Cancer Causes Control (2013) 24:1–12
DOI 10.1007/s10552-012-0107-7

REVIEW ARTICLE

Lung cancer risk at low cumulative asbestos exposure: meta-regression of the exposure–response relationship

Sjoukje van der Bij · Hendrik Koffijberg · Virissa Lenters · Lützen Portengen · Karel G. M. Moons · Dick Heederik · Roel C. H. Vermeulen

Received: 8 February 2012 / Accepted: 14 November 2012 / Published online: 28 November 2012

Abstract
Purpose Existing estimated lung cancer risks per unit of asbestos exposure are mainly based on, and applicable to, high exposure levels. To assess the risk at low cumulative asbestos exposure, we provide new evidence by fitting flexible meta-regression models, a notably new and more robust method.
Methods Studies were selected if lung cancer risk per cumulative asbestos exposure in at least two exposure categories was reported. From these studies ($n = 19$), we extracted 104 risk estimates over a cumulative exposure range of 0.11–4,710 f-y/ml. We fitted linear and natural spline meta-regression models to these risk estimates. A natural spline allows risks to vary nonlinearly with exposure, such that estimates at low exposure are less affected by estimates in the upper exposure categories. Associated relative risks (RRs) were calculated for several low cumulative asbestos exposures.
Results A natural spline model fitted our data best. With this model, the relative lung cancer risk for cumulative exposure levels of 4 and 40 f-y/ml was estimated between 1.013 and 1.027, and 1.13 and 1.30, respectively. After stratification by fiber type, a non-significant three- to fourfold difference in RRs between chrysotile and amphibole fibers was found for exposures below 40 f-y/ml. Fiber-type-specific risk estimates were strongly influenced by a few studies.
Conclusions The natural spline regression model indicates that at lower asbestos exposure levels, the increase in RR of lung cancer due to asbestos exposure may be larger than expected from previous meta-analyses. Observed potency differences between different fiber types are lower than the generally held consensus. Low-exposed industrial or population-based cohorts with quantitative estimates of asbestos exposure a required to substantiate the risk estimates at low exposure levels from our new, flexible meta-regression.

Keywords Amphiboles · Asbestos · Chrysotile · Exposure · Lung cancer · Meta-analysis

Electronic supplementary material The online version of this article (doi:10.1007/s10552-012-0107-7) contains supplementary material, which is available to authorized users.

S. van der Bij · H. Koffijberg · K. G. M. Moons · D. Heederik · R. C. H. Vermeulen
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands

S. van der Bij (✉)
Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, P.O.Box 85500, 3508 GA Utrecht, The Netherlands
e-mail: s.vanderbij@umcutrecht.nl

V. Lenters · L. Portengen · D. Heederik · R. C. H. Vermeulen
Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Jenalaan 18d, 3584 CK Utrecht, The Netherlands

Introduction

It is widely accepted that exposure to asbestos is related to an excess risk of lung cancer [1]. However, studies exploring the exposure–response relationship have shown a large variability in excess risk per unit of exposure. Berman and Crump [2] showed in a meta-analysis that such variations might be related to different fiber size distributions and fiber type. Within fiber type, relatively longer

fibers were associated with a higher increased lung cancer risk compared to shorter fibers. Moreover, chrysotile was estimated to be less potent than amphiboles by a factor ranging between 6 and 60. The meta-analysis of Hodgson and Darnton [3] had comparable findings with respect to potency differences between chrysotile and amphiboles. In a recent meta-analysis by Lenters et al. [4], it was shown that variations in risk estimates of lung cancer might additionally be explained by differences in quality aspects of the applied exposure assessments methodology besides fiber type.

In all previous meta-analyses [2, 4, 5] except for the one of Hodgson and Darnton [3], a fixed, average excess risk per fiber year (expressed as the potency, that is, the so-called K_L value, of asbestos for causing lung cancer) was estimated by combining the K_L values obtained for each study. However, most of the lung cancer studies included in the meta-analyses were not very recent and notably involved heavily exposed individuals. Currently, certainly in the Western world, it is unlikely that individuals are exposed to levels previously generally studied, because handling of asbestos declined gradually after the 1970s and dropped severely in the 1990s due to directives on protecting workers exposed to asbestos [6]. As a consequence, current interest lies in estimating excess risk accurately at relatively low exposures.

Previously, linear extrapolation has been applied to estimate risks at low exposure levels. However, such extrapolation is heavily dependent on estimates at high exposures, rendering extrapolated risk estimates at low exposure uncertain. For example, the population-based study of Gustavsson et al. [7] found a significant excess risk of lung cancer at low levels of cumulative asbestos exposure, which was much higher than could be expected by simple linear extrapolation from cohorts with higher exposures.

