

Asbestos fiber dimensions and lung cancer mortality among workers exposed to chrysotile

Dana Loomis¹, John Dement², David Richardson³, Susanne Wolf³

¹School of Community Health Sciences, University of Nevada, Reno NV, USA

²Duke University Medical Center, Durham NC, USA

³School of Public Health, University of North Carolina, Chapel Hill NC, USA

Address for correspondence: Professor Dana Loomis, School of Community Health Sciences/MS-274, University of Nevada, Reno NV 89557, USA

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ABSTRACT

Objectives: To estimate exposures to asbestos fibers of specific sizes among asbestos textile manufacturing workers exposed to essentially pure chrysotile using data from transmission electron microscopy (TEM) and to evaluate the extent to which the risk of lung cancer varies with fiber length and diameter.

Methods: 3803 workers employed for at least 1 day between 1 January 1950 and 31 December 1973 in any of 3 plants in North Carolina, USA that produced asbestos textile products and followed for vital status through 31 December 2003 were included. Historical exposures to asbestos fibers were estimated from work histories and 3578 industrial hygiene measurements taken 1935-1986. Exposure-response relations for lung cancer were examined within the cohort using Poisson regression.

Results: Indicators of fiber length and diameter obtained by TEM were positively and significantly associated with increasing risk of lung cancer. Exposures to longer and thinner fibers tended to be most strongly associated with lung cancer, and models for these fibers fit the data best. Simultaneously modeling indicators of cumulative mean fiber length and diameter yielded a positive coefficient for fiber length and a negative one for fiber diameter.

Conclusions: The results support the hypothesis that the risk of lung cancer among workers exposed to chrysotile asbestos increases with exposure to longer fibers. More research is needed to improve the characterization of exposures by fiber size and number and to analyze the associated risks in a variety of industries and populations.

The occurrence of cancer among workers exposed to asbestos has been studied extensively and while the carcinogenicity of asbestos is established there is significant variation in risk both among and within the industries using asbestos [1, 2]. It has been suggested that this might be explained by variations in the distribution of asbestos fiber sizes and shapes in addition to differences in the types of asbestos [2-5]. Fiber size distributions have been shown to vary between industries and processes [3, 6], and data from experimental studies generally suggest that long, thin fibers may have greater carcinogenic potency than shorter, wider fibers [7-9].

The hypothesis that the risk of cancer from exposure to asbestos may depend on fiber size is of scientific and regulatory interest, but relevant epidemiologic data are limited because size distributions of all airborne fibers cannot be determined by the approaches usually used to measure asbestos concentrations in air. Since the 1960s, most exposure measurements have been made using phase-contrast light microscopy (PCM) to count fibers retained on filters according to standard protocols that yield fiber-number concentrations. While PCM methods remain the standard procedure for regulatory compliance, the counts exclude significant numbers of fibers that may be biologically relevant. The standard protocol includes only fibers $>5 \mu\text{m}$ long with length:width aspect ratios ≥ 3 and fibers less than about $0.25 \mu\text{m}$ in diameter are usually omitted because they are too small to resolve with most light microscopes. Fibers shorter than $5 \mu\text{m}$ account for the majority of airborne fibers, in several industries [3, 5, 10].

Use of more recently developed methods using electron microscopy allows all fibers to be counted and classified, and may offer an opportunity to significantly improve the quantification of asbestos exposures and refine risk estimates. The objectives of this study were to use transmission electron microscopy (TEM) to estimate exposures to asbestos fibers of specific sizes among a cohort of asbestos textile manufacturing workers, and to evaluate the extent to which the risk of lung cancer varies with fiber length and diameter.

METHODS

Study Sites and Population

The facilities and workers included in the study were described in detail in an earlier paper [10]. Briefly, the study includes 2419 men and 1384 women (total N=3803) employed in any of 3 asbestos textile plants in North Carolina, USA, for at least one day between 1 January 1950 and 31 December 1973. All 3 plants engaged in the full process of textile production, which involved conversion of raw asbestos and cotton fibers into yarn and woven materials. Two of the plants were producing asbestos textiles in the 1920s and the third began in the 1940s; one plant closed in 1970, while the others continued to produce asbestos products as late as the 1990s. Records indicate that only chrysotile asbestos was used with the exception of a small insulation operation in one plant, where limited amounts of amosite were carded, twisted and woven between 1963 and 1976.

