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The Interaction of Asbestos and Smoking in Lung Cancer

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Both cigarette smoke and inhaled asbestos fibres can cause lung cancer, but the assessment of how these agents act in combination is a matter of great difficulty. In non-smokers, the condition is so rare that, in any cohort of asbestos workers, the standardised mortality ratio (SMR, that is the ratio of the numbers of deaths observed and expected) is quite imprecise. The SMR for smokers, with which it has to be compared, is also subject to sampling error, making the interaction even more unstable. This accounts for much of the variation that has bedevilled evaluation.

The debate has been concentrated on two hypotheses: additive (asbestos and cigarette smoke act independently) and multiplicative (asbestos produces an effect proportional to the effect of smoking). The very few data available until 1977 failed to fit the former and fitted the latter only poorly. They would have fitted better a hypothesis of greater synergism, but the only one proposed was too convoluted. So the multiplicative model appeared the only alternative, and was deemed 'accepted'.

The ratio of lung cancer SMRs for non-smokers and smokers was generalised into the *relative asbestos effect*, RAE, with all the advantages of a parametric statistic (Berry *et al.*, 1985, *British Journal of Industrial Medicine* 42, 12). On the multiplicative hypothesis, RAE=1, while RAE>1 indicates less synergism. The RAEs for the three most recent of the six results then available were >1; for one, $P<0.005$. From the six results combined, it was concluded that 'overall non-smokers have a relative risk of lung cancer due to asbestos that is 1.8 times that of smokers'. Some admitted uncertainty about the figure 1.8 was seized upon and even the thrust of the conclusion has been very largely disregarded. So too has the RAE and all its benefits. As a result, all later reviewers have been led into error, much of it serious: in particular, they have failed to appreciate how much of the variation arises from the inevitable imprecision of all RAEs. This failure led reviewers in 1994 to discard, quite without justification, those interactions which were less than multiplicative and came from cohort studies. Although case-referent studies seemed to support the multiplicative hypothesis, the information from them is essentially unreliable. Thus it cannot weaken the conclusions from the cohort studies, that the multiplicative hypothesis is untenable and that the relative risk of lung cancer from asbestos exposure is about twice as high in non-smokers as in smokers; the best estimate of RAE is 2.04, with 95% confidence interval 1.28–3.25. This finding is not only of high statistical significance but of great social and scientific importance.

Keywords: additivity; asbestos exposure; cigarette smoking; independence; interaction; lung cancer; multiplicativeness; synergy

INTRODUCTION

For almost four decades, it has been accepted that both cigarette smoke and asbestos dust are potential causes of lung cancer, but the effects of the combination of these two agents remain in doubt. Doll (1971) observed that the very sparse data available fitted the multiplicative hypothesis better than the additive one. Certainly, the additive hypothesis, that the two agents act independently, was quite unsatisfactory; however, the fit to the multiplicative hypothesis, that the effect of asbestos is proportional to the effect of smoking, was far from convincing. In the

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first review of interactions (Saracci, 1977), covering three more studies, the indications were of greater synergism, but the formal tests of significance did not indicate the need to reject the multiplicative hypothesis, and a third 'more elaborate' hypothesis was too extreme. Thus, the multiplicative hypothesis, although just one of infinitely many putative forms of synergy, was generally taken as 'accepted'—and still is, despite contrary evidence accumulating from 1980.

For example, Doll and Peto (1985) expressed the view that the interaction of asbestos with smoking was either exactly multiplicative or nearly so, and the difference was unimportant because the (absolute) risk to non-smokers is quite small. However, the degree of synergism is of great significance in considerations of attributability. It is frequently claimed, on the basis of the multiplicative hypothesis, that the amount smoked by a lung cancer patient does not affect the probability that his condition can be attributed to asbestos exposure. Intuitively at least, this is unreasonable: on the one hand, when a non-smoker presents with lung cancer, another cause must be sought, and asbestos exposure, even if fairly minor, is likely to be accepted as the attributable cause. On the other hand, in a patient who is a heavy smoker, asbestos may have exacerbated his condition, but his exposure would have had to be severe for it to be treated as the main cause.

The form of this interaction is also of importance for many other reasons. As one example, Kane (1996), investigating the mechanisms of the relationship between fibrosis and bronchogenic carcinoma, proposed a model postulated on the grounds that 'cigarette smoke and asbestos fibres are multiplicative in the induction of bronchogenic carcinoma'.

The assessment of the interaction is, however, a matter of great difficulty, dominated by the fact that the condition is rare in non-smokers. The simplest approach is to compare the standardised mortality ratio (SMR, or O/E, where O and E are the numbers of deaths observed and expected) for non-smokers in a cohort of asbestos workers with the SMR for smokers, and the accepted means of comparison is to find confidence limits for the ratio of the two SMRs (Breslow and Day, 1987). In the various cohorts of asbestos workers that provide useful information, the totals of lung cancer deaths observed and expected from population mortality rates were very low, in most studies five or less and 0.8 or less, respectively, and so each SMR for non-smokers is quite imprecise. The corresponding SMR for smokers is also subject to error, so that the instability is increased; this can be recognised by the great width of all the confidence intervals.

Further difficulties have arisen for two reasons. First, although a parametric measure of interaction (a generalisation of the ratio of SMRs) was introduced in 1985, together with the concept of confidence intervals, later reviewers have ignored them, and thus fallen into unnecessary error. Second, eschewing the parametric approach means that tests of homogeneity across studies and methods of combining results, with confidence limits adjusted in the light of observed heterogeneity, could not be adopted; thus, further error has resulted.

This paper presents a historical perspective, and then reviews all the evidence, with the aim of determining the most reliable assessment of the interaction between asbestos exposure and cigarette smoking in the causation of lung cancer. The sources of evidence are listed in Table 1, where they are given an alphabetic reference, in square brackets, for use in what follows; also given are the reference numbers used by Saracci (1987). A few early reports mentioned by Saracci (1977) but without useful information have been excluded. For most of the cohort studies, the data consist of the numbers of deaths from lung cancer observed (O), and expected (E) on the basis of mortality rates of some specified population, among smokers and non-smokers, together with SMRs. In case-referent studies, the corresponding measures, called odds ratios, are formed from the cross-product of numbers in two double dichotomies, each of cases/referents; exposed/unexposed.

HISTORY

In 1964, the Geographical Committee of l'Union internationale contre le cancer convened a Working Group on Asbestos and Cancer, which accepted that there was an association between exposure to asbestos dust and carcinoma of the lung and recommended *inter alia* comprehensive investigation of 'the relationship of dust dosage (including concentration and duration of exposure) to the incidence of ... carcinoma of the lung...' with special attention directed to smoking habits (Working Group on Asbestos and Cancer, 1965). At about the same time, Doll and Hill (1964) published the results of 10 years' observations of mortality in relation to smoking among British doctors, in which 'the most pronounced association is shown by cancer of the lung for which the annual death rate rises linearly from 0.07 per 1000 men who are non-smokers to 3.15 per 1000 in men smoking 35 or more cigarettes daily'.