To accurately derive acceptable exposure limits and underpin compensation claims, better evidence is needed about the asbestos-related risk of lung cancer at low exposures. We provide new evidence by fitting nonlinear meta-regression models to existing data, which is notably new in meta-analyses. The flexibility of these models ensures that the exposure–response relationship can vary with exposure levels and is less affected by estimates in the upper exposure categories [8]. Moreover, the advantage of our method is that we combine all existing risk estimates at low exposures and obviate the need to extrapolate below the study-specific exposure range. Hence, our method provides a more robust estimate of exposure-specific lung cancer risks than previous meta-analyses. In addition, we stratified our results by fiber type to explore a potential potency difference between chrysotile and amphibole fibers at relatively low cumulative exposure levels.

Methods

Identification of included studies

The same selection criteria were applied as in the meta-analysis by Lenters et al. [4]. Briefly, occupational studies from MEDLINE and EMBASE were selected if lung cancer risk per cumulative exposure in at least two exposure categories was reported. Furthermore, the cumulative exposure needed to be reducible to units of total number of fiber years (f-y/ml), which is defined as the product of the concentration of asbestos fibers per milliliter of air measured by phase-contrast microscopy (PCM), and the duration of exposure in years. PCM measures fibers that are longer than 5 μm, thicker than approximately 0.25 μm, and with an aspect (length-to-width) ratio >3. Studies with only one exposure category were excluded because no study-specific exposure–response relationship could be derived. The selection criteria resulted in 18 industry-based cohort studies, including one nested case–control, and one general population-based case–control study (see Table 1 for details). In all studies, exposure to asbestos was based on data from stationary or personal monitoring.

Extraction of data from the incorporated studies

Information about the study design, study characteristics, and exposure categories were extracted from each study. To obtain risk estimates for the 15 studies with standardized mortality ratios (SMRs), observed and expected lung cancer cases were extracted for each exposure category. The relative risks (RRs) and their confidence intervals (CIs), size of the study population, and number of lung cancer cases were extracted for each exposure category with lung cancer occurrence among the two cohort studies with an assigned reference group. For the two case–control studies, the odds ratios (ORs) and their confidence intervals, and the number of lung cancer cases and controls were included. The adjusted ORs and corresponding CIs for the study of Gustavsson et al. [7] were obtained via direct communication with the authors. For the purpose of this meta-analysis, all measures of association, that is, ORs, RRs, and SMRs, were considered estimates of the RR of asbestos exposure and lung cancer occurrence.

To assign a specific point estimate of cumulative exposure to the extracted risk estimates, we used the mean of the exposure category, when described in the original publication. If not described, the midpoint of the range of the exposure categories was used. For open-ended, uppermost exposure categories, the midpoint was calculated as 5/3 times the lower bound of those categories (as proposed by the asbestos advisory committee of the Unites States Environmental Protection Agency in 2008). For example,

the midpoint estimate for an open-ended category of >100 fiber years was calculated as 5/3 * 100 = 167. For additional details on data extraction, we refer to Lenters et al. [4].

Modeling the exposure–response relationship

We hereby expanded on the study of Lenters et al. [4] in which they investigated the role of quality of the asbestos exposure assessment to potentially explain heterogeneity in linear exposure–response slope estimates. They showed that the linear exposure–response slope estimates can be influenced by measurement error. Moreover, linear extrapolations to lower exposures based on these estimates likely yield a large uncertainty as they did not focus on the actual shape of the exposure–response curve. To improve estimates in the low exposure range, we assessed the shape of the exposure–response curve by fitting nonlinear meta-regression models to all available data estimates.

From the 19 studies, we extracted 104 risk estimates (i.e., study points of the RR for lung cancer at a given exposure level) over a cumulative exposure range of 0.11–4,710 f-y/ml. To accurately estimate associations in the lower exposure range based on all available data points, we used a previously developed macro for applying linear and nonlinear regression models to the reported risk estimates [8]. In this macro, the natural logarithm (LN) of the reported risk estimates was inversely weighted by their variance [9]. As risk estimates (ORs and RRs) within a single study are correlated, the variance of the risks was corrected by estimating the covariance between different risk estimates using the method of Greenland [10]. For studies reporting SMRs, no covariance was estimated as it can be assumed that the independence assumption does hold for SMRs since the total population is used as the reference group instead of a subsample.

The regression models applied consisted of full linear models (model type 1), and natural splines with prespecified knots at the 20th, 50th, and 80th percentiles (model type 2). The natural spline is a flexible model and allows risks to vary nonlinearly with exposure, such that estimates at low exposure are less affected by estimates in the upper exposure categories [11]. The two model types were fitted with (option A) and without (option B) an intercept where model A assumes a difference in background rate of lung cancer between exposed and non-exposed individuals and model B assumes no difference. A model with intercept has been used in previous studies to account for potential differences in background risk [2, 4, 5, 12]. However, if an intercept above RR = 1 is due to measurement error instead of differences in background risk, it is more appropriate to model the exposure–response relationship without intercept [13]. To accommodate potential between-study heterogeneity, the regression models allowed for random study-specific intercepts and exposure effects [9]:

$$\text{LN RR} = \boldsymbol{\beta_0} + \boldsymbol{\beta_1^*}\,\text{exposure} + \boldsymbol{\sigma^2_{u0}} + \boldsymbol{\sigma^2_{u1}} + \boldsymbol{\sigma^2_{e0}}\ (\text{model option A});$$