The study population was enumerated from several sources [10] and their vital status was ascertained through 31 December 2003. Causes of death, including underlying cause, immediate causes and other significant conditions were coded to the International Classification of Diseases (ICD) in effect at the time of the death. Procedures involving human subjects were approved by the Institutional Review Boards of the University of North Carolina, Chapel Hill and the University of Nevada, Reno.

For the analyses reported here, workers who did not have a complete occupational history specifying at least the department for all jobs and those who had ever been employed in non-production areas were excluded because their exposures could not be estimated. The population included in this study is thus identical to the one for which exposure-response

findings were reported by Loomis et al. [10] and includes 124,029 person-years of follow-up, 1681 total deaths and 180 deaths from lung cancer.

Exposure Assessment

The assessment of exposure for this study is described briefly here and in more detail in previous publications [5, 10, 11]. The first phase of exposure assessment focused on estimating asbestos fiber concentrations according to the standard PCM method, which was used in the study plants from 1964. 3420 historical industrial hygiene measurements covering the period 1935 to 1986 were available for this purpose. Measurements taken before 1964 used the impinger method, and these were converted to PCM units as described by Dement et al. [11]. PCM-equivalent fiber concentrations specific to plant, department, job, and time period were then estimated by fitting multivariable linear mixed models to the data. The fitted values obtained from the model were used to construct a job-exposure matrix of estimated PCM fiber concentrations by plant, department, job and year.

In the second phase of exposure assessment, fiber concentrations were estimated according to fiber length and diameter. Transmission electron microscopy (TEM) was used to estimate the distribution of fibers for each combination of plant and department in categories defined by diameter (4 categories) and length (6 categories). A stratified random sample of 77 historical dust samples captured on membrane filters was selected from among 333 samples available from industrial hygiene studies the US Public Health Service conducted in the study plants during 1964-1971 and now archived at the National Institute for Occupational Safety and Health. The TEM fiber-counting protocol was based on the ISO direct-transfer method [12] and data reduction and derivation of size-specific exposure estimates followed the procedure described by Dement, et al. [5, 11]. A total of 22,776 fibers or fiber bundles were counted and sized.

The bivariate fiber diameter/length distributions from TEM were then used to estimate size-specific fiber exposures using a method proposed by Quinn et al. [13], in which standard fiber concentration measures determined by PCM are adjusted to size-specific fiber concentrations using proportions from bivariate fiber size distributions. Adjustment factors were developed for each length-diameter category and applied to the matrix of plant-, department-, job- and time-specific PCM fiber concentrations to produce fiber size-specific estimates of exposure [11]. Biologically-based indices of fiber size proposed by Lippmann [8] and Berman et al. [14] were also computed.

Estimated exposures to fibers of different dimensions were linked to workers' occupational histories for assignment of individual cumulative exposure. Work histories and exposure estimates were coded using the same categories. Cumulative exposures to each class of fibers were estimated in fiber-years/ml (f-y/ml).

Because textile production generates fibers with a wide range of length and diameter, individual workers were exposed to fibers of multiple sizes simultaneously and throughout their careers. Consequently, indicators of exposure based on categories of fiber length and diameter tend to be highly correlated. To reduce collinearity and allow the effects of fiber length and diameter to be modeled simultaneously, we developed indicators to represent the mean length and diameter of the fibers to which workers were exposed. Cumulative mean fiber length was estimated by the quantity $\sum \bar{L}_i c_i d_i / \sum c_i$, where \bar{L}_i is the mean length of fibers in length-diameter category i , and c_i and d_i are the concentration of fibers and the duration of employment in category i , respectively. Cumulative mean fiber diameter was estimated similarly by substituting the mean diameter of fibers in length-diameter category i for \bar{L}_i . Both indicators have units of $\mu\text{m-years}$ ($\mu\text{m-y}$).