Early theories

In the earliest studies of asbestos workers, there were no cases of lung cancer in men who did not smoke cigarettes, and so a theory evolved that asbestos caused lung cancer only in smokers. Then Doll (1971), in an important and wide-ranging paper, examined the effects of the combination of two agents. As one example, he made use of the data in [h]: Selikoff *et al.* (1968) had followed 370 asbestos insulation workers for 52 months, 1963–67, and reported 24 lung cancer deaths, all in cigarette smok-

Table 1. Sources of evidence

Text ref.	First author (date)	No. in cohort or nos of cases/controls	Period	RS ref
Quebec chrysotile miners and millers				
[a]	Braun (1958)	5958 men	1952–55	–
[b]	McDonald (1980)	a cohort of 10 939 men	1950–75	–
[c]	McDonald (1980)	245/245 from the cohort	to 1975	–
[d]	Liddell (1984)	223/715 from the cohort	to 1975	15
[e]	McDonald (1993)	5335 survivors into 1976	1976–88	–
Wittenoom crocidolite miners				
[f]	Baker (1985)	unknown	1944–81	16
[g]	de Klerk (1991)	40/1799 from a cohort of 2400 men	1979–86	–
Insulation workers				
[h]	Selikoff (1968)	370 men in New York and Newark NJ	1963–67	–
[i]	Hammond (1973)	the same 370 men	1963–71	–
[j]	Selikoff (1975)	the same 370 men	1963–73	21
[k]	Hammond (1973)	17 800 men in USA and Canada	1967–71	–
[l]	Selikoff (1975)	the same 17 800 men	1967–72	–
[m]	Hammond (1979)	the same 17 800 men, with 73 763 not exposed	1967–76	22
Factory workers				
[n]	Berry (1972)	2492 workers in Barking, London	1960–70	19
[o]	Berry (1985)	the same 2492 workers: revision	1960–70	–[a]
[p]	Berry (1985)	1676 workers in the same factory	1971–80	20
[q]	Selikoff (1980)	582 men in Paterson, NJ	1961–77	17
[r]	Acheson (1984)	5969 men in Uxbridge, London	to 1980	18
[s]	Hilt (1985)	287 men in a nitric acid plant	1953–80	–
[t]	Cheng (1992)	1172 workers in China	1972–87	–
Population studies: exposure factor under consideration				
[u]	Martischnig (1977)	201/201: 'unsuspected' occupational exposure; NE England	1972–73	25
[v]	Blot (1978)	535/659: shipyard employment; Georgia, USA	1970–76	23
[w]	Blot (1980)	405/492: shipyard employment; Virginia, USA	1972–76	24
[x]	Pastorino (1984)	204/351: industrial exposure; Northern Italy	1976–79	26
[y]	Kjuus (1986)	176/176: industrial exposure; SE Norway	1979–83	27

[a]The results quoted are as revised in [o] although the reference is given as [n].

ers, against the 'expected deaths from non-occupational causes alone' of 2.98, with corresponding expectations for pipe or cigar smokers and for non-smokers of 0.13 and 0.05, respectively. Doll allocated the 24 observed deaths according to 'two hypotheses about the way asbestos and cigarette smoking interact. In one, it is assumed that asbestos produces the same additional risk in men who smoke cigarettes as in those who do not; in the other, it is assumed that asbestos produces an effect that is proportional to the effect of other agents'. He observed that, despite few data, 'they fit[ted] a multiplicative hypothesis better than an additive one', but the fit was far from convincing.[1]

[1] In his other example, Doll made corresponding calculations in relation to 60 lung cancer deaths in uranium miners (Lundin *et al.*, 1969), concluding that 'the hypothesis that [the agents (radon irradiation and smoking)] act independently is hardly tenable'; the data fitted the multiplicative hypothesis closely.

The review by Saracci (1977)

For 'an analysis of the epidemiological evidence on the asbestos–smoking interaction', Saracci (1977) considered what Doll (1971) and Berry *et al.* (1972) had called hypotheses and theories, terming them 'models of interaction'. Models 1 and 2 described the additive and multiplicative hypotheses, respectively. Model 3 was a 'more elaborate alternative', incompletely defined, to be considered only 'should model 2 (*sic*) be rejected'; it was considered 'refuted' by one case of lung cancer in a non-smoker, and has never been given serious consideration. He then rejected model 1, on the grounds given above by Doll (1971) and endorsed by Berry *et al.* (1972). Thus, all that was possible was to see whether model 2 also had to be rejected, and the only data came from four studies.

From [a] and [j] (extension of the report [h] examined by Doll, 1971), Saracci obtained lung cancer SMRs after some adjustments of the expected numbers with regard to smoking: for smokers, they were 9/2.9 = 3.10 and 45/7.47 = 6.02, respectively; there

were no lung cancer deaths among non-smokers and the expected numbers were very small, 0.2 and 0.15, respectively. With such very low expectations, it was quite unlikely that there would be any deaths, or of course any SMR other than zero; the (95%) confidence intervals for zero SMRs[2] are so very wide (here, the upper limits were 18.4 and 24.6), that the corresponding intervals of the smokers' SMRs (here, 1.7–5.9 and 4.4–8.1) could hardly fail to lie well within them. Thus, it is difficult to see that the observations provided any substantial information about the interaction. Nevertheless, formal tests of the difference between the two SMRs in each study yield low values of the χ^2 statistic and high values of P; this is how Saracci proceeded, claiming for both studies 'the ensemble of the data conforms to the multiplicative model'.

Of the 51 deaths from lung cancer among the 1816 workers in [n] for whom smoking habits had been determined, only one occurred among the 230 non-smokers. After subjecting the numbers of lung cancer deaths to several ingenious adjustments, Berry *et al.* (1972) used what data they could to see which of the only two 'theories' that had been postulated was the more likely. The evidence, acknowledged to be rather sparse, was in favour of the multiplicative, rather than the additive. There are many major difficulties with the remaining study [u], but if the data are taken at face value, Saracci's conclusion that they 'conform to a multiplicative model...' could be justified.

In fact, all four fits to model 2 were quite poor but those to model 1 were worse still. Better fits would have been provided by any number of hypotheses of greater synergism, but not by model 3 which was too elaborate. So, with model 1 also dismissed, the multiplicative hypothesis appeared the only alternative. With only one model under consideration, it was not unreasonable to claim it as the most plausible, and Saracci (1977) claimed support on two counts, one of plausibility, the other speculative. First, the model could derive from a multi-stage chain of discrete carcinogenic 'hits' and so was plausible. Second, it would be reasonable to expect that asbestos would act in similar ways on the smoking effect and on other respirable carcinogens, known or unknown, which may contribute to the 'natural' incidence of human lung cancer—although lung cancer in non-smokers was extremely rare in the available data.

It remains clear that the choice was essentially of the least of evils. Doll (1971) had introduced just two hypotheses of joint action, one of which had to be rejected, and both Berry *et al.* (1972) and Saracci (1977) seemed to accept that the multiplicative hypothesis was the only viable alternative. This appears to have been the general view.

The parametric approach

Berry *et al.* (1985) made a seminal contribution by introducing the ratio of the relative risk (RR) due to asbestos exposure in non-smokers to that in smokers as a parameter of interaction, which they termed the *relative asbestos effect* (RAE). On the multiplicative hypothesis, the relevant RRs for non-smokers and for smokers will be the same, and the RAE, the ratio of these two RRs, will be equal to 1. When, as had been observed previously, the non-smokers' RR is less than that for smokers, the interaction is greater than multiplicative (tending towards model 3), and RAE<1. If the interaction is less than multiplicative, which includes the additive, RAE>1. In other words, if the RAE were equal to 1, the asbestos effect would be the same for non-smokers as for smokers; a value of RAE greater than 1 would indicate that the effect of asbestos is greater in non-smokers than in smokers, and vice versa.

Berry *et al.* (1985) also indicated that confidence intervals around the point estimates of RAE could be calculated. This was another important advance because, as a result of the inevitably small numbers involved, the statistical reliability of any RAE must be very low so that its confidence interval is wide, the 'width' of a confidence interval being measured by the ratio between the upper and lower limits. No point estimate of RAE is of any real value in the absence of an interval estimate. With the parametric approach, results can be combined readily into a (weighted geometric) mean RAE, and the homogeneity of several RAEs can be tested by means of an approximate χ^2 statistic, following DerSimonian and Laird (1986). Details of the approach are given later in this paper.