$$\text{LN RR} = \boldsymbol{\beta_1^*}\,\text{exposure} + \boldsymbol{\sigma^2_{u1}} + \boldsymbol{\sigma^2_{e0}}\ (\text{model option B});$$

where $\boldsymbol{\beta_0}$ is the common intercept across studies, $\boldsymbol{\beta_1}$ is the common slope associated with exposure across studies, $\boldsymbol{\sigma^2_{u0}}$ is the estimated variance of the intercept between studies, $\boldsymbol{\sigma^2_{u1}}$ is the estimated variance of the slope between studies, and $\boldsymbol{\sigma^2_{e0}}$ is the variance of the individual risk estimates. (For the spline models an additional spline variable was estimated by using third-order polynomials to fit a nonlinear slope [11]).

As a result, an additional component of the variance explaining the between-study heterogeneity was considered in weighting each observation [14]. Models were fitted using maximum likelihood (ML) estimation, and goodness of fit was assessed with the deviance (-2 log likelihood) criterion. For accurate estimation of the parameters, models were refitted using restricted maximum likelihood (REML). A variance components structure was used to compute the between-study variances for option A.

The results on the LN scale were retransformed to the 'normal' scale to identify the variation in RR as a function of exposure. We calculated the RRs and their CIs for low cumulative exposure levels of 4 and 40 f-y/ml. These levels were selected because occupational exposure standards have been endorsed from levels of 2 to 0.1 f/ml over an 8-h time weighted average in the past decades [15, 16]. Over a working life exposure of 40 years, we expect the cumulative exposure levels of workers over the last decades to be somewhere between 4 and 40 f-y/ml. For models with an intercept (option A), the predicted RR at zero exposure may not be equal to 1. To relate the estimated risk at a specific exposure level to an RR of 1 at zero exposure, models were refitted to the data points from which the common predicted intercept was subtracted. Results were stratified by fiber type (i.e., chrysotile, amphibole, or mixed). For comparison, RRs were also calculated based on estimates from previous published meta-analyses [2–5].

Sensitivity analyses

The sensitivity of the predicted risk to the inclusion of specific studies was assessed with a 'jackknife' analysis, in which studies are excluded one by one [17]. The sensitivity of the predicted risk at low exposure to the inclusion of risk estimates corresponding to high exposures (>100 f-y/ml) was assessed by fitting models excluding these data. In addition, results were stratified to studies that included a latency in their estimates between exposure and lung cancer and studies that included no latency.

Table 1 Characteristics of the included studies

Study	Author	Study design	Type of risk estimates	Fiber type	Lowest–highest exposure category (f-y/ml)	Lagged CE
Quebec mines and mills	Liddell et al. [27]	Cohort	SMR	Chrysotile	4.71–4,710	CE to age 55
Italian mine and mill	Pira et al. [28]	Cohort	SMR	Chrysotile	50–666.7	CE
Connecticut plant	McDonald et al. [29]	Cohort	SMR	Chrysotile	15–400	CE
South Carolina textile plant	Hein et al. [30]	Cohort	SMR	Chrysotile	0.75–200	CE10
North Carolina textile plants	Loomis et al. [31]	Cohort (internal reference)	RR adjusted[a]	Chrysotile	5.69–408.3[b]	CE10
Wittenoom, Australia mine	Berry et al. [32]	Cohort	SMR	Amphibole (crocidolite)	0.11–219.9	CE
Patterson, New Jersey insulation factory	Seidman et al. [33]	Cohort	SMR	Amphibole (amosite)	3–416.7	CE
Tyler, Texas, insulation manufacture	Levin et al. [34]	Cohort	SMR	Amphibole (amosite)	11.25–375.00	CE
Libby, Montana, Vermiculite mines and mills	Sullivan [35]	Cohort	SMR	Amphibole (amosite)	2.25–167	CE10
British friction products factory	Berry and Newhouse [36]	Nested case–control, (matched design; internal reference)	OR	Amphibole (tremolite)	29.5–228[b]	CE
Ontario cement plant	Finkelstein [37]	Cohort	SMR	Mixed	15–250	CE
New Orleans cement plants	Hughes et al. [38]	Cohort	SMR	Mixed	4.2–256.2	CE10
Swedish cement plant	Albin et al. [39]	Cohort (external reference)	RR adjusted[a]	Mixed	3.1–88.2	CE
Belgium cement plant	Laquet et al. [40]	Cohort	SMR	Mixed	25–1200[c]	CE
US factory retirees	Enterline et al. [41]	Cohort	SMR	Mixed	186–2,928	CE
US insulation workers	Selikoff and Seidman [42]	Cohort	SMR	Mixed	37.5–375	CE10
Pennsylvania textiles plant	McDonald et al. [43]	Cohort	SMR	Mixed	15–330	CE10
Rochdale, England textile plant	Peto et al. [44]	Cohort study	SMR	Mixed	5.92–256.57	CE5
Stockholm County population	Gustavsson et al. [7]	Case–control (matched design)	OR adjusted[a]	Mixed	0.56–8.80	CE

