

100 down to 0.005 f/ml years. But the proof of the pudding is in the eating, and nowhere do they subject their calculations and guesses to the test of reality. They neither acknowledge those who have done so, e.g. Liddell (1991) and Camus *et al.* (1998), and have found the earlier estimates, based on the linear dose-response found at higher exposures, to be inapplicable, nor those who have adopted the alternative approach based on intensity rather than simple cumulative exposure (Liddell *et al.*, 1998; Vacek and McDonald, 1990), which provides other corrective information on the lower ranges of the dose-response curve.

The first half of the paper contains many good points and one or two gems, but the second half, sadly, adds nothing to our understanding of the risks of low level asbestos exposure, providing risk estimates that have no sound basis and that do not match up with reality.

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Asbestos and Cancer

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PII: S0003-4878(01)00030-8

Hodgson and Darnton (2000)—referred to below as H&D—have done a great service, if only for presenting mortality rates for cohorts of asbestos workers in a way that facilitates close examination of what has been called 'the fibre gradient' or the 'amphibole hypothesis'.

FIBRE TYPES

The three principal types of asbestos (bearing the same generic name but alike only in being fibrous silicates) are *chrysotile*, which has always accounted for at least 90% of commercial usage, and two amphiboles, *crocidolite*, the more commonly used, and *amosite*, the amphiboles having chemical consti-

tutions quite disparate from that of chrysotile. The (microscopic) respirable forms of the three types also differ greatly not only in shapes and sizes, so affecting penetration, but also in their durability in lung and other tissue. Markedly different health effects were therefore only to be expected.

Largely because of differences in their (macroscopic) physical characteristics, the three types of fibre have had varied commercial uses, but in most industrial practices workers exposed to amphibole asbestos have also been exposed to chrysotile. Such exposures are said to be to *mixtures*, or to mixed

fibres, although there were few processes that involved simultaneous use of more than one type of fibre; chrysotile was often the major component of the mixtures.

THE FIBRE GRADIENT

Nevertheless, it was possible to write two decades ago that 'The findings from [all but one of the epidemiological] studies to date appear to support the hypothesis of a *fibre gradient*, such that crocidolite has much the most severe health effects, and chrysotile the least, with amosite somewhere in between' (Liddell, 1981). The one exception (Dement *et al.*, 1981) was at the chrysotile textile factory in Charleston SC, which H&D call the Carolina cohort; it was soon confirmed that this cohort was completely out of line with all other chrysotile findings (McDonald *et al.*, 1983).

Ten years ago, more than 30 cohort studies had been reported, although most were without adequate information on asbestos exposure. However, Hughes (1991) provided standardised mortality ratios (SMRs) for lung cancer as 1.26 for chrysotile (including the Charleston result), 3.07 for amphiboles (crocidolite and amosite) and 2.18 for mixtures; while McDonald and McDonald (1991) calculated proportional mortality ratios (PMRs) for mesothelioma as 0.24%, 3.97% and 4.21%, respectively. As SMR and PMR for chrysotile were both very much lower than where amphibole had been used, this went a long way towards confirming a gradient, now better termed the 'amphibole hypothesis'. However, there remained an influential body of opinion claiming that all types of asbestos fibre have similar toxicity.

THE AMPHIBOLE HYPOTHESIS

H&D have, first, identified 17 reports on mortality in cohorts of asbestos workers—half too recent for the earlier summaries—in which some estimate is possible of the average cumulative exposure. Secondly, they have introduced two measures of mortality that take cumulative exposure into account, and so permit much more reliable comparisons between cohorts.

For these measures, R_L and R_M , which they call 'exposure-specific risk estimates', they use X to represent average cumulative exposure, estimated in (fibres/ml)×years, or f/ml.yr. The first is 'excess over all lung cancer mortality... expressed as a percentage excess of expected lung cancer mortality per unit of cumulative exposure'. It can be written

$$R_L = 100(\text{Excess})/(E_L \times X) = 100(\text{SMR} - 1)/X,$$

where E_L is the expected number of deaths from lung cancer. The second estimate is of 'mesothelioma mortality... expressed as a percent of expected mortality

from all causes (adjusted to an age of first exposure of 30) per unit of cumulative exposure', and this can be written

$$R_M = 100(\text{No of mesotheliomas})/(E_T \times X) \times A \\ = 100(\text{PMR}/X)/A,$$

where the PMR is based on the expected total number of deaths, E_T , rather than the observed number, and A is the adjustment factor.

