The next year Steenland and Thun[4] considered the nature of the interaction between tobacco smoking and occupational exposures in the causation of lung cancer more generally, looking at evidence for "the only four established occupational lung carcinogens for which there are data on smoking: radon daughters, asbestos, arsenic, and

chloromethyl ethers." They assessed departure from both an additive model and a multiplicative model, considering that only nine studies (four on asbestos; HAMMOND, SELIKOFF 2, BERRY and LIDDELL) "provided sufficient information on tobacco use and occupational exposure to evaluate interaction." They concluded that the existing data were "contradictory" for asbestos (and also for radon and arsenic) and pointed out that it was "noteworthy that, for these four agents, whenever smoking did modify the effect of occupational exposure, the lung cancer ratio was greater for nonsmokers (compared to non-exposed nonsmokers) than smokers (compared to non-exposed smokers)." In commenting on this review, it should be noted that the summary of conclusions by Steenland and Thun in their Table 12 regarding departure from the multiplicative model is open to question. While they noted, consistent with our own analyses, that there is no departure for HAMMOND but there is departure for SELIKOFF 1 (though see below), they somewhat surprisingly noted that there was departure for BERRY and may be departure for LIDDELL. For BERRY their conclusion of departure from the multiplicative model, and also of no departure from the additive model, is inconsistent not only with our own analyses, but also with those reported by the original authors. For LIDDELL, their conclusion that there may be departure from both models is actually inconsistent with an analysis by the original authors cited by Steenland and Thun that "both an additive and multiplicative model fit the data, although the fit of the multiplicative model was slightly better."

In 1987 Saracci[2] reviewed the interactions of tobacco smoking and other agents in cancer aetiology. Based on lung cancer data from 11 studies they classified the interaction between smoking and asbestos exposure on a seven point scoring system as follows:

> M	More than multiplicative	Risk for the combined exposure group at least 25% more than that predicted by the multiplicative model (i.e. the product of the relative risks in the two groups exposed to one agent only)

≃ M	Near multiplicative	Risk for the combined exposure group 10-25% more or 10-25% less than that predicted by the multiplicative model
M	Multiplicative	Risk for the combined exposure group within ±10% of that predicted by the multiplicative model
I	Intermediate	Risk for the combined exposure group less than 75% of that predicted by the multiplicative model and more than 125% of that predicted by the additive model (i.e. the sum of the relative risks in the two groups exposed to one agent only less 1)
A	Additive	Risk for the combined exposure group within ±10% of that predicted by the additive model
≃ A	Near additive	Risk for the combined exposure group 10-25% more or 10-25% less than that predicted by the additive model
< A	Less than additive	Risk for the combined exposure group no more than 75% of that predicted by the additive model

Thus, if the relative risk for asbestos only is 3 and for smoking only is 5, one would classify relative risks for the combined group as follows:

Relative risk for combined exposure group	Saracci's classification
>18.75	>M
16.50-18.75	≃M
13.50-16.50	M
11.25-13.50	≃M
8.75-11.25	I
7.70-8.75	≃A
6.30-7.70	A
5.25-6.30	≃A
<5.25	<A

Using this scheme they classified 15 estimates from these studies as follows:

>M	5	I	3	A	1
≃M	4			≃A	1
M	1			<A	0

They noted that “a somewhat variable pattern of interaction has been observed between asbestos and tobacco smoking” and that “although all studies could be formally reconciled with the multiplicative model, this variation in the strength of interaction may also reflect real differences stemming from the fact that both asbestos and smoking act at different stages of the carcinogenic process”.

In an updated review paper, Vainio and Boffetta[5] discussed mechanisms of the combined effect of asbestos and smoking in the etiology of lung cancer. Using the same classification scheme as in the review by Saracci in 1987[2], and the same scores for the studies considered in both reviews, they classified 18 estimates from 13 studies as follows:

>M	7	I	3	A	1
≃M	5			≃A	1
M	1			<A	0

They noted that "the overall evidence indicates an interaction in the multiplicative region, although the pattern across studies was not uniform" and concluded that "a variable pattern of interaction has been observed which may reflect both the fact that asbestos and smoking act at different stages of the carcinogenic process and the fact that there are differences in the biological effects of different types of asbestos fibres." Although it is conceivable that the interaction may vary for these reasons, the major problem with this review was that sampling error was not taken into account in their analyses. While they noted that studies may lack power to discriminate between alternative models, they do not appear to have realised that their analysis did not actually demonstrate a variable pattern of interaction actually exists at all, since formal testing of

the overall adequacy of the multiplicative model over all studies combined was not conducted.