Data Analysis

Lung cancer mortality rates were modeled using Poisson regression following the approach employed in previous internal analyses of this cohort [10]. The association of lung cancer with indicators of fiber exposure was estimated as $e^{\beta X}$, where β is a regression coefficient for exposure X , and 95% confidence intervals (CI) were estimated from the standard error of β using a normal approximation [15]. The overall fit of the models was evaluated by the Akaike Information Criterion (AIC), which uses a penalty for the number of terms to allow the fit of non-nested models to be compared directly [16]. The contribution of the exposure term was evaluated by likelihood ratio (LR) X^2 test. The ungrouped form of Poisson regression was used to allow predictors to be entered in continuous or categorical form in the same model [17]. Deaths with any mention of lung cancer on the death certificate were included in the analysis.

For consistency with previous analyses, the final model included age entered with categories <60, 60-69, 70-79 and 80+ years, sex, race with categories of white and other or unknown, calendar time with categories for each of the decades 1950-2000, and birth cohort with categories of <1920, 1920-1939, and 1940 or later. All exposure indicators were lagged by 10 years to account for latency. Although lags longer than 10 years are also biologically plausible, previous analyses of this cohort showed that the lag interval had little effect on the regression coefficients or on model fit [10]. Indicators of fiber exposure were entered as continuous variables using both linear terms and penalized spline functions, which allow exposure response relations to take smooth, nonlinear forms [18]. Models in which exposure was entered as a spline function suggested a linear response and did not result in improved fit, so only results for standard linear terms are reported here. Regression analyses were carried out using R version 2.7.2 for Mac OS X [19].

Comparisons of models for different fiber-size indicators were based on model goodness of fit

and the LR for the exposure term, as well as on the magnitude and precision of the regression coefficients. Although rate ratios or regression coefficients are normally of primary interest, in this case direct comparison of these measures is complicated because the number of fibers varies among categories while the number of deaths is fixed, so coefficients or (rate ratios) for categories with fewer fibers will be larger given equal cancer rates. To facilitate comparisons among fiber-size indices with different distributions, we scaled the regression coefficients by the interquartile range (IQR) for each indicator.

RESULTS

Fiber Exposures

As expected, total cumulative exposure to fibers among the 3803 workers included in the cohort was far greater when estimated by TEM (mean 989.4 f-y/ml lagged 10 years) compared to the estimate obtained by PCM methods (mean 59.2 f-y/ml lagged 10 years). When cumulative exposure was estimated by fiber-size category, exposures were highest for the smallest fibers <0.25 μm long and $\leq 1.5 \mu\text{m}$ long and tended to decrease with both fiber length and fiber width. Detailed descriptive data on cumulative exposure are given in supplementary table S1.

Lung cancer risk and TEM fibers

Cumulative exposure to all fibers counted by TEM was significantly associated with lung cancer risk (table 1). Models for TEM-based indicators did not fit as well as a model using exposure estimated by PCM, however, and the LR was larger for PCM than for TEM-based indicators (LR 9.6, $p=0.002$ for PCM vs. maximum of LR 8.5, $p=0.004$ for TEM). Models for TEM fibers > 5 μm long, which correspond most closely to PCM estimates, and for long thin fibers $\geq 10 \mu\text{m}$ long and <0.25 μm in diameter fit the data better than models for other TEM exposure indicators and the exposure terms were more highly significant ($p=0.004$). The strength of the association with lung cancer was similar for all TEM and PCM exposure indicators, with risk increasing about 3%

for an increase in exposure equivalent to one interquartile range.

Lung cancer risk by fiber size category

Cumulative exposure to fibers in every length and diameter category was associated with lung cancer risk when each dimension was considered separately (table 2). Goodness of fit and strength of association with lung cancer tended to increase in models for fibers $>10\ \mu\text{m}$ in length, but similar results were obtained for very short fibers $\leq 1.5\ \mu\text{m}$ long and for fibers $>3\ \mu\text{m}$ in diameter. Both the best model fit and the strongest associations with lung cancer were achieved for cumulative exposure to fibers 20–40 μm in length (table 2).