The review by Berry et al. (1985)

After revising their results for 1960–70, which had appeared in [n], these authors reported mortality in the following 10 years of 1253 men and 423 women at the same factory. The principal finding from [p] was that: 'after allowing for the effect of smoking on lung cancer the relative risk due to asbestos was highest for those who had never smoked, lowest for current smokers, and intermediate for ex-smokers; the trend was statistically significant ($P<0.05$)'. However, for inclusion in their review of the six available studies, they combined the sexes and the two levels of exposure, and pooled ex-smokers with smokers; the resultant RAE, 3.0 (0.8–7.5), was not significantly different from 1.

In the six studies available for this review, i.e. [h], [m], [q], [o], [p] and [d], RAEs ranged from 0 to 5.3. For this last RAE, from [q], the interval estimate was given as 1.8–12.2, and this evidence taken on its own

[2] The $(1-\alpha)$ limits for a zero SMR are 0 and $[-\ln(\alpha/2)]/E$, where E is the expected number of deaths (Liddell, 1984); for $\alpha = 0.05$, the upper limit is greater than one unless $E>3.69$.

provided a clear case for rejection of the multiplicative hypothesis. However, all six confidence intervals overlapped the range 1.8–2.6, and the authors found 'little evidence of heterogeneity of [RAE]'. Then they calculated the RAE for the studies combined as 1.8, with 95% confidence interval 1.1–2.8. However, with commendable caution, Berry *et al.* (1985) noted possible biases and sampling variation, and so 'would not claim that it is *established* that non-smokers have a higher relative risk due to asbestos than smokers, although overall the data suggest that this may be the case' (added emphasis).

Although Doll and Peto (1985) concurred with the conclusion, they seized on the caveat, and argued that the excess might be due 'perhaps entirely' to methodological artefacts, particularly in the classification of smoking habits. They then stated they were 'inclined to believe' that the interaction was close to being exactly multiplicative because this was suggested in the largest study with prospectively obtained smoking habits (Hammond *et al.*, 1979, i.e. [m]).

Steenland and Thun (1986) considered how several occupational carcinogens, asbestos among them, interacted with smoking in the development of lung cancer, with the aim of discovering 'departures' from the additive and/or multiplicative models. In the four asbestos data sets available, all covered by Berry *et al.* (1985), they observed one interaction, for [m], quite close to the multiplicative model and definitely departing from the additive; two, [q] and [p], close to the additive model and departing from the multiplicative; and the fourth, [d], perhaps departing from both models. The authors considered these findings 'contradictory', but the test of homogeneity of RAEs led to $P>0.2$, so that the suggested explanations are unnecessary and could be misleading. Thus, little had been gained.

For whatever reasons, the conclusion by Berry *et al.* (1985), with or without the support from Steenland and Thun (1986), was widely disregarded.

The reviews from the International Agency for Research on Cancer, 1987 and 1994

Saracci (1987) made a wide-ranging review of interactions of tobacco smoking and several other agents in the aetiology of cancer, with discussion of implications for public health. Thirteen studies relating to asbestos exposure were identified; they are indicated, under 'RS ref.', in Table 1 by the numbers in the list of references in the review. The data consist of relative risks of lung cancer due to asbestos exposure, in non-smokers—but see below—and smokers, for 15 data sets, and they are presented in Table 2, arranged by class of interaction magnitude; two of the results are inadmissible as explained in footnotes b and d. It is regretted that the footnotes have to be voluminous; even then, footnote f requires the following development.

Two groups of studies, say A and B, can be identified according to the definition of 'non-smokers'. In eight studies, forming *Group A*, light smokers and ex-smokers were excluded from 'non-smokers', but in the other five, *Group B*, the so-called non-smokers were a 'mixed category' in which light smokers and/or ex-smokers had been combined with non-smokers (for whom details were not given). Ex-smokers were excluded entirely in three of the studies in Group A.

The review suffers from several major shortcomings, especially the lack of adequate quantification, by which fundamental errors could have been avoided. Relative asbestos effects and, of course, confidence intervals were eschewed;[3] instead, Saracci (1987) proffered a seven-point classification of the observed interactions, in terms of what is called 'absolute interaction magnitude'. This classification is without obvious merit, and has the major demerit that there is no way of assessing reliability, nor of judging the degree of variability. The numbers of cases among non-smoking asbestos workers were very small, totalling only 34 in the eight studies of Group A—just half in ref. [d], the other counts being 5, 4, 4, 2, 1, 1 and 0—and 53 in the five studies of Group B (25, 11, 8, 7 and 2). As a consequence, almost all the estimates of RAE are very imprecise. Even so, the RAE and its confidence interval are more revealing than any non-numeric classification: for example, the four admissible results classed >M are seen to vary by a factor of 4.8; and classes I, ~A and A relate poorly to RAEs and to the judgements of Steenland and Thun (1986).

It is simply untrue that 'None of these studies provides enough evidence to formally reject, at a conventional level of significance ($P = 0.05$), the multiplicative interaction', as claimed by Saracci (1987). In fact, as shown by Berry *et al.* (1985), the lower 95% confidence limit on the RAE for [q] is considerably greater than 1; in a test of the hypothesis that the interaction is multiplicative, in other words that RAE = 1, $P\approx0.004$. But even if this fact is ignored, one cannot accept the ensuing remark that 'one could be satisfied that [the multiplicative interaction] is the best common representation of all [remaining] available data'.

Saracci (1987) continued: 'Alternatively, one may think that the observed variation in the size of the interactions ... reflects real differences...', but that variation requires examination. In a test for homogeneity of the RAEs calculated from the relative risks quoted by Saracci (1987), but excluding [h] (for technical reasons explained later) and [f] (see footnote e to Table 2), the χ^2 was 15.17, with 11 df, which does not indicate serious heterogeneity. Although this may appear surprising at first sight, it is easily accounted

[3] This is particularly unfortunate as the methods must have been familiar at IARC, Lyon.

Table 2. Relative asbestos effects in relation to the 'interaction magnitudes' of Saracci (1987)

Text ref.	RR due to asbestos[a]		Relative asbestos effect		Comment
	NS	S	RAE	95% CI	
>M—more than multiplicative					
[o] ♂		2.25	Inadmissible		–[b,c]
[j]	0	6.0	Inadmissible		–[d]
[h]	0	8.05	0	0–9.90	
[f]	0.71	4.98	0.14	0.02–1.00	Narrowest possible interval[e]
[u]	1.08	3.19	0.35	0.10–1.15	'Non-smokers' inflated[f]
[o] ♀	5.00	7.36	0.68	0.02–4.46	Listed as from [n][c]
~M—near multiplicative					
[v]	1.28	1.61	0.79	0.34–1.84	'Non-smokers' inflated[f]
M—multiplicative					
[m]	5.71	5.25	1.05	0.29–2.73	
~M—near multiplicative					
[y]	2.40	2.05	1.17	0.10–13.17	'Non-smokers' inflated[f,g]
[w]	1.88	1.57	1.20	0.55–2.59	'Non-smokers' inflated[f]
[r]	2.00	1.57	1.27	NA	Replaced by [r] revised[h]
[r] revised	2.70	1.65	1.65	0.04–10.48	–[h]
I—intermediate					
[x]	2.80	1.80	1.56	0.25–9.91	'Non-smokers' inflated[f]
[p] ♀	12.50	4.27	2.93	0.52–11.36	–[i]
[q]	25.00	4.69	5.33	1.65–13.39	
~A—near additive					
[d]	2.97	1.67	1.79	0.64–5.01	–[i]
A—additive					
[p] ♂	6.25	2.01	3.12	0.07–18.13	–[j]