Lagged cumulative exposure (CE) indicates whether exposures in the CE(x) years previous to follow-up were discarded. More details on the studies and their risk estimates can be found in the Supplemental Material of the study of Lenters et al. [4]

[a] In the North Carolina textile plants study, results were adjusted for age, gender, race, calendar year, and birth cohort; In the Swedish cement plant study, results were adjusted for age and calendar year; In the Stockholm County population study, results were adjusted for age, inclusion year, residential radon, environmental nitrogen dioxide, diesel exhaust, and combustion products

[b] The lowest exposure category (corresponding to 0.383 f-y/ml in the North Carolina textile plant and 4.5 f-y/ml in the British friction factory) for which no risk estimate could be calculated was excluded from the analyses because it was used as the reference category

[c] The highest exposure category (corresponding to 2,400 f-y/ml) for which no risk estimate could be calculated was excluded from the analyses because of lack of observed cases

Software

All analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Significance tests between fiber-type-specific estimates were assessed with use of simulating the fiber-type-specific risk distribution in R version 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study characteristics

Study characteristics of the 19 studies that were included in the meta-regression are listed in Table 1. The 104 risk estimates extracted from these 19 studies and corresponding CIs are shown in Fig. 1. From this figure, it is apparent that the risk estimates vary substantially even at the lower end of the cumulative exposure range. Of all risk estimates, 38 (37 %) were assessed at a cumulative exposure level of 40 f-y/ml or less, and 10 (10 %) at a cumulative exposure level of 4 f-y/ml or less.

Predictions

Table 2 shows the predicted risks based on the different exposure–response relationships. In all models, inclusion of cumulative exposure as an explanatory variable significantly reduced model deviance. Compared to the linear model, a significantly better fit was observed for the model including a natural spline (for the explanatory variable) when a random intercept and slope was fitted (model 2A: deviance = 105.6, model 1A: deviance = 111.7; χ^2 test (1 *df*), $p = 0.01$). The natural spline suggested a nearly linear increase in the relative lung cancer risk at low levels as a function of exposure (Fig. 2). The slope slightly decreased after exposure of 150 f-y/ml. Based on this model, the relative lung cancer risk for 4 and 40 f-y/ml was estimated to be 1.502 (95 % CI: 1.173–1.922) and 1.680 (95 % CI: 1.317–2.142), respectively. After correction for the common estimated intercept, these RRs were RR = 1.013 for 4 f-y/ml and RR = 1.133 for 40 f-y/ml. Similarly, when fitting regression models without intercept, a significantly better fit was observed for the spline model over the linear model (χ^2 test (1 *df*), $p = < 0.001$). The RR that we predicted based on the natural spline model (model 2B) was 1.027 (95 % CI: 1.020–1.034) for 4 f-y/ml and 1.301 (95 % CI: 1.215–1.392) for 40 f-y/ml cumulative exposure.

Sensitivity analyses

A jackknife analysis, leaving one study at a time, was applied to the natural spline with intercept model (model 2A). Exclusion of the Ontario study (#11) resulted in the highest slope estimates, whereas the Pennsylvania study (#17) resulted in the lowest. However, their influence on

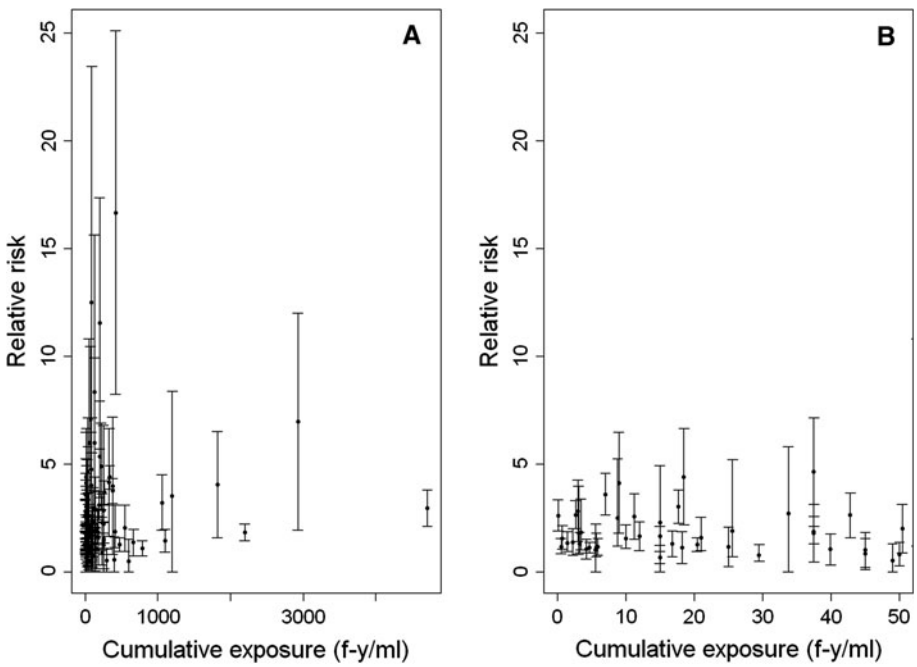

Fig. 1 Scatter plot of the relative risk estimates and their 95 % confidence intervals extracted from the 19 studies included in the meta-regression (**a** full range of cumulative exposures and **b** lower range of cumulative exposure <50 f-y/ml)