When fiber length and diameter were considered in combination, exposures to several categories of shorter, larger-diameter fibers were not significantly associated with lung cancer, while stronger, statistically-significant associations were observed for longer and thinner fibers, particularly those $>20\ \mu\text{m}$ long and 0.25– $<1.0\ \mu\text{m}$ in diameter (table 2). Models for fibers $>20\ \mu\text{m}$ long fit the data best, but in contrast to the general pattern favoring thinner fibers, the best fit for any single fiber length-diameter category was obtained for fibers 20–40 μm long and $>3\ \mu\text{m}$ in diameter. The model for the smallest fibers $\leq 1.5\ \mu\text{m}$ long and $<0.25\ \mu\text{m}$ in diameter was also an exception to the overall pattern, with both better fit and a stronger association with lung cancer compared to adjacent categories (table 2). Models that included terms for multiple length-diameter categories simultaneously failed to converge, probably because of collinearity.

Alternative indicators of fiber exposure

The biologically-based exposure indicators we examined were significantly associated with increasing lung cancer risk (table 3). The best fit was obtained with an index based on Lippmann's suggestion that fibers $>10\ \mu\text{m}$ long and 0.3– $1.0\ \mu\text{m}$ thick should be most relevant to lung cancer risk [8]. The change in risk per IQR was modestly greater, however, for the index

proposed by Berman which assigns empirical weights for relative potency to fibers in the categories $<0.3 \mu\text{m}$ in diameter and $5\text{-}40 \mu\text{m}$ long, $<0.3 \mu\text{m}$ in diameter and $>40 \mu\text{m}$ long and $>3 \mu\text{m}$ in diameter and $>40 \mu\text{m}$ long [14]. We also considered exposure to long, thin fibers $<0.25 \mu\text{m}$ in diameter and $\geq 10 \mu\text{m}$ long, which are similar to the size range hypothesized by Stanton to be most relevant for carcinogenesis [7]. This index of exposure was also associated with lung cancer, but less strongly than others (table 3).

The indicators of cumulative mean fiber length and diameter we developed for this study were positively and significantly associated with lung cancer risk; the model for mean fiber length provided the best fit to the data (table 3). When terms for mean fiber length and diameter were entered simultaneously, the coefficient for length remained positive, while the one for diameter became negative, consistent with increasing risk associated with longer, thinner fibers (table 3). A term for the interaction of fiber length and diameter was not statistically significant, but the coefficient was negative, consistent with the effect of greater fiber length diminishing with increasing fiber diameter (data not shown). Interactions of total TEM fibers with fiber length or fiber diameter were also non-significant (data not shown).

DISCUSSION

We found that indicators of asbestos fiber length and diameter obtained by analyzing historical dust samples via transmission electron microscopy were positively and significantly associated with increasing risk of lung cancer in a cohort of asbestos textile workers exposed to essentially pure chrysotile. The strength of the association varied modestly among indicators of cumulative exposure to fibers of varying length and diameter, but in general models for exposure to longer fibers fit the data best and indicated the strongest associations with lung cancer. Findings for fiber diameter were less consistent, but simultaneously modeling indicators of cumulative mean fiber length and diameter yielded a positive coefficient for fiber length and a negative one for

fiber diameter, as would be expected if risk increased with greater fiber length and smaller fiber diameter.

Only one other study has directly examined the effect of asbestos fiber dimensions on lung cancer risk in humans. That study was based on a cohort that was employed in an asbestos textile plant in South Carolina, USA, which was located in the same region as the plants we studied here, operated during the same era with similar production processes, and also used chrysotile [10, 20]. Fiber exposures were assessed using the same methods and TEM protocols we used, and the fiber-size distributions were similar [5, 11]. The major findings from analysis of the relationship of lung cancer fiber size in the South Carolina cohort reported by Stayner et al. [21] were similar to those we present here. All of the TEM-based indicators of fiber length and diameter considered in that study were associated with lung cancer, with the strongest associations observed for long fibers (length >10 μm) and very thin fibers (diameter <0.25 μm), most notably for those with diameter <0.25 μm and length 20-40 μm [21]. In contrast to our findings, however, TEM-based exposure indicators for the South Carolina cohort were more strongly associated with lung cancer than estimates based on PCM measurements [21].