According to Hughes (1991), those studies 'which have been able to quantitatively estimate the cumulative asbestos exposure of individual workers and to examine the relationship between the level of lung cancer risk and the amount of exposure... generally reported an approximately linear trend of risk... with increasing exposure' and 'Assuming no elevated risk for zero asbestos exposure, the model may be expressed as $\text{SMR}[(\%)] = 100 + b(\text{ce})$ where b is the slope of the line and ce is cumulative exposure'. Individual exposures not being generally available, H&D used this model, where the (lung cancer) SMR is for the cohort, while b and ce are replaced by R_L and X . Although the assumptions are not fully justified, R_L is more than adequate for most purposes. R_M also relies on an assumption of linearity, which again is suitable for most purposes.

A major advantage is that both R_L and R_M compare observed numbers of deaths with expected numbers, and do so in relation to the same measure of exposure, and thus are commensurate. The pairs of measures for the 21 cohorts are plotted in Figure A,¹ which reveals that the points lie in six clusters according to type of fibre, with remarkably little overlap. The three cohorts exposed to crocidolite, the two to amosite and four to chrysotile occupy quite separate regions of the space. Most of the cohorts exposed to mixtures fall just above the two chrysotile mining groups and well away from the amphibole cohorts, but Albin and Ontario are quite exceptional. The male and female Carolina cohorts lie completely apart from all other clusters, and it might appear that the amphibole hypothesis is well substantiated by this material.²

H&D raise, and rightly dismiss, some of the arguments to the contrary that have been put forward. Smith and Wright (1996) ranked 25 cohorts according to PMR for pleural mesothelioma, and found chrysotile-rich mixtures among the highest ten. However, these authors excluded 18 other cohorts because the PMRs were too low, and so thrust aside the very sub-

¹ On log scales after transformations to allow for negative values of R_L and zero values of R_M .

² Mean values of R_L and R_M for the clusters either are in or can be obtained from Tables 2 and 1 of H&D. However, confidence limits are, as H&D point out, not very useful (a common problem in epidemiology); better indications of variability are obtained from the *range*, i.e. the difference between the highest and lowest of the observed values.

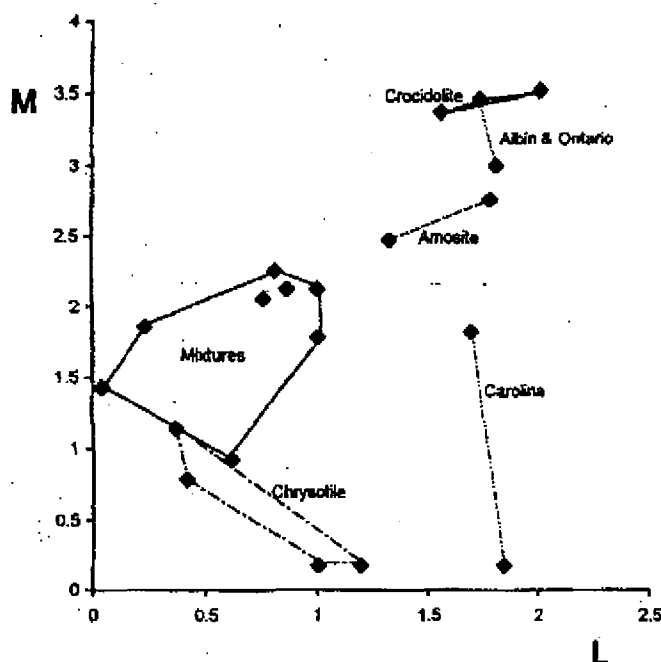


Fig. A. Exposure-specific estimates of risk of lung cancer and of mesothelioma for 21 cohorts. $L = \log(R_L + 0.2) + 1$; $M = \log(R_M + 0.0003) + 3.7$. The $\diamond$ s for cohorts 4 and 130 are coincident.