Table 2 Comparison of predicted risk at different exposure levels

	Deviance (*df*)[a]	Intercept[b] (95 % CI)	RR 4 f-y/ml[b] (95 % CI)	RR 40 f-y/ml[b] (95 % CI)
Models[c]				
1A. Linear model	111.7 (100)	1.580 (1.243–2.008)	1.592 (1.252–2.023)	1.701 (1.338–2.164)
Corrected for intercept		1.000 (0.787–1.271)	1.007 (0.793–1.280)	1.077 (0.847–1.370)
1B. Linear model without intercept	806.9 (102)	1.000 (1.000–1.000)	1.017 (1.009–1.024)	1.182 (1.096–1.274)
2A. Natural spline	105.6 (99)	1.483 (1.157–1.900)	1.502 (1.173–1.922)	1.680 (1.317–2.142)
Corrected for intercept		1.000 (0.780–1.281)	1.013 (0.791–1.296)	1.133 (0.888–1.444)
2B. Natural spline without intercept	703.6 (101)	1.000 (1.000–1.000)	1.027 (1.020–1.034)	1.301 (1.215–1.392)

RR relative risk, *df* degrees of freedom calculated as the number of data points minus the number of coefficients estimated

[a] Fitted using ML estimation

[b] Fitted using REML estimation

[c] The deviance of the empty and intercept-only model was 3,433.9 and 309.9, respectively.

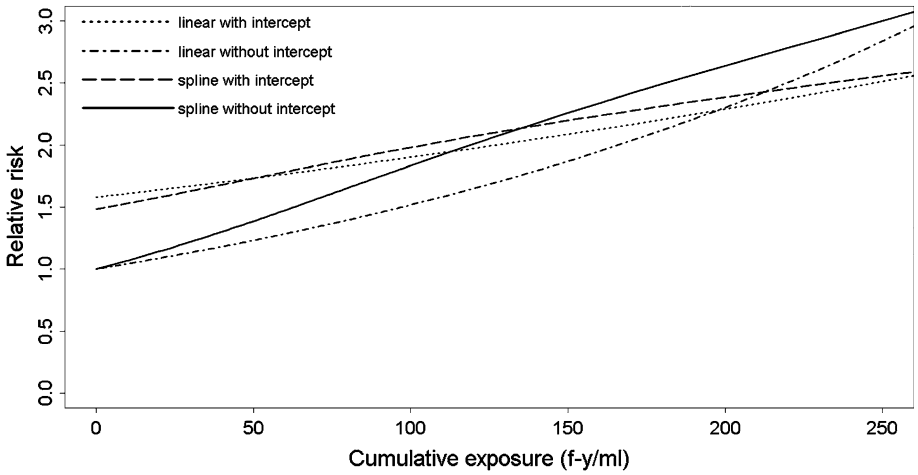

Fig. 2 Predicted exposure–response relationship based on a linear and spline regression models fitted with and without intercept, shown over an exposure range of 0–250 f-y/ml (results were retransformed to the 'normal' scale)

the predicted risks was negligible after correction for the intercept (data not shown). After correction for the intercept, the predicted risks increased most, and considerably, upon exclusion of the Quebec study (#1) from the analysis (RR = 1.019 for 4 f-y/ml and RR = 1.211 for 40 f-y/ml), and decreased most, but only slightly, upon exclusion of the South Carolina study (#4) (RR = 1.010 for 4 f-y/ml and RR = 1.103 for 40 f-y/ml).

When models were fitted on exclusively risk estimates corresponding to exposures of 100 f-y/ml or less, a non-significant better fit was observed for the spline model as compared to a linear model (Supplementary data Table S1). Based on this sensitivity analyses, predicted risk ranged from RR = 1.012 for 4 f-y/ml to RR = 1.152 for 40 f-y/ml, which are comparable to the estimates based on the full range. Moreover, the predictive risk was about three times higher in studies that used a latency time of 10 years (RR = 1.030 for 4 f-y/ml and RR = 1.329 for 40 f-y/ml) compared to studies that used no latency (RR = 1.012 for 4 f-y/ml and RR = 1.126 for 40 f-y/ml) between lung cancer and exposure (Supplementary data Table S2, after correction for intercept).

Fiber type

After stratification of the results by fiber type, we observed a non-significant three- to fourfold higher combined RR for studies investigating exposure to mixed and amphibole fibers compared to studies investigating exposure predominantly to chrysotile fibers (Table 3, model 2A after correction for intercept). Additional analyses showed that these potency differences decreased to about twofold at higher exposures (Supplementary data Table S3, model 2A). The relative potencies across the exposure range are also shown in Fig. 3. When spline regressions were fitted without intercept (Table 3, model 2B), amphiboles had an 8–12-fold increased risk compared to chrysotile which was statistically significant. However, the exposure–response relationship based on the spline without intercept seems to be unrealistic and uncertain at higher cumulative exposures for amphiboles since the risk decreased after exposure of 150 f-y/ml (Fig. 3).