All other epidemiologic studies to date have used exposure estimates based on standard PCM fiber-counting methods. Berman and Crump [22] conducted a meta-analysis of 20 such studies of workers exposed to asbestos in diverse industries to examine the effects of asbestos fiber type and size on the risk of cancer. The authors generated surrogate estimates of the proportions of fibers in several length and diameter classes of for 19 cohorts by applying TEM fiber-size distributions from external data, and directly estimated fiber-size distributions for the South Carolina asbestos textile cohort using published TEM data for that cohort. Their results suggest that lung cancer risk is associated most strongly with exposure to fibers longer than 10

μm long, but no notable variation in risk with fiber diameter was reported and exposure indicators based on fiber-size estimates fit the data only marginally better than estimates of PCM-equivalent fibers [22]. The authors concluded that their analysis failed to fully explain the differences in cancer risk among asbestos-using industries. Nevertheless, their finding of stronger associations with longer fibers is consistent with our findings for North Carolina asbestos textile workers and with those of Stayner et al. [21] for South Carolina workers, as well as with expectations from toxicological data.

Our major findings are consistent with several experimentally- and theoretically-based expectations about the relative carcinogenicity of fibers according to their length and diameter. Lippmann [8] concluded from a review of findings of experiments with animals exposed to asbestos by inhalation that long fibers ($>10 \mu\text{m}$ long) are likely to be most carcinogenic to the lung. We found that these long fibers were consistently associated with lung cancer in North Carolina asbestos textile workers. Lippmann also suggested that, while all fibers $>0.15 \mu\text{m}$ in diameter may be relevant to tumor induction, those $0.3\text{-}0.8 \mu\text{m}$ in diameter are most likely to be retained in the lung and therefore associated with higher risk. We could not evaluate fibers in these specific diameter ranges, but we found that long fibers in the most similar diameter class ($0.25\text{-}1.0 \mu\text{m}$) were more strongly associated with lung cancer risk than thinner or thicker fibers of the same length. Berman et al. [14] concluded from a re-analysis of previous rodent inhalation experiments that fibers $>5 \mu\text{m}$ long and $<0.3 \mu\text{m}$ thick appeared to predict lung tumor risk most strongly, with possible contributions from both very long fibers $>40 \mu\text{m}$ and very thick fiber bundles and structures $>5 \mu\text{m}$ in diameter, as well. The authors suggested that thick structures observed under TEM might decompose into long, thin fibers in the lung. While we found that exposures to fibers $<0.25 \mu\text{m}$ in diameter (the category nearest Berman's proposed $0.3 \mu\text{m}$ cut-point) and $>5 \mu\text{m}$ long were associated with lung cancer risk, associations were weaker for fibers $5\text{-}10 \mu\text{m}$ long. We did, however, find relatively strong associations for thin

fibers >40 μm long, and for thick fibers >10 μm long, consistent with Berman's proposal.

Other potential indices for biologically-active fibers have been reviewed by Quinn et al. [13] and Dement et al. [5]. We did not conduct analyses with these indices because of differences in the length and diameter cut-points and aspect ratios used in our TEM protocol. The Hypothetically Active Fiber (HAF) index developed by Quinn [23] also requires data on fiber persistence in the lung. Perhaps more importantly, the hypotheses advanced by Stanton [7] and by Pott [9] about the etiologic importance of specific fiber-size ranges were based on studies of pleural toxicity in animals exposed to fibers by implantation or injection, but the fiber size ranges that are relevant to inhaled fibers and lung cancer are likely to be different [8]. It is worth noting, nevertheless, that the categories of fibers <0.25 μm in diameter and >10 μm long and fibers >5 μm long are similar to the range proposed by Stanton and the size component of the HAF index, respectively, and were both associated with lung cancer risk.