stantial evidence from all cohorts exposed only to chrysotile. For all 43 cohorts, the fibre gradient is obvious, even without knowledge of average exposures. Smith and Wright (1996), Nicholson and Landrigan (1996) and Stayner *et al.* (1997) all use arguments based on the ratios of PMRs for mesothelioma and for lung cancer, claiming that these do not vary greatly; what this really means is that fibre with high potency for lung cancer tends also to have high potency for mesothelioma, and *vice versa*. Another theme common to these authors is that small proportions of amphibole cannot be responsible for major carcinogenic effects; as H&D point out, this is quite fallacious, failing to take into account the facts that the mesothelioma risks from exposure to amosite were at least an order of magnitude greater than from chrysotile, and the risks from crocidolite five times higher still.³ Finally, the appeal to animal inhalation experiments is futile, because the massive doses of asbestos given to rats cannot be cleared in the animals' lifetime, whereas the clearance from human lungs of chrysotile is much more rapid than that of amosite or crocidolite.

H&D end this section with an axiom of biological science, often denied: if there is conflict between experimental and human evidence, the latter must prevail. It can also be remarked that if there is conflict between theory and experiment, the former must be changed to explain the latter.

Resolution of the difference of belief in the amphi-

bole hypothesis is clearly of great importance, and a full evaluation is in hand.

CATEGORISATION FOR RISK ASSESSMENTS

For their risk assessments, H&D consider lung cancer according to three categories: (i) the two amphiboles together; (ii) chrysotile; and (iii) 'chrysotile in exceptional circumstances', the last based on the results from the Carolina cohort. With regard to mesothelioma, they treat the three types of fibre separately, providing only one set of assessments for chrysotile. All save this last categorisation can be justified by the material on which Fig. A is based. However, the Carolina cohort is as exceptional for mesothelioma as for lung cancer. For men in this cohort, $R_M = 0.013$, whereas, averaged over the four 'other' chrysotile cohorts, $R_M = 0.001$, the one 13.6 times larger than the other. Also, one of the two mesotheliomas at Charleston was peritoneal, whereas there were no peritoneal cases among the 35 mesotheliomas in the 'other' chrysotile cohorts; by contrast, the proportions of peritoneal mesotheliomas were substantial elsewhere: between 15 of 97 (15%) for crocidolite and 282/453 (62%) among US/Canada insulators. This makes it all the more likely that some agent other than chrysotile is responsible for the huge excesses of cancer in the Carolina cohort. What that agent may be, although debated at length, as H&D point out, is still unknown, but it should be recognised as causing much higher risks than posed by chrysotile.

³ These ratios were obtained from the values of R_M in H&D's Table 1.

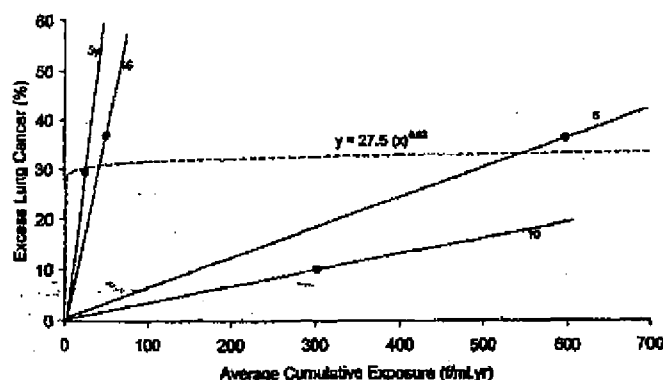


Fig. B. Exposure-response for four chrysotile cohorts: each is a straight line through the origin and the specific mean (•). In the equation of the curve, x = average cumulative f/ml.yr and y = % excess lung cancer.

THRESHOLDS, CONCAVITIES AND CONVEXITIES

For exposures upwards from about 10 f/ml.yr, H&D are content to accept linearity and rely on values of R_L and R_M , 'in round figures', in the categories described above. Questions of thresholds etc do not arise.

Turning to extrapolation to lower exposures, H&D endorse the statement (HEI, 1991) that 'The assumption of dose-linearity for low-dose assessment purposes is... a widely accepted and scientifically reasonable compromise rather than an established scientific principle of carcinogenesis', commenting that it is more a *cautious* default assumption (added emphasis) than anything more soundly based.