The predicted risk for chrysotile at low cumulative exposure ranges was heavily influenced by the Quebec and South Carolina studies. For exposures of 4 f-y/ml, the

Table 3 Predicted risk at different exposure levels stratified by fiber type based on the natural spline

	Intercept (95 % CI)	RR 4 f-y/ml (95 % CI)	RR 40 f-y/ml (95 % CI)
Chrysotile			
Natural spline (model 2A)	1.325 (1.115–1.575)	1.334 (1.124–1.583)	1.411 (1.157–1.719)
Corrected for intercept	1.000 (0.841–1.188)	1.006 (0.848–1.194)	1.064 (0.873–1.297)
Fitted without intercept (model 2B)	1.000 (1.000–1.000)	1.013 (0.999–1.028)	1.142 (0.991–1.315)
Amphiboles			
Natural spline (model 2A)	1.888 (1.047–3.402)	1.929 (1.073–3.468)	2.326 (1.297–4.170)
Corrected for intercept	1.000 (0.555–1.802)	1.022 (0.568–1.837)	1.232 (0.687–2.209)
Fitted without intercept (model 2B)	1.000 (1.000–1.000)	1.109 (1.084–1.134)	2.637 (2.120–3.280)
Mixed			
Natural spline (model 2A)	1.291 (0.872–1.912)	1.314 (0.890–1.940)	1.541 (1.065–2.231)
Corrected for intercept	1.000 (0.675–1.481)	1.018 (0.690–1.503)	1.194 (0.825–1.727)
Fitted without intercept (model 2B)	1.000 (1.000–1.000)	1.028 (1.019–1.038)	1.322 (1.208–1.446)

RR relative risk

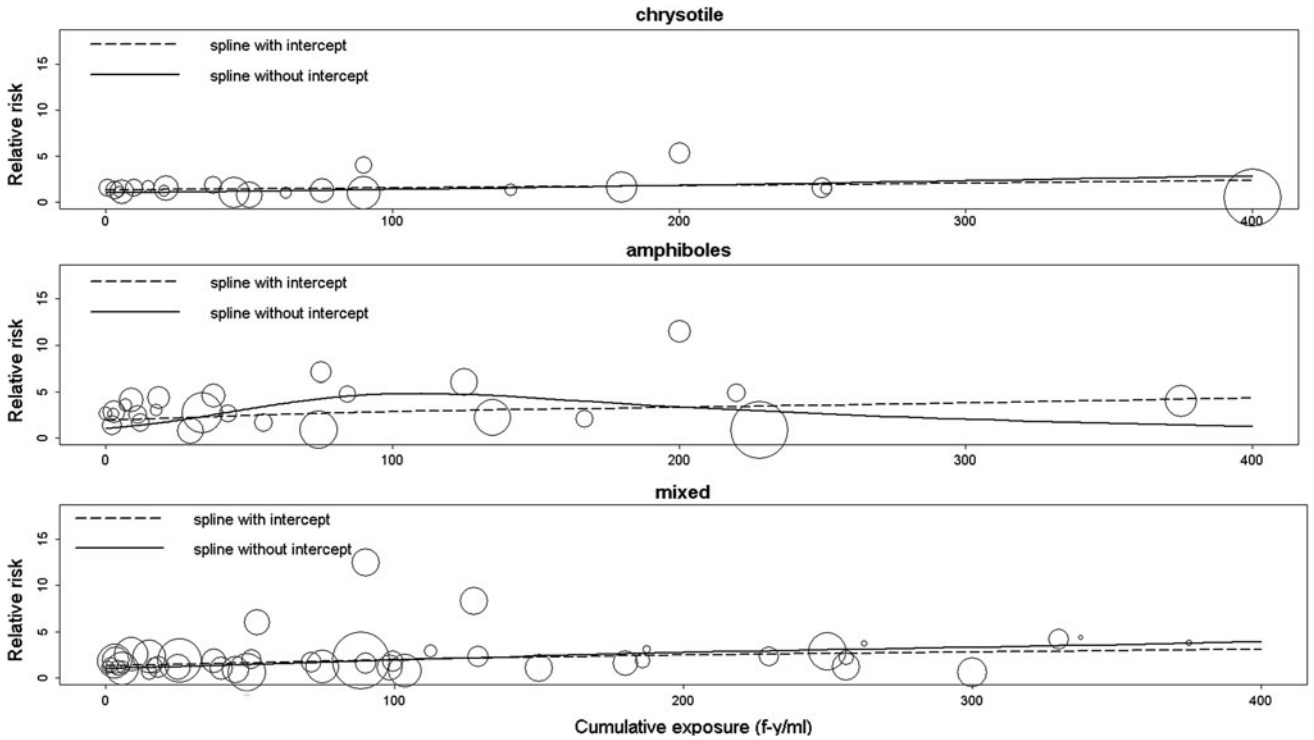

Fig. 3 Predicted exposure–response relationship over an exposure range of 0–400 f-y/ml stratified by fiber type (based on a spline regression model fitted with and without intercept)