The role of the smallest fibers less than 1.5 μm long and 0.25 μm in diameter requires further investigation. It has been hypothesized on toxicological grounds that such short, thin fibers may not have a role in the genesis of lung cancer [7, 8, 14, 24]. We found that short, thin fibers were the majority of those counted by TEM, and exposure to them was associated with lung cancer. However, we cannot yet determine whether the association with lung cancer is a spurious effect due to correlations among fiber-size categories or evidence that small fibers do play a role in carcinogenesis.

The strengths of the study include the large size of the cohort, the long follow-up period, the high proportion of workers who were successfully traced and the availability of extensive historical information on exposures. The epidemiologic data have several limitations, which have been discussed previously [10]. These include: inadequate information on smoking, the

small number of deaths from mesothelioma (n=8), which precluded exposure-response analysis for that disease, occupational histories specifying only the plant and department, and not the job title, for about a quarter of the cohort, and the effects of a medical surveillance program, which terminated exposures of at-risk workers, possibly attenuating the association of lung cancer with cumulative asbestos exposure.

The current analysis of fiber-dimension data obtained by TEM has further limitations. While archived dust samples were analyzed for every combination of plant and department and a reasonably large number of structures were counted for each sample, these samples were available only for the years 1964-1971. Production processes and equipment did not change markedly during the years of the study, so it is reasonable to assume that fiber-size distributions were stable throughout the period, but we have no data to test this assumption. In addition, we did not have sufficient resources to count large numbers of samples for each plant and department or to estimate exposures for specific jobs within departments. It is likely that small numbers and lack of finer detail introduced random measurement error, which can reduce the power to detect associations between disease outcomes and exposures measured on a quantitative scale [25]. Additional uncertainty, which was not accounted for in the epidemiologic analysis, arises from variability in the proportion of fibers in each length-diameter category and in the adjustment factors used to estimate exposure to specific fiber-size classes from concentrations obtained by PCM. Finally, workers were exposed to fibers of a wide range of lengths and diameters, but strong correlations among fiber-size metrics prevented modeling multiple fiber indicators simultaneously to search for evidence that specific fiber-size ranges have independent effects.

In summary, the results of this study support the hypothesis that the risk of lung cancer among workers exposed to chrysotile asbestos increases with exposure to longer fibers and provide

some evidence that those effects are most pronounced for long fibers between 0.25 and 1.0 μm in diameter. There is still uncertainty about the relative carcinogenicity of specific fiber-size fractions, however. Assessments of asbestos exposure should account for fiber size, as well as number, and more epidemiologic research is needed to examine the variation of cancer risk with fiber size in a variety of industries and populations.

WHAT THIS PAPER ADDS

- Animal evidence suggests that the carcinogenicity of asbestos fibers increases with their length, but only limited human data are available to test this hypothesis
- This study found that exposure to longer fibers was associated with higher rates of lung cancer among workers historically exposed to chrysotile asbestos.
- Assessments of exposure to asbestos should account for fiber sizes, as well as numbers, and the associated cancer risks should be examined in future epidemiologic studies.

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LICENCE

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Table 1. Model goodness of fit and association of lung cancer risk with indicators of cumulative exposure to asbestos fibers, estimated by Poisson regression with adjustment for age, sex, race, calendar time and birth cohort.

Exposure indicator (f-y/ml)	β	SE(β)	Δ^*	LR*	(p)	AIC*
PCM fibers	0.00101	0.00028	0.0333	9.6	(0.002)	2343.1
Total TEM fibers	0.00005	0.00002	0.0310	7.6	(0.006)	2345.1
TEM fibers $\geq 5 \mu\text{m}$	0.00039	0.00012	0.0312	8.5	(0.004)	2344.2
TEM fibers $< 5 \mu\text{m}$	0.00006	0.00002	0.0297	7.4	(0.010)	2345.3

* β and SE, regression coefficient and associated standard error; Δ change in lung cancer risk for increment in exposure equal to 1 interquartile range; LR, likelihood ratio test statistic (equivalent to X^2 with 1 degree of freedom) and associated p-value; AIC, Akaike Information Criterion (smaller values indicate better fit).