The desire for a sounder basis is worthy, but non-linearity is extremely difficult to detect epidemiologically, especially at low levels of exposure. As instance, in the Quebec cohort, there have been no discernible trends in lung cancer risk over at least seven levels of exposures up to 300 mpcf.y⁴ (McDonald *et al.*, 1980, 1993; Liddell *et al.*, 1997); however, when modelling over the whole range of exposures, thus embracing undoubtedly elevated risks, linear fits are very good, and even the best curvilinear fits give little hint of 'concavity' (using H&D's term) at low exposures. However, specially developed methods of analysis have shown that there are exposure levels below which excess lung cancer risks are so low as to be unmeasurable, not only in the same cohort (Liddell *et al.*, 1998) but in four others (Vacek and McDonald, 1990). These results imply some degree of concavity; but whether or not there are true thresholds is immaterial here. (It may also be noted that many toxicologists argue, often quite vehemently, for concavity, but it would, of course, be wrong to rely on experimental evidence, even if it does support theory.)

On the other hand, H&D cite what appears to be

the only relevant observational evidence concerning mesothelioma; see their Figure 8. When the data are transformed back from logs and replotted, they are seen to lie close to a straight line, which may be about as good a fit as the convex relationship in Figure 8. This material can do no more than suggest convexity.

H&D approach the problem differently, carrying out many ingenious analyses (albeit with a tendency to discard results that cause heterogeneity). In particular, they use Poisson regressions the results of which lead them to believe that the exposure-response relations for mesothelioma are not linear. However, so few degrees of freedom are available that it would be difficult to sustain this belief; but even more important, the argument contains a fatal flaw. This can best be exposed in relation to lung cancer in the four chrysotile cohorts other than at Carolina.

Each value of R_L is the sole parameter of an underlying exposure-response relation for varying levels of exposure. This is so even if the detail of the relation is, as here, hidden; and in that situation, no further light can be cast on the relation, which may or may not be in accord with the assumptions of linearity and of zero excess at zero exposure. The assumed line has the equation

$$100\{(O-E)/E\}|_x = R_L(x),$$

where x is cumulative exposure of a group of cohort members, classified by their individual exposures, and $|_x$ means 'given x '. For several cohorts, such lines fan out from the 'origin' and pass through the co-ordinates of R_L , i.e. are determined by the points (0, 0) and (X , $X.R_L$); see Fig. B which relates to the four chrysotile cohorts. When rewritten as

$$\log[100\{(O-E)/E\}|_x] = \log[R_L] + \log[x],$$

the equation defines a series of lines with the same slope, i.e. unity; the lines are separated by amounts proportional to R_L . Fig. C corresponds to H&D's Figure 9(b) for the four chrysotile cohorts; the X s are

⁴ 300 (million particles per cubic foot) $\times$ years, very roughly equivalent to 1000 f/ml.yr.

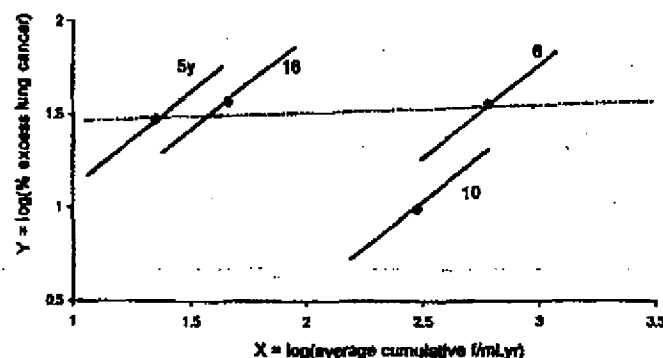


Fig. C. Exposure-response for four chrysotile cohorts: lines $Y = X + \log(R_c)$. The broken line has equation $Y = 1.44 + (0.03)X$.

taken from H&D's Table 2, and the necessarily assumed lines have been introduced between $X/2$ and $2X$.