In the same year, Saracci and Boffetta[6] also reviewed the evidence on possible interactions of smoking with other agents on the risk of lung cancer. The studies reviewed and the scores assigned were identical to those in the review by Vainio and Boffetta[5] and the conclusions with regard to asbestos and smoking essentially the same.

The latest published review, appearing in 1999, was by Erren et al[7] and concerned "synergy between asbestos and smoking on lung cancer risks." Their analyses concerned 12 data sets from 10 of the 23 studies considered in this document, selected to allow relative risks and standard errors to be calculated for groups exposed to asbestos only, smoking only and asbestos plus smoking (relative to the group exposed to neither). Defining E_A, E_S and E_C as the excess risks in these groups (i.e. the relative risks minus 1), they calculated the following 3 statistics for each of the 12 data sets:

(i) "the synergy index":

$$Y = E_C / (E_A + E_S)$$

(ii) "the relative excess risk due to interaction":

$$RERI = E_C - E_A - E_B$$ and

(iii) "the attributable proportion of risk due to interaction":

$$AP = RERI / (E_C + 1)$$

Y will take the value 1.0 if the additive model holds and will be greater than 1.0 if synergy exists. All 12 estimates of S reported by Erren et al[7] were greater than 1.0, consistent with our general conclusions that the additive model is inadequate.

RERI similarly takes the value 0.0 if the additive model holds and will be positive if Y is greater than 1.0.

AP is explained by Erren et al[7] as "that fraction of the total lung cancer risk among those exposed to both factors in the population concerned (including the background risk in the absence of the two factors) that is attributable to the combined (as

distinct from the separate) effects of the two effects." Thus for example, if relative risks are 1, 3, 5 and 23 for, respectively, unexposed, asbestos only, smoking only and combined exposure, 1 of the risk of 23 (4.3%) in the combined group can be attributed to background, 2 (8.7%) to asbestos only, 4 (17.4%) to smoking only, with the remaining 16 (69.6%) to the combination. The authors found that estimates of AP varied from 16 to 72% in the various data sets, and averaged 33%, leading to their conclusion that "one-third of cancer cases among smokers who were exposed to asbestos can be attributed to the synergistic behavior of the two carcinogens."

It was notable that the review did not attempt to test whether the multiplicative model actually fitted the data. For some studies, Erren et al used rather different relative risk estimates than presented in the current report. There were various reasons for this, including exclusion by Erren et al of data for ex-smokers for BERRY, use of different assumed relative risk estimates for smoking in the reference populations for BERRY and SELIKOFF 1 and failure to include the latest published data for LIDDELL. In no case did the alternative data used by Erren et al affect the general conclusions of this report.

The analyses described in the current review are more comprehensive than any of the seven reviews referred to above[1-7] and clarify the situation considerably. The analyses described in section 5 appear to show clearly that:

1. asbestos exposure does increase risk of lung cancer in never smokers;
2. the joint relationship of asbestos exposure and smoking to risk of lung cancer is not well fitted by the additive model; and
3. the joint relationship is quite well fitted by a multiplicative model.

Before accepting these apparently clear conclusions various points have to be considered.