[a]Relative risk in non-smokers (NS) and in smokers (S).
[b]In [n], the relative risk for non-smokers is indeterminate, because the expected number of deaths was zero, and so there is no possible measure of interaction. The classification as >M is unacceptable.
[c]These results, revised from those given in [n], were taken from [o], but the reference for them is given as [n].
[d]Reference [j] concerns mortality in two periods from 1963 to 1973: the first is covered in [h]; the second is incorporated into [m], and cannot stand alone.
[e]As analysis fails to reject the multiplicative hypothesis, the confidence interval shown is the narrowest possible, i.e. with upper limit = 1. On that basis, the RAE is an obvious outlier; it remains so unless the correct confidence interval is so wide that the influence of the RAE in any combination of results becomes quite small.
[f]'Non-smokers' included either light smokers or some ex-smokers or both.
[g]The smokers for whom the RR is quoted as 2.05 were those who smoked 20 or more cigarettes a day; the RR for all smokers of ≥10 cigarettes a day was 3.67, so that RAE = 0.66 (0.17–2.55).
[h]The relative risks quoted by Saracci (1987) cannot be recognised. Using the observed numbers of deaths and the authors' adjustments of expected numbers, among non-smokers and current smokers in the highest exposure group, the relative risks are as in the line labelled: '[r] revised'.
[i]Berry *et al.* (1985) combined men and women and standarised to give 'excess ratios', for non-smokers and current smokers, of 7.3 and 2.2, leading to RAE = 3.32, not very far from the estimates, 2.93 for females and 3.12 for males, in Table 2. The confidence interval is, however, very much narrower, i.e. 0.88–8.96.
[j]The authors of [p] gave the 'mixture coefficient' (which would be 0 for the additive model or 1 for the multiplicative) as 0.78, implying that the interaction was not 'near additive' but closer to multiplicative.

for by the very small numbers involved. Further, most of the variation is accounted for by differences between Groups A and B ($\chi^2 = 6.35$: 1 df), that within groups being quite slight ($\chi^2 = 8.81$: 10 df), so that the many other possible explanations of the variation become unnecessary. As the 'mixing' of non-smokers with some others would have been expected to reduce the value of RAE and as Group B consisted of case-referent studies in all of which work histories as well as smoking habits were obtained retrospectively, they must be considered less reliable than those in Group A, for which RAE = 2.20, with 95% confidence interval 1.29–3.78. The evidence that the multiplicative hypothesis is not adequate is very strong; it remains strong even when the RAE for [f] is included.

Vainio and Boffetta (1994) simply copied from Saracci (1987), without correction, but adding material from three more recent studies. Sadly, all are rather unilluminating: [g] falls into Group B; [s] is a tiny study; and [t] is clearly irrelevant to western

experience.[4] On the other hand, they ignored an important report, [e], published before their own had been received for publication, and thus long before the proof stage. What Saracci (1987) had called 'interaction magnitude' these authors termed a 'measure of interaction' and, while accepting that these 'measures' were very imprecise, they stated that statistical variability was not taken into consideration.

All the shortcomings of the earlier review were perpetuated; in particular, the findings from the survey by Berry *et al.* (1985) were ignored. Compounding these defects, Vainio and Boffetta (1994) stressed variation, and disparaged or dismissed all results that did not, in their view, conform to the multiplicative model. Then they cited four reports that 'pointed towards a multiplicative interaction'; these were said to be of insulation workers who could be taken as exemplars of those severely exposed to asbestos. Two of the reports, [v] and [w], were of shipyard employment in which only a minority of the workers were reported to have handled asbestos, let alone to have been insulators—in [v], the minority was a mere 5% and included only one insulator—while the original authors mentioned other possibly carcinogenic exposures. The third cited report contains results from two periods: the earlier, [h], was so small it is best incorporated into the fourth report [m], into which the results from the later period had been assimilated. The only relevant result is from [m], augmented as above, namely RAE = 0.96, with 95% confidence interval 0.26–2.49. Also, it is certain that other workers suffered severe asbestos exposure, in particular those in [p] for which both RAEs in Table 2 were greater than the upper confidence limit of the RAE for [m]. Indeed, the interaction for insulators is hardly typical.

Vainio and Boffetta (1994) claimed support for the multiplicative pattern from three case-referent studies. However, all three ([u], [x] and [y]) were in Group B, and even without going into detail, which is given later in this paper, it is clear that the problems are of sufficient moment to endorse the generally accepted view that findings from case-referent studies are less reliable than those from cohort studies. Thus, they provide no grounds for overturning the conclusion from the cohort studies that the interaction is markedly less than multiplicative.

Nevertheless, Vainio and Boffetta (1994) flew in the face of this evidence by concluding in favour of 'an interaction that approximates the multiplicative model'. Perhaps because this was prefixed with the word 'overall', many workers appear to have been misled into believing that the multiplicative hypothesis could be accepted generally. In particular, Henderson *et al.* (1997) quoted Vainio and Boffetta's (1994) summary table (re-ordered and slightly simplified, but still containing all the errors, with another added) and endorsed this conclusion.

The survey by Erren et al. (1999)

For the latest survey—of the 'biologic synergy' between asbestos and smoking in lung cancer—Erren *et al.* (1999) found 17 relevant research papers in the MEDLINE base (1966–96), all considered by Vainio and Boffetta (1994). For various reasons, only 12 data sets were considered suitable: the bizarre result from China, [t], was included; the 1993 report from Quebec, [e], was not. The present author cannot reproduce from [o] and [p] the material cited by Erren *et al.* (1999); in it the relative risks from smoking alone are extraordinarily high, 12.1 and 11.8; on the other hand, the corresponding risks in [t] and [u] were exceptionally low, 1.6 and 1.8. These could be grounds for excluding all four sets, but they have little effect on the conclusions.

The paper uses a 'synergy index' S, due to Rothman (1976),[5] calculated from the relative risks of lung cancer due to smoking and asbestos, separately and combined, to examine departures from the additive model, for which $S = 1$. The values of S ranged from 1.22 to 5.30, but the heterogeneity was really quite slight ($P \approx 0.32$), so it is not unexpected that the authors found no explanation for it, whether in methodological differences or in type of fibre, and despite wide variations of the smoking relative risks and of the relative risks due to asbestos alone (1.1–25.0). It was concluded that the excess lung cancer arising from exposure to both asbestos and smoking is higher, by a factor of about 1.64, than the sum of the two risks—in other words the additive model did not fit in general.

It may be noted that, not surprisingly, there was a considerable degree of association between S and the value of RAE (as calculated from Table 3 of Erren *et al.*, 1999). Even where RAE was large, that is where the interaction was much less than multiplicative, S remained greater than unity, indicating that the interaction was greater than additive, if not by much.

The 'forgotten' result of McDonald et al. (1993)

As the latest surveys failed to include this result, it has to be placed here out of chronological sequence.

[4] The relative risks of lung cancer due to smoking were only 1.6 in both unexposed and exposed, thus vitiating the whole study, at least from a western point of view. Incidentally, the relative risks from asbestos exposure in non-smokers and smokers were 5.44 and 5.54 (not 1.6 and 1.6, as listed by Vainio and Boffetta, 1994).

[5] In what follows, the results of Erren *et al.* (1999) are taken at face value. However, they were obtained by a simplified formula, 'for small effects' (Rothman, 1976), which is not strictly applicable in the present context; it produces estimates of S lower, by amounts which depend largely on the risk for unexposed non-smokers but are usually quite small, than those from the correct version.

Report [e] is of mortality in the cohort of Quebec chrysotile miners and millers in the years 1976–88, quite distinct from the follow-up to 1975, reported in [b], [c] and [d]; smoking histories had been ascertained in advance, by means of a questionnaire completed in 1970 by every member of the cohort alive then, including all who survived into 1976. In brief, the relative asbestos effect was 1.63 (0.67–3.96), quite similar to the value found for deaths before 1976. In relation to the preceding section, it is of interest that the synergy index S was 0.86 (0.58–1.26); the point estimate suggests antagonism, but it is much more likely that additivity, or perhaps quite slight synergy, obtains.