Had data been available to fit the cohort-specific relationships, the situation would have called for analyses of the forms described by Armitage and Berry (1994) as 'regression in groups'—to determine the slope for each cohort and whether there is a common slope (for the data of Fig. C, a common slope is predicated, so this step is not needed)—followed by 'analysis of covariance'—to see whether the parallel within-cohort regression lines differ in position (answered from the between-cohorts regression, i.e. the line fitted to the four $\diamond$ s of Fig. C). This line has parameters determined essentially by the co-ordinates of the X s; they are given in H&D's Table 7 and define the broken line on Fig. C (and also the curve in Fig. B). This between-cohorts regression demonstrates marked differences between cohorts. This was of course obvious from the widely different slopes of the lines in Fig. B, and it is patently clear that between-cohorts regression has nothing to do with the form of the exposure-response relations, whether within cohorts or common to them. This is true in general—regression *between* cohorts is irrelevant to the question of interest. So, sadly, the present

approach also comes to naught; indeed it is probable that this complex and intriguing problem is insoluble.

PARAMETERS FOR RISK ASSESSMENT

Although forced to abandon this approach for lung cancer in relation to chrysotile, H&D follow it for their other assessments, which of course suffer from the same flaw. All the parameters in H&D's Tables 5, 6 and 7 have been obtained from between-groups regressions and thus, even if they appear reasonable, are irrelevant. As a result, the estimated coefficients in Tables 8 and 10 are seen to be without solid foundation, even ignoring a degree of arbitrariness in the choice of 'best', 'low', and 'high' slopes. In fact, for their 'best slopes', H&D have abandoned linearity, embracing a high degree of concavity for lung cancer, while for mesothelioma the marked convexity for pleural conditions at extremely low exposures is later swamped by the severe concavity for peritoneal mesotheliomas—except for chrysotile. The effects of these assumptions can be judged by comparing the risk estimates they produce with those from linearity with the slopes accepted earlier. The ratios of these two estimates are given in Table A, which shows that, at very low exposures, the 'best slopes' predict risks

Table A. Ratios between risks estimated from 'best slopes' and from linear interpolation

Exposure (f/ml.yr)	Excess lung cancer		Mesothelioma		
	Amphiboles	Chrysotile	Crocidolite	Amosite	Chrysotile
0.005	0.07	0.06	7.08	4.80	17.67
0.01	0.08	0.07	5.94	4.10	14.86
0.1	0.16	0.14	3.34	2.31	8.36
1	0.32	0.28	1.88	1.31	4.70
10	0.64	0.56	1.11	0.81	2.64
50	1.03	0.91	1.03	0.93	1.77
100	1.27	1.11	1.29	1.36	1.49
300	1.77	1.55	2.79	3.50	1.13

of excess lung cancer much lower than given by linear interpolation, but the reverse for mesothelioma.

Although the concavity assumed for lung cancer may well be realistic, it has not been justified and it seems better to rely upon the linear estimates, which are higher for exposures below say 50 f/ml.yr. These estimates are from slopes of 4.8 and 0.5 for amphiboles and chrysotile, compared with R_{LS} of 5.0 and 0.1 (and slope 2 for 'chrysotile in exceptional circumstances'). For higher exposures, linearity would seem appropriate, with slopes 5 and 0.5, the latter cautious, even over-cautious.

Convexity of the risk of mesothelioma due to the amphiboles may also be realistic for exposures up to about 50 f/ml.yr. Although it too has not been justified, it leads to estimates, the so-called 'best' estimates, that are more cautious than given by linearity, and should perhaps be accepted from the viewpoint of regulation. At higher exposures, however, the convoluted shapes appear untenable; the best compromise would seem to be linearity, for which slopes of 0.5 and 0.1 are given by the values of R_{LM} and 'confirmed' from the 'high slope' estimates. The risk of peritoneal mesothelioma due to chrysotile exposure is minuscule, and the 'best' curve for pleural tumours is convex and leads to the particularly large ratios in the last column of Table A; even if convexity is accepted on the grounds of 'caution', the risks for very low exposures estimated from the 'best' curve appear considerably too high.

It would seem desirable to amend Table 11 on the lines indicated above. But, with or without amendments, the amphibole hypothesis is supported. Thus, excess lung cancer risks are at least 10 times higher for amphibole exposure than for chrysotile, and the risks from 'chrysotile in exceptional circumstances' lie midway. Also, mesothelioma risks due to crocidolite and to amosite are in the ratio of roughly 5:1, and the risk from chrysotile is at least an order of magnitude less again.