exclusion of Quebec and the South Carolina study yielded a corrected predicted risk of 1.016 and 1.001, respectively, as compared to the overall estimate of 1.006. When both studies were excluded, this risk was estimated to be 1.004. The estimated risks for amphiboles were largely driven by the Wittenoom study (#6) and the New Jersey study (#7). When both studies were removed from the analyses, the risk for exposures of 4 f-y/ml dropped from 1.022 to 1.005. For mixed fibers, the predicted risk was most heavily influenced by the Belgian study (#14). Upon exclusion of the Belgian study, the risk increased from 1.018 to 1.027 for mixed exposures of 4 f-y/ml. Removing these five most influential studies from the analyses resulted in a 1.3–7-fold higher combined risk for studies investigating exposure to amphibole and mixed fibers compared to studies investigating exposure predominantly to chrysotile fibers.

Table 4 Overview of predicted risk based on previously published meta-analyses

Predictions	K_L*100	RR 4 f-y/ml	RR 40 f-y/ml
Spline (results of this study)			
Overall (corrected for intercept)		1.013	1.133
Amphiboles (corrected for intercept)		1.022	1.232
Chrysotile (corrected for intercept)		1.006	1.064
Mixed (corrected for intercept)		1.018	1.194
Based on meta-analysis of Lenters et al. (for fibers measured by PCM) [4][a]			
Overall	0.13	1.0052	1.052
Amphiboles	0.33	1.0132	1.132
Chrysotile	0.04	1.0016	1.016
Mixed	0.13	1.0052	1.052
Based on meta-analysis of Lash et al. (for fibers measured by PCM) [5][b]			
Overall	0.26	1.0104	1.104
Based on meta-analysis of Hodgson and Darnton (for fibers measured by PCM as assigned by TEM) [3][c]			
Amphiboles	5[d]	1.097	2.936
Chrysotile	0.1[d]	1.002	1.034
Mixed	0.32[d]	N.A.[d]	N.A.[d]
Based on meta-analysis of Berman and Crump [2][e]			
For fibers measured by PCM			
Overall (when restricting the relative potency of chrysotile to amphibole to 1)[f]	0.34	1.0136	1.136
For long fibers (length > 10 μm) of al width measured by TEM			
Amphiboles	2.7	1.108	2.08
Chrysotile	0.29	1.0116	1.116
For long fibers (length > 10 μm) with width <4 μm measured by TEM			
Amphiboles	7.7	1.308	4.08
Chrysotile	0.49	1.0196	1.196

RR relative risk, K_L the excess relative risk per unit of fiber year, *PCM* phase-contrast microscopy and measures fibers of longer than 5 μm, thicker than approximately 0.25 μm, and with an aspect (length-to-width) ratio >3. *TEM* transmission electron microscopy

[a] Estimates were based on a random effect model by combining K_L values that were derived by fitting an additive linear risk model with a variable intercept to each study.

[b] Overall estimates were based on a random effect model by combining K_L values that were derived by fitting an additive linear risk model to each study (the K_L values and the intercepts were assumed to have a log normal distribution).

[c] Estimates were based on exposure-risk relationships across cohorts by calculating an average exposure and an excess risk for each cohort.

[d] K_L values shown in the table are based on moderate or higher exposures. For low exposures, risks were calculated by applying the sub-linear model: RR = 1.6*cumulative exposure^1.3 for amphiboles and RR = 0.028*cumulative exposure^1.3 for chrysotile (as assessed by the authors for the best fitted model). No model for low exposures of mixed fibers was assessed.

[e] Estimates were based by fitting K_L values and matching fiber type and size dimensions (as determined by TEM). The K_L values were derived by fitting an additive linear risk model with a variable intercept (with a maximum of RR = 2) to each study.

[f] The K_L value based on PCM was assessed by fitting a metric with fibers of >0.2 μm width in which the relative potencies of long fibers versus short fibers and chrysotile versus amphibole were restricted to 1.

Comparison with risk estimates from other meta-analysis

An overview of the risk estimates based on previously published meta-analyses for cumulative exposure estimates of 4 and 40 f-y/ml is shown in Table 4. Our overall point estimates were higher compared to the risks that we calculated based on the meta-K_L value presented for the same 19 studies in the study of Lenters et al. [4]. Under a random linear effect model, they observed a K_L value (*100) of 0.13 (95 % CI: 0.04–0.22) with an intercept of 1.47 when all 19 studies were considered. Also, they showed that the meta-K_L value was higher for studies with a better exposure measurement strategy. When studies with two or more limitations in the exposure assessment component were excluded, their meta-K_L value was about two times higher. An ad hoc analysis showed that predictions based on our model also yielded higher risk estimates for studies with fewer limitations in the exposure assessment component (Supplementary data Table S4).