Table 2. Model goodness of fit and association of lung cancer risk with cumulative exposure to asbestos fibers by size category, estimated by Poisson regression with adjustment for age, sex, race, calendar time and birth cohort.

Length (μm)	Diameter (μm)				
	<0.25	0.25-1.0	1.0-3.0	>3.0	All
≤ 1.5					
AIC*	2343.9	2350.2	-	-	2344.1
Δ^*	0.0328	0.0149			0.0323
LR*	8.8	2.5			8.6
1.5-5					
AIC	2347.5	2349.1	2349.7	-	2347.8
Δ	0.0229	0.0127	0.0133		0.0156
LR	5.2	3.6	3.0		5.0
5-10					
AIC	2346.4	2345.3	2347.4	2350.2	2345.7
Δ	0.0210	0.0288	0.0157	0.0007	0.0250
LR	6.3	7.4	5.3	2.5	7.0
10-20					
AIC	2345.4	2343.9	2346.3	2349.3	2344.3
Δ	0.0290	0.0327	0.0208	0.0082	0.0327
LR	7.3	8.8	6.4	3.4	8.4
20-40					
AIC	2342.6	2340.7	2344.1	2338.2	2340.0
Δ	0.0337	0.0326	0.0203	0.0265	0.0371
LR	10.1	12.1	8.6	14.5	12.7
>40					
AIC	2344.1	2340.9	2346.9	2345.1	2341.8
Δ	0.0367	0.0367	0.0225	0.0144	0.0367
LR	8.6	11.8	5.9	7.6	10.9
All					
AIC	2344.9	2347.5	2346.4	2342.6	2345.1
Δ	0.0310	0.0202	0.0242	0.0256	0.0310
LR	7.8	5.2	6.3	10.1	7.6

*AIC, Akaike Information Criterion (smaller values indicate better fit); Δ change in lung cancer risk for increment in exposure equal to 1 interquartile range; LR, likelihood ratio (equivalent to X^2 with 1 degree of freedom).

Table 3. Model goodness of fit and association of lung cancer risk with alternative indicators of cumulative exposure to asbestos fibers, estimated by Poisson regression with adjustment for age, sex, race, calendar time and birth cohort.

Exposure Indicator	β^*	SE(β)	Δ^*	LR (df)*	p	AIC*
Biologically-based indices[†]						
Modified Lippmann Index (0.25≤D≤1 μm and L≥10 μm) [‡]	0.00283	0.00073	0.0279	11.1 (1)	0.001	2341.56
Berman Index	0.01880	0.00551	0.0326	8.8 (1)	0.003	2343.56
TEM fibers D <0.25 μm and L ≥10 μm	0.00171	0.00054	0.0321	8.3 (1)	0.004	2344.56
Ad hoc indices (μm-y)						
Mean fiber length	0.00869	0.00257	0.0757	9.7 (1)	0.002	2343.56
Mean fiber diameter	0.15098	0.04558	0.0726	9.2 (1)	0.002	2343.56
Mean fiber length +	0.01919	0.02400	0.1329	9.8 (2)	0.007	2344.56
Mean fiber diameter	-0.18835	0.42987	-0.0735			

* β and SE, regression coefficient and associated standard error; Δ change in lung cancer risk for increment in exposure equal to 1 interquartile range; LR (df), likelihood ratio test statistic (equivalent to X^2) with df degree of freedom and associated p-value; AIC, Akaike Information Criterion (smaller values indicate better fit).

[†]Units are f-y/ml. All of the indices also include the criterion that the aspect ratio (length:diameter) is at least 3:1.

[‡]Lippman proposed minimum diameters of 0.15 μm or 0.3 μm, but we used a cutoff of ≥ 0.25 μm since that was the closest category in our TEM protocol.

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