SMOKING

For all but one of the cohorts listed in H&D's Table 2, lung cancer mortality reflects the smoking habits of the cohort many decades before publication, when smoking was a common habit, particularly among blue collar workers who formed the great majority of these cohorts. It is well-known that the risk of lung cancer increases steeply with the number of cigarettes smoked, and this factor must be taken into account when assessing risks due to asbestos exposure. A single estimate of risk based on the 'average worker' cannot be adequate: the risk will differ not only for non-smokers and lifetime smokers, but also according to the amount smoked, and for ex-smokers. Thus, the inference from note (2) to Table 11 that the risks for lifetime smokers will be about

12 times those for non-smokers is a major oversimplification.

Further, the risks depend on the interaction between asbestos and smoking, which is not multiplicative, but substantially less (Liddell, 2001). Doubling of the risk for non-smokers is reasonable, but the risks for smokers need amendment—greater for light smokers, less for heavy smokers—beyond that required in the preceding paragraph.

CONCLUSION

John Hodgson and Andrew Darnton are to be congratulated on their magnificent effort. They have presented important data for lung cancer and mesothelioma, and in commensurate terms. From these revealing data, they were enabled to acknowledge the amphibole hypothesis in relation to both lung cancer and mesothelioma, and to demolish the false contrary arguments. Also, they have grasped the nettle of the Carolina results (at least for lung cancer), recognising how inexplicably exceptional they are. The analyses and arguments presented are challenging; but they lead to estimates of risk of asbestos-related cancer at very low exposures that require some amendment.

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PII: S0003-4878(01)00031-X

The critical requirement for asbestos is to be able to identify occupational and environmental exposure limits, which, if adequately enforced, would reduce excess deaths to "acceptable" levels. Such limits would also permit objective prioritisation of remediation work with asbestos-containing materials. The excellent paper by Hodgson and Darnton (2000) partly answers the above needs. However, from an occupational hygienist's viewpoint there are some aspects of the paper which require comment or further information.

The risk estimates are based on observed disease in the study cohorts. However, cohort mortality in the majority of the cohorts is low, particularly for those exposed to amphiboles, e.g. 13% in SA crocidolite mines and 21% in SA amosite mines (Sluis-Cremer *et al.*, 1992), 20% at Wittenoom (de Klerk *et al.*, 1994) and 26% in Ontario asbestos-cement workers (Finkelstein, 1984). Given that the median ages for deaths from lung cancer and mesothelioma are both 70-74 and 75th percentile ages at death are both 75-79, from RGS (1996-2000), it is evident that until almost all cohort members have either died or reached about age 80 only a small proportion of both lung cancers and mesotheliomas will be observed. All else being equal, cohorts with low mortality are relatively young and have not had the chance to develop the eventual numbers of lung cancers or mesotheliomas. This can be seen, for example, from Selikoff and Seidman (1973) where deaths due to mesothelioma, expressed as a proportion of the cohort, increased with mortality from 0.32% at 12% mortality, to 1.1% at 38% mortality to 5.1% at 68% mortality. That is, the proportion of the cohort dying from mesothelioma increased about 16-fold as mortality increased from 12% to 68%. Risk estimates based on data from cohorts with low mortality are therefore likely to underestimate the eventual risk, the degree of underestimation increasing as cohort mortality decreases. Standards based on such underestimates are likely to put those intended to be protected at unnecessary and avoidable risk.

To ensure that unduly low Standards are not adopted, estimates should be made for each cohort of

the eventual consequences of exposure, e.g. see de Klerk *et al.* (1989) and Berry (1991), and Standards should be based on such final consequence estimates.

It is appreciated that the risk estimates in the paper were based on first exposure at age 30 to aid analysis. However, to be useful in the context of setting Standards it is necessary for occupational exposures that the estimates cover the age range 16 to 60 and for environmental exposures cover the age range 0 upwards. From the information provided in the paper it is not unambiguously possible to derive such estimates.

The inclusion of data for mining severely skews the risk estimates, particularly for chrysotile where the mining data reduce the lung cancer risk estimate by about a factor of 37. Given that asbestos mining is of no relevance outside asbestos producing areas, the inclusion of mining data for chrysotile must be questioned.

Given the limited data for crocidolite and amosite and the much higher potency of these forms of asbestos for mesothelioma and lung cancer, it seems unsafe to base any assumption on the nature of the dose-response relationships for these types on a summation of their data with those for chrysotile, particularly for lung cancer where it is assumed that risk falls faster than exposure levels.

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