Conclusion

Of the two hypotheses proposed by Doll (1971) about the way asbestos and smoking interact, one, additive, has been rejected consistently. The other, multiplicative, was supported by the first finding of any reasonable degree of reliability, that is among insulation workers (Hammond *et al.*, 1979). However, the results from five more recent cohort studies are consistent in indicating a much weaker interaction. When all studies of this nature are combined, the relative risk of lung cancer in asbestos workers who are non-smokers is about double the corresponding risk in smokers. Nevertheless, reviewers have been reluctant to accept this fact.

The evidence from the case-referent studies, if taken at face value, tends to support the multiplicative hypothesis. However, all these studies are badly flawed because light smokers or some ex-smokers or both were classed with non-smokers. Moreover, the doubts that always arise over this type of study are exacerbated by the fact that not only smoking habits but also employment histories were obtained retrospectively, often by proxy. Reviewers have failed to recognise these facts or have ignored them.

Thus, many workers have been led to believe that the interaction has been demonstrated to be multiplicative, or at least close to multiplicative. Thus, it is necessary to review the whole corpus of evidence systematically, in relation to the general synergistic model, that is without restriction on the parameter d in expression (1), introduced below.

REVIEW OF EVIDENCE

Materials and methods

The sources of evidence, which is all epidemiological because no experimental approach is feasible, have been listed in Table 1. The numbers in the third column are of the totals, which act as aids to recognition; the numbers actually studied were considerably reduced, if only because of unobtainable smoking habits. In what follows, evidence is cited by the 'text ref.', in the first column of the table. Certain papers appear more than once because they report different analyses. Report [f] was superseded by [g], and so is removed from review. The 370 men of [h], [i] and [j] were among the 17 800 in [k], [l] and [m], and all the results from 1967 were reported in [m]; thus, [i] through [l] were superseded by [m], and are also removed. As the results in [h], although independent of later reports, were very sparse and not out of line with those in [m], they have been assimilated to form [m+h]. Report [t] has been discarded because of unacceptably low relative risks due to smoking. The different analyses, in [b], [c] and [d], of essentially the same data are retained for expository purposes—but not for summarisation. Studies [b] and [e], although of the same cohort, relate to non-overlapping periods and so are independent of each other; studies [o] and [p] are similarly independent.

Formulations of models

Algebraic models are presented in this section; the argument here in terms of SMRs applies equally to odds ratios. Although Saracci (1977) had mentioned 'formal representations', algebraic formulations for SMRs were introduced by Hanley and Liddell (1985) as follows: (1) they took s_i to represent levels of smoking, increasing with $i = 0, 1, 2, \ldots$; (2) they let x_j represent the mean exposure to asbestos at various levels, $j = 0, 1, 2, \ldots$; (3) they defined SMR for subgroup i, j as the ratio of O_{ij} to E_{ij} (that is the ratio of the observed and expected numbers of deaths for the subgroup); (4) they formed the product term $s_i x_j$; and (5) they adopted the simplest relationship between these variables, namely a straight line, with four parameters. For non-smokers in a cohort exposed to asbestos, the expected number of lung cancer deaths reflects the risk among non-smokers in the reference population, which is not of course occupationally exposed to asbestos, and this risk is taken as base. In other words, when both s and x are 0, it is taken that SMR$\equiv$1, thus reducing the number of parameters to three; the relationship becomes:

$$\text{SMR} = 1 + bs + cx + dsx \qquad (1)$$

where b, c and d are the three parameters that have to be estimated. When each agent acts alone, the relations become SMR = 1 + bs and SMR = 1 + cx.

Additive model. If the effect of asbestos is simply added to that of smoking, then

$$\text{SMR} = 1 + bs + cx.$$

This is the additive model and, in expression (1), $d \equiv 0$. There is no synergism, no interaction; the term 'additive interaction' is an oxymoron.

Multiplicative model. If $d \equiv bc$, expression (1) can be written

$$SMR = \{1 + bs\} \times \{1 + cx\}$$

and this model is seen to be multiplicative.

General synergistic model. There is of course no theoretical restriction on the parameter d, and expression (1) describes a model allowing any degree of synergism: it includes not only the two special cases noted above but an infinity of others. The general model, without restriction on d, has three parameters and so is less simple than the special cases, each with two parameters.

Asbestos effects: relative asbestos effect

If, in expression (1), both s and x take values of 1 and 0 only (that is, if the subgroups are defined, as they usually have been, as smokers or non-smokers, exposed or not exposed), the ratios of SMRs (or of odds ratios) are: $(1 + b + c + d)/(1 + b)$ and $(1 + c)$, for smokers and non-smokers, respectively; these ratios are the *asbestos effects* (Berry *et al.*, 1985). The ratio of the asbestos effects is the *relative asbestos effect* (Berry *et al.*, 1985), or RAE. Clearly,

$$RAE = (1 + b)(1 + c)/(1 + b + c + d)$$

and this is seen to be the hypothetical multiplicative effect divided by the observed effect. Thus, if an observed interaction is less-than-multiplicative, multiplicative, or more-than-multiplicative, then $RAE > 1$, $=1$, or <1, respectively.[6] In other words, if the RAE were equal to 1, the asbestos effect would be the same for non-smokers as for smokers; a value of RAE greater than 1 would indicate that the effect of asbestos is greater in non-smokers than in smokers, and vice versa.

Confidence

Except in studies with large numbers of cases, the statistical reliability of any RAE must be very low; thus, no point estimate of RAE is of any real value in the absence of an interval estimate. Berry *et al.* (1985) indicated that *confidence intervals* around the point estimates of RAE could be calculated by use of likelihood methods, but the simpler techniques now available have been used. Exact confidence intervals of a ratio of SMRs were obtained from the F-distribution (Breslow and Day, 1987, as simplified from Liddell, 1983). Approximate limits for a ratio of odds ratios were obtained (by use of the square-root transformation, which both normalises and stabilises the variance of the Poisson distribution) as described by Armitage and Berry (1994; and in the 1987 edition). We have followed Berry *et al.* (1985) by adopting 95% as the confidence coefficient, and in what follows the confidence interval is normally placed in brackets immediately after the point estimate. The *width of a confidence interval* is measured by the ratio between the upper and lower limits.

Combination of results: homogeneity

Results were combined by finding the weighted geometric mean of the relevant RAEs: its logarithm was calculated as

$$\ln[GM(RAE)] = (\Sigma\{w_j \ln[RAE_j]\})/\Sigma\{w_j\},$$

where the various studies are indicated by j ($= 1, 2, \ldots$), and the weights w_j are the reciprocals of the variances of $\ln[RAE_j]$. The variance of $\ln[GM(RAE)]$ was found as $1/\Sigma\{w_j\}$. For most cohort studies, the variance of the RAE had to be estimated from its confidence interval. The homogeneity of several, say k, RAEs was tested by means of a statistic, Q, which is approximately a χ^2 statistic with $k-1$ degrees of freedom, df (DerSimonian and Laird, 1986).

If RAE = 0, then ln(RAE) tends to $-\infty$, its variance has to be taken as infinite, the weight w becomes zero, and the product $w \ln(RAE)$, at first sight indeterminate, has limiting value zero. Thus, in the process of combination, zero RAEs are eliminated; this is in accord with the fact that all the observed zero RAEs relate to minuscule expectations, separately and in combination, and so are uninformative. Another approach is, however, possible: the deaths observed in each subject-years analysis can be allocated (analogously to the method of Doll, 1971) according to the expectations after adjustment in terms of the mean RAE, and a 'goodness of fit' χ^2 statistic can be calculated. A 'minimum χ^2' estimate of average RAE can then be obtained by trial and error; this will not be the optimum estimate, its sole advantage being that zero RAEs can be accommodated.