First, there were two studies where there was evidence of statistically significant departure from the multiplicative model. In SELIKOFF 1 there were 45 deaths from lung cancer among ever smokers of cigarettes, as against 9.6 expected based on men with the

same smoking history in the American Cancer Society million person study. In contrast there were 5 deaths based on 0.2 expected among men who had never smoked regularly. Based on these data the relative effect of asbestos in cigarette smokers was estimated to be 0.19 (95% CI 0.07-0.61) times that in never cigarette smokers. This analysis was based on death certificate diagnosis to make it on the same basis as the ACS comparison data. However, as shown in Table 3.20.1, based on the best available medical evidence, there were 55 lung cancer deaths (not 45) in the cigarette smokers and 3 deaths (not 5) in the never cigarette smokers. Berry et al[3] state that if one allowed for the differential misdiagnosis, the departure from the multiplicative model would no longer be statistically significant. If one simply used the revised observed numbers of deaths U becomes 0.38 (95% CI 0.12-1.91), which is not significant, agreeing with Berry et al. Though this analysis does not take into account misdiagnosis in the reference population, which certainly exists, it does cast some doubt on the validity of the conclusion that the study misfits the multiplicative model. In any event, one study misfitting the model hardly provides major evidence against it, especially when the fit to the model is so good in the other studies.

In LIDDELL, two alternative analyses were conducted to test the adequacy of the multiplicative model. The first analysis was equivalent to testing whether the relative increase in risk of lung cancer associated with smoking was similar in men with high and low asbestos exposure. Though the relative risk was less in those with high exposure, 2.73, than in those with low exposure, 4.46, the difference was not significant, implying no departure from the model. The second analysis tested whether the relative increase in risk of lung cancer associated with smoking in men with high asbestos exposure was similar to that seen in the British Doctors Study[64]. Here the difference, 2.73 vs 7.13 was statistically significant. The first analysis is less subject to bias, as it avoids the implicit assumption that smoking habits in British Doctors and Quebec asbestos miners were similar and the problem that the smoking of pipes and cigars was only taken into account in the British Doctors Study. Certainly it is unclear that the data from LIDDELL actually indicate any true departure from the multiplicative model.

It is also relevant to consider the possible effect of misclassification of smoking status on the observed results. If there is in fact no true effect of asbestos exposure on lung cancer risk in never smokers, then misclassification of some ever smokers as never smokers will create an apparent effect of asbestos exposure in never smokers. However the observed relative increase will be markedly less than that seen in smokers and the multiplicative model will not hold.

If, on the other hand, a true multiplicative relationship exists, then it should still be observed following misclassification of smoking status, provided that such misclassification is independent of asbestos exposure.

The same is true in reverse. Provided a true multiplicative relationship exists, then it should still be observed following misclassification of asbestos exposure, provided that the misclassification is independent of smoking habits.

It is important to note that, even if the true relationship is multiplicative, an exact multiplicative relationship may not be observed in practice because of differences in average asbestos exposure between asbestos exposed never smokers and asbestos exposed ever smokers, or conversely because of differences in average amount smoked between smokers exposed to asbestos and smokers unexposed to asbestos. A limitation of many of the analyses of interaction is that the data are simply subdivided into four groups (A^-S^-, A^+S^-, A^-S^+ and A^+S^+). In principle, it is better to develop a logistic or log linear regression analysis with terms for extent or duration of smoking and for extent or duration of asbestos exposure and then see whether addition of interaction terms (implying inadequacy of the multiplicative model) are statistically significant. The analysis by Garshick et al[56], which appears to have found no interaction (but see section 3.23), is one such example.

The general conclusion from this review is that the joint relationship of asbestos exposure and smoking to risk of lung cancer is well described by a multiplicative model. This increase in risk associated with smoking is well documented to vary by number of cigarettes smoked, duration of smoking, inhalation and product smoked. The increase

in risk associated with asbestos exposure also depends on many factors, including not only extent and duration of exposure, but also type of asbestos and nature of exposure. This doubtless largely explains why the increases seen in certain occupational groups are larger than in others, though differences in occupational exposures to other carcinogens might also contribute.

The multiplicative nature of the joint relationship implies that attributable risks for smoking and for asbestos exposure may exceed the total risk. Thus, the data from the HAMMOND study, with an approximate 5-fold increase in lung cancer risk associated with asbestos exposure and an approximate 10-fold increase associated with smoking, taken at face value and ignoring any confounding by other exposures, implies that among the insulation workers who smoked, about 90% of their lung cancers would have been avoided had they not smoked, and about 80% would have been avoided had they not been insulation workers.

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