Methods of analysis: relative asbestos effects

Cohorts can be examined by subject-years analysis (Berry, 1983), with either external or internal reference mortality, or by case-referent analysis (Armitage and Berry, 1994). In the first approach, the members of the cohort, all taken as exposed, are classified as non-smokers and smokers, and the numbers of deaths in the two classes are compared with expectations, from the reference population, after adjustment for the smoking habits of the population. This provides two SMRs, the ratio of which is the relative asbestos effect, RAE; the confidence interval can be obtained exactly, on the assumption that the expectations are fixed (Breslow and Day, 1987). In the second approach, non-smokers and smokers are further subdivided according to whether their exposure was

[6] Although 1/RAE might have had greater intuitive appeal, it would have led to an infinite value when there were no deaths among unexposed non-smokers.

Table 3. Results from subject-years analyses of cohort studies (Group A)

Text ref.	Non-smokers			Smokers			Relative asbestos effect	
	O	E	SMR	O	E	SMR	RAE	95% CI
[s]	0	0.41	0	9	2.38	3.79	0	0–2.96
[r]	1	0.37	2.70	18	10.92	1.65	1.65	0.04–10.48
[o][a]	1	0.2	5.0	14	1.9	7.4	0.68	0.02–4.46
[p][a]	4	0.55	7.27	75	31.02	2.42	3.01	0.80–8.03
[m+h]	4	0.82	4.88	292	57.60	5.07	0.96	0.26–2.49
[q]	5	0.2	25.00	45	9.6	4.69	5.33	1.65–13.39
[e][b]	11	6.67	1.65	146	144.25	1.01	1.63	0.67–3.96
[b][b]	14	4.18	3.35	137	94.23	1.45	2.31	0.80–6.63

[a]These are the most reliable figures from these cohorts (Berry *et al.*, 1985).
[b]Values of E were adjusted by means of the SMR for minimal exposures and those for the other exposures; see text.

minimal or otherwise, and the numbers of deaths in the four classes are compared with expectations, from the reference population (without smoking adjustment). This provides four SMRs, the cross-ratio of which is the RAE. The denominators of the SMRs are taken as fixed, but the numerators are counts of deaths assumed subject to Poisson variation. As a result, the confidence interval, approximated by an extension of the method for an odds ratio (Armitage and Berry, 1994), will be wider than if based on the invalid assumption of fixed expectations.

Case-referent analysis, whether within a cohort or not, requires two double dichotomies—cases/referents; exposed/unexposed—one for non-smokers, the other for smokers. Each provides an odds ratio, as a cross-product of the four relevant numbers, and RAE is the ratio of the odds ratios; its confidence interval can be obtained in a further extension of the method for a single odds ratio (Armitage and Berry, 1994), and is of course approximate.

Each of the observed interactions has been evaluated in terms of the relative asbestos effect (RAE), and the 95% confidence interval has been calculated. The 'precision' of an estimated RAE is governed by the smallest numbers, usually of cases among non-smokers; unless all the relevant numbers are really substantial, the confidence interval will be wide. One of the most precise estimates is for [m + h], but the confidence limits are 3.7 times lower and 2.6 times higher than the point estimate. The width of the interval is thus (3.7×2.6 =) 9.6, and most intervals are considerably wider still. There are two corollaries: no single estimate can cast much light on the general problem; and what may appear to be great variation in estimates may be no more than a reflection of inherent instability.

In the light of these comments, other methodological differences, in particular inconsistencies in the treatment of smokers of pipe or cigar, appear unimportant and no attempt has been made to provide details. Some of the published figures have been amended, usually in correction.

Grouping of studies

The studies have been placed in the two groups, A and B, already defined, depending on the definitions of smoking status. In Group A, the class 'non-smokers' occasionally includes men who smoked pipe or cigar only along with non-smokers of cigarettes, but in Group B the same label covers some light smokers and/or some ex-smokers as well as non-smokers of cigarettes. Group A contains all the cohorts except [a] and [g], whereas all the case-referent designs, together with [a] and [g], fall into Group B. Group A is considered first.

Cohort studies: subject-years analyses

The results from analysis by the subject-years method (Berry, 1983) of the various cohorts in Group A are summarised in Table 3, where O and E represent the numbers of lung cancer deaths observed and expected in subjects exposed to asbestos; the expectations have been adjusted, in various ways, for the smoking habits of the reference population. SMR is the ratio O/E, and the RAE is the ratio of the SMRs for non-smokers of cigarettes and for smokers (sometimes including ex-smokers). The last column gives the 95% confidence interval for the RAE. The results are arranged in Table 3 in order of increasing O for non-smokers. They are also depicted, in sequence of increasing RAE, in Fig. 1, where the wide confidence intervals are evident.

As explained above, if the expected number of lung cancer deaths in non-smokers is very low, the absence of cases provides no useful information about the interaction. A zero RAE would not, of course, be uninformative given a large enough expectation but, in [s], the expected number of deaths among non-smokers was only 0.41. So even a single death would have been less likely than the observed absence of deaths; thus this zero RAE is uninformative. The same can be said about [h], and this is a further reason for incorporation into [m + h].

For six of the seven non-zero estimates, the lower confidence limits are <1 and so each, on its own, is

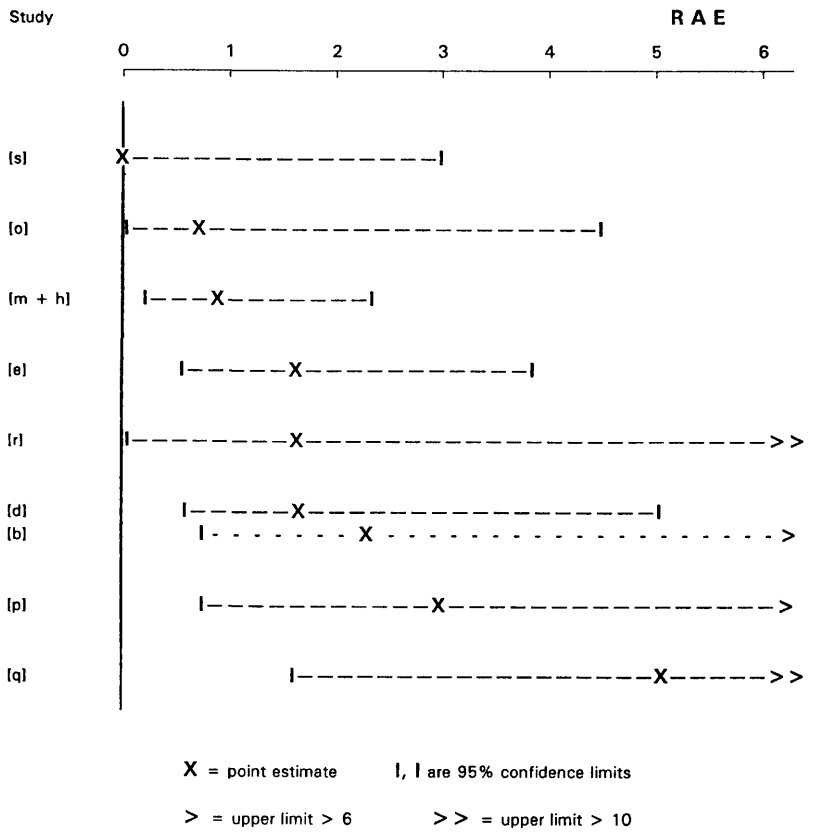

Fig. 1. Relative asbestos effects in Group A studies.

compatible with RAE = 1. However, the seventh is not: for [q], the lower limit is 1.65, indicating highly significant departure from the multiplicative model. However, none of the seven can be considered in isolation; instead, the wide confidence intervals with their very considerable overlaps must be taken into account. Indeed, a test of homogeneity yields $Q = 5.82$ with 6 df, and nominal value of $P \approx 0.44$. As this provides no contraindication, the estimates can be combined into the weighted geometric mean RAE: this is 2.14 (1.36–3.37).

The minimum χ^2 approach to the same seven estimates leads to a tiny reduction (by 0.23%) in the relevant statistic; and for all eight studies, that is including [s], the statistic is only marginally less (by 0.45%) than that for the average RAE, as estimated by this method but without [s]. These improvements in goodness of fit are quite insufficient to justify amendment, which in any case could only have been small, to the more soundly based geometric mean estimate. The one gain from the alternative approach has been confirmation that the zero RAE makes quite an insignificant difference.

Cohort studies: case-referent analyses

Berry *et al.* (1985) commended the approach by case-referent-within-a-cohort analysis, as in [d], but pointed out that, although working entirely within a cohort was preferable, it would have been too inaccurate in their own study, [p], because there were only four deaths from lung cancer in non-smokers. Table 4 gives the results of two analyses of this type, from refs [c] and [d]: the relative asbestos effects were estimated as 2.32 and 1.79, which are closely similar to 2.31 for ref. [b]; the result for [d] is included in Fig. 1. Agreement from the three analyses was to be expected (see for example Liddell *et al.*, 1977) and would have been even closer had it not been for the variation in definitions.

Summary of results from Group A

All the analyses in the last two sections are of studies in Group A, but only one of the three analyses, [b], [c] and [d], of data from the same cohort can be included in any summary. The RAE from [d] is undoubtedly the most reliable and has, therefore, been substituted for that from [b] in the weighted average from the subject-years analyses. The test of homogeneity yields $Q = 6.29$, which is so close to the df (6) that corrections for heterogeneity affect only the third place of decimals for the point estimate and widen the interval estimate very slightly; the corrected RAE (replacing the earlier estimate of 2.14) is 2.04 (1.28–3.25).

Table 4. Results from case-referent analyses of a cohort study (Group A)

Text ref.		Non-smokers			Smokers			Relative asbestos effect	
		Exposure		Odds ratio	Exposure		Odds ratio		
		Yes	No		Yes	No		RAE	95% CI
		a b	c d	ad/bc	e f	g h	eh/fg		
[c]	Deaths	15	5		141	84			
	Referents	10	10	3.00	127	98	1.30	2.32	0.57–9.31
[d]	Deaths	17	6		131	69			
	Referents	98	103	2.98	274	240	1.66	1.79	0.64–5.01

Cohort studies: case-referent analyses (continued)

In [g], there were even fewer lung cancer deaths in non-smokers than in [p], and long-term ex-smokers were included with non-smokers. The result has therefore to be placed in Group B, and the ratio of the asbestos effects cannot be considered a true RAE; it has been termed here the *supposed relative asbestos effect* (SRAE). As the numbers of deaths were very small, the confidence interval around the SRAE of 0.80 is particularly wide; see Table 5. A matched analysis yielded SRAE marginally lower, 0.74 (de Klerk *et al.*, 1991), but the confidence interval was slightly wider. The authors also used conditional logistic regression to estimate relative risks, but as there were only 40 cases spread over at least 12 combinations of smoking class and exposure groups, all estimates were quite unreliable. Thus it would have been most surprising if any value of P had been 'significant'; and it is quite clear that '$P>0.4$ in all cases' gives no justification for accepting the relevant

Table 5. Results from case-referent analyses (Group B)

Text ref.		Non-smokers and light smokers and/or ex-smokers[a]			'Smokers'			Supposed relative asbestos effect	
		Exposure		Odds ratio	Exposure		Odds ratio		
		Yes	No		Yes	No		SRAE	95% CI[b]
		a b	c d	ad/bc	e f	g h	eh/fg		
[u]	Cases	7	28		51	115			
	Referents	12	52	1.08	17	120	3.13	0.35	0.10–1.15
[y]	Cases	8	29		36	103			
	Referents	11	96	2.41	6	63	3.67	0.66	0.17–2.55
[v]	Cases	11	50		84	313			
	Referents	35	203	1.28	45	270	1.61	0.79	0.34–1.84
[g][c]	Deaths	4	2		25	9			
	Referents	357	399	2.24	521	522	2.78	0.80	0.12–5.21
[w]	Cases	25	38		163	186			
	Referents	36	103	1.88	39	70	1.57	1.20	0.55–2.59
[x]	Cases	2	7		31	66			
	Referents	7	69	2.82	31	119	1.80	1.56	0.25–9.91

[a]Definitions are as follows: [g] non-smokers and ex-smokers for more than 10 years; [u] smokers of 0–14 cigarettes a day; [v], [w] non-smokers and ex-smokers for more than 10 years and smokers of less than half a pack of cigarettes a day; [x], [y] smokers of 0–9 cigarettes a day.
[b]Interval estimate of Supposed RAE, based on the tabled counts: a through h.
[c]Case-referent-within-a cohort analysis.

hypothesis(es). In particular, the statement that 'the multiplicative model fitted the data reasonably well' has little meaning.

Population case-referent studies

All five conventional case-referent studies also have to be relegated to Group B, and so each suffers from the fundamental problem that, without knowledge of the double dichotomy—by case or referent and by exposed or not—of the non-smokers (separate from light and ex-smokers), there is no means of obtaining an estimate of the true RAE. The Supposed RAE is subject to bias, especially where non-smokers formed a quite small minority of the 'mixed' category. It is true that, if the multiplicative model obtained, the bias would be small; otherwise, however, it will tend to mask deviations from the model. The results, for what they are worth, are presented in Table 5, along with that from [g]: the Supposed RAEs are seen to range from 0.35 to 1.56.

'Mixing' has another important consequence concerning confidence intervals. The numbers a, b, c and d shown in Table 5 have been inflated, sometimes grossly inflated, above those for non-smokers, and so the intervals calculated from them, and listed in Table 5, are narrower, sometimes much narrower, than would apply for the true (unknown) RAEs. Some examination is possible for ref. [u]: four of the cases and 25 of the referents were non-smokers, but how many in each of these groups had been assessed as exposed is not known. It can be shown that the RAE could have lain anywhere between zero and infinity, and that the narrowest possible confidence interval would have been an order of magnitude wider than that listed in Table 5. Again, for [g] the RAE could have taken almost any value, above or below 1, and the tightest confidence interval would be almost four times as wide as that listed. The other intervals in this table should also be widened correspondingly, but there are no bases for this process. It is, nevertheless, clear that the Supposed RAEs in Table 5 are quite unreliable because of both bias and imprecision.

Another major difficulty is that there must always be some doubt in population case-referent studies that the exposures of cases and referents are commensurable. In all five of those summarised in Table 5, information about occupation and smoking was obtained by interview, inevitably carried out after the subjects had been selected for the investigation. The interviews were, in most cases, intended to be of the subjects themselves, but proxies were frequently needed. The potential for bias in eliciting smoking histories is well-known, and it can be particularly great in attempts to assess exposure (Schlesselman, 1982; Case, 1995). Thus, the Supposed RAEs observed may be subject to further biases, but there is no means of knowing in which ways.

An additional general problem is that there are uncertainties over what the subjects in the population studies were exposed to, for it is far from obvious that asbestos was the only carcinogen, other than tobacco smoke, in their environment. Indeed, in several reports there is mention of other exposures thought at the time to be possibly carcinogenic but now accepted as such. In particular, many carcinogenic hazards in shipyard work are well documented, whereas the risks from exposure to asbestos have tended to be quite low; cf. refs [v] and [w]. As for study [u], the claim that over a quarter of the hospital cases (and 14% of the controls) had had occupational exposure must be treated with great caution in the light of the facts that none of the cases had ever worked in asbestos manufacturing, none had ever used asbestos as a principal material, and none had asbestosis.

Further examination of [u] is relevant here. There was a five-fold difference in risk of lung cancer, without regard to exposure, for smokers of 1–14 cigarettes a day compared with non-smokers; because of this difference, it was quite unacceptable to combine the two groups. Nevertheless, they were combined to provide the 'base risk'; relative to that, the risk for smokers of $\geq$15 cigarettes a day was a mere 2.2, as distinct from 7.6 relative to non-smokers. Further, among those deemed not exposed, the corresponding risk was only 1.8, and this is so low that all the results must be considered particularly unreliable.

Summary of results from Group B

Because of all these problems with the case-referent studies, the results from them are highly suspect. However, for the sake of completeness, the data in Table 5 have been used to calculate the average SRAE for [u]–[y] together with [g]: it is 0.83 (0.53–1.30). This is markedly different from the mean from Group A ($Q = 7.66$, with 1 df, and $P \approx 0.006$), and it is obvious there are no grounds for combining the results from the two groups; those from Group A must prevail.

Also for the sake of completeness, study [a] is mentioned: its result was a zero SRAE that was uninformative[7] and so could be disregarded.

SUMMARY AND CONCLUSIONS

There have been some 20 reports, although with considerable overlap, containing information regarding the interaction between asbestos exposure and smoking in the aetiology of lung cancer, but the numbers of lung cancer deaths have been very small, especially of course among non-smokers. In the seven cohort studies in Group A, that is where the non-smoker class was not augmented by ex-smokers or light smokers, there were only 43 deaths of non-smokers, 5.6% of all lung cancer deaths; and in the six

[7] Among non-smokers 0.2 deaths were expected and none observed.

case-referent studies, all in Group B, the corresponding figures were 57 and 12.8%. There were four analyses with 11–25 such deaths, but in six the counts were four or less. These very small numbers lead to instability in the estimate of relative asbestos effect and to extremely wide confidence intervals. This is an inherent problem which makes evaluation less straightforward than has frequently been believed.

It is generally accepted that, of the various types of observational study, the most definitive information about disease aetiology is provided by cohort studies analysed by the subject-years method (Berry, 1983) or by the case-referent method carried out within the framework of the cohort (see for example Breslow and Day, 1987). It follows that results from population case-referent studies have to be considered less reliable. It is also clear that the mixing of light smokers and/or ex-smokers with non-smokers, which defines Group B, leads to bias and to misleading estimates of precision.

It is fortunate that all seven cohort studies (Table 3) with non-zero RAEs are in Class A. The best estimate of the average relative asbestos effect from their combination is 2.04, and this must be the starting point for overall evaluation. Although the seven estimates of RAE from those studies range from 0.68 to 5.33, a test of homogeneity yields $P \approx 0.39$, which gives little indication of heterogeneity. The estimates of RAE for workers with chrysotile, amosite, crocidolite and insulation materials are 1.69, 4.62, 2.43 and 0.96, respectively, which may not appear entirely homogeneous. However, the relevant test still yields a value of $P \approx 0.19$, and all four estimates are compatible with RAE = 2.04.

The basic flaw in the studies in Group B means that their results cannot be taken into account, and so there are no grounds for amending this evidence from the cohort studies. The confidence interval around RAE = 2.04 is 1.28–3.25 and, in a test of the hypothesis that RAE = 1, i.e. that the interaction is multiplicative, $P \approx 0.003$. This appears powerful evidence that, on average, the interaction between smoking and asbestos exposure is not multiplicative.

The conclusion must therefore be that non-smokers have a relative risk of lung cancer due to asbestos that is higher, probably about two times higher, than that of smokers.

Aggregation bias

Although expression (1) above allows for several levels of smoking and/or exposure, the great majority of the findings have distinguished only two levels of each. Such aggregation would be of little moment if the interaction were truly multiplicative; with other forms of interaction, important effects can be obscured. One example comes from [p]: when ex-smokers were aggregated with smokers, the RAE did not differ significantly from unity; but that aggregation had concealed the statistically significant trend, reported by Berry *et al.* (1985), that those who had never smoked had the highest relative excess and smokers had the lowest, with ex-smokers intermediate. Trends of this nature are exactly what would be expected when the interaction is not multiplicative; another example is in [e]. However, they cannot be detected from the usual double dichotomy. Corresponding effects may be obscured by aggregation of exposure levels.

The general pattern of less-than-multiplicative interaction has been discerned despite aggregation; it is not unreasonable to believe that, were more detailed (that is dis-aggregated) analyses possible, they would provide further evidence of departure from the multiplicative.

Persistence of belief in the multiplicative hypothesis

The multiplicative hypothesis of interaction was originally 'accepted', in the 1970s, but only as the least of evils. The very few data available fitted a multiplicative hypothesis better than an additive one, but 'better' was only relative: in fact, the fits to the former were quite poor but those to the latter were worse still. Another hypothesis, of greater synergism, was too extreme and had to be discarded; so, with the additive also dismissed, the multiplicative hypothesis appeared the only alternative. Support was claimed on two counts, but one was only of plausibility, and the other was speculative.

In 1985, it was reported that, over the available six studies, non-smokers had a relative risk of lung cancer due to asbestos that was higher than that of smokers, by a factor of 1.8; in one of the studies the factor was 5.3 and of high statistical significance. The general finding was disbelieved, and the specific overlooked. The authors had entered a caveat concerning the accuracy of the figure 1.8, and this was seized on. The findings were treated as having been due 'perhaps entirely' to methodological artefacts, particularly misclassification of smoking habits. Doll and Peto (1985) expressed the belief that the interaction was close to being exactly multiplicative because this was suggested in the largest study with prospectively obtained smoking habits.

Two years later, it was claimed that the multiplicative hypothesis could not be rejected (with $P < 0.05$) from any one study, although this was in a review that included the factor of 5.3, just mentioned. It was also stated that one 'could be satisfied' that the multiplicative hypothesis is the best common representation, apparently on the entirely false assumption that if no single interaction among many departs significantly from a hypothesis, that hypothesis can be 'accepted'.

Reviewers have consistently stressed variation (or contradiction) in the interaction without appreciating that most of it stems from the differences between Groups A and B, while the remainder is very much what was to be expected in the light of the impre-

cision of the individual RAEs. It has been obvious for over a decade that the groups cannot both be 'right', but reviewers have made no attempt to elucidate the difference, let alone appreciate that the many problems with Group B render these results unacceptable.

On the contrary, it was claimed in 1994 that the 'variation' was caused mainly by the those interactions which were less than multiplicative, and which therefore could be disregarded. This disposed of all the evidence inconvenient for believers in the multiplicative hypothesis. Strong evidence of this nature—and with prospectively obtained smoking habits—had been given in 1993, but was ignored both in 1994 and subsequently.

The multiplicative hypothesis is of course simpler—more parsimonious in parameters—than any hypothesis of other degrees of synergism. Hempel (1966) writes 'simplicity is highly prized in science', but adds that a simpler hypothesis is not more acceptable than alternatives unless it accounts for the same phenomena. It may be that the great reluctance to discard the multiplicative hypothesis is largely because of its simplicity. However, convenient as it may be, it does not account for the phenomena of the results from the cohort studies.

The multiplicative hypothesis is, nevertheless, still accepted by many workers, perhaps the majority; see for example Kane (1996) and Henderson *et al.* (1997).

ENVOY

The hypothesis that the interaction is multiplicative has been shown to be untenable: non-smokers have a relative risk of lung cancer due to asbestos exposure that is about twice as high as the relative risk for smokers, an effect that is of high statistical significance. The implications are of considerable importance, both scientifically and socially, but are not within the scope of this paper.

The absolute risks are, of course, substantially less in non-smokers than in smokers.

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