Estimates based on the overall meta-K_L value from the meta-analysis of Lash et al. [5] were similar albeit slightly lower. Overall estimates based on the analyses of Berman and Crump were comparable to our estimates [2]. However, they used a proxy for PCM measurements based on transmission electron microscopy (TEM), which complicates direct comparisons. If analyses would have been performed with results based on PCM measurements, their estimates would have been considerably lower (Supplemental Material, Table 6 of the meta-analysis of Lenters et al. [4]). Although we observed higher or comparable overall risks, we observed a much lower potency difference between amphiboles and chrysotile compared to those observed by Berman and Crump, and Hodgson and Darnton [2, 3].

Discussion

We used all available quantitative exposure–response data from observational epidemiological studies to assess the association between cumulative asbestos exposure and the risk of lung cancer. Our estimates for low-level exposures are of particular interest to predict the impact of exposures on individuals occupationally exposed to low levels and the general population. We estimated the RR for lung cancer to be 1.013 (95 % CI: 0.791–1.296) for 4 f-y/ml and 1.133 (95 % CI: 0.888–1.444) for 40 f-y/ml cumulative exposure. These predictions were based on a natural spline model that best fitted our data. When no intercept was fitted, significantly higher RRs were observed ranging from 1.027 (95 % CI: 1.020–1.034) for 4 f-y/ml to 1.301 (95 % CI: 1.215–1.392) for 40 f-y/ml. Our most conservative predicted risks were equal or higher than estimates based on additive linear relative risk models applied in previously published meta-analysis [4, 5]. Furthermore, our results indicated a moderately higher increased risk at low exposure in studies investigating amphiboles and mixed fibers compared to studies investigating chrysotile. These potency differences, however, were strongly influenced by a few studies. In general, we observed a lower potency difference between fiber types compared to those observed in previous meta-analyses [2, 3].

We adjusted the predicted estimates for the intercept. This assumes that the intercept fully represents a difference in baseline risk, and in practice, this may not be true. In fact, the observed intercepts suggest a very high excess risk (about 50 %) among workers compared to the general population that is attributable to other factors than asbestos exposure. Besides differences in risk factors between the exposed and unexposed population, systematic and random measurement errors can lead to an intercept greater than one [13]. In the study of Lenters et al. [4], a critical review was performed on the quality of the exposure assessment methodology of the included studies. Here, it was shown that only a few studies had few limitations in the exposure assessment component and were of high quality. Furthermore, studies with lower quality had on average higher intercepts. Therefore, it is reasonable to assume that the observed intercept above RR = 1 is at least partly due to measurement error. Therefore, we also showed results of the natural spline fitted without intercept, since one might suggest that fitting a line through the origin (ln(RR) = 0 at zero exposure) would be more appropriate in the case of random measurement error. Our results also showed a lower intercept for the studies that included a latency time compared to those that did not include a latency time. Including no latency between exposure and lung cancer could also lead to measurement error in the exposure assessment when it incorrectly reflects the etiological time window of exposure.

Potential publication bias may have affected our risk estimates. However, this effect seemed minimal in previous analyses (see Supplemental Material of the study of Lenters et al. [4]). Moreover, the studies included in the meta-analyses differ from each other in terms of effect measure (ORs, RRs, and SMRs), place, time, follow-up, and exposure assessment. To limit the effect of differences across studies, our analysis are based on exposure–response relationship fitted within studies allowing for a random intercept and slope. However, we still observed a substantial variability in the exposure–response relationship which might be explained by various factors. For instance, the included studies might not have fully adjusted for differences in covariates between internal exposure categories. This may especially hold for studies in which the effect measure is adjusted only for age and gender. However, the effect of differences in background rates between exposed and non-exposed individuals on the exposure–response relationship can be addressed to a certain extend by adding an intercept to the model. Also, differences in smoking prevalence and mean length of follow-up per person could have resulted in different exposure–response relationships. The limited information available on these aspects did not allow further exploration of the potential bias they may incur.

The large heterogeneity between individual study results motivated the use of a random intercept and slope model consistent with previous meta-analyses [2–5]. The natural spline model provided the best fit to the data. After re-transforming the results to the original scale, our results substantiated the evidence that the RR increases virtually linear with increasing exposure. Our findings are in contrast to data of Hodgson and Darnton suggesting a sub-linear relationship [3]. One might also have expected a more supra-linear effect based on substantial high risks

observed at very low exposures in a population-based study [7]. Although this population-based study was included in the current meta-regression, our results were statistically compatible with a more-or-less linear exposure–response model. The advantage, however, of our new method is that it provides a more accurate estimate of the lung cancer risk at low exposure since all available information could be used, and estimates did not need to be based on extrapolations below the study-specific exposure range. Moreover, our predictions are not heavily dependent on estimates at high exposure levels which are vulnerable to measurement error [18]. Substantially higher risk at low exposure has been observed in population-based studies with semi-quantitative results [19, 20]. Although estimates from these studies are quite high, they are in the range of our results when we included only high-quality studies.

Low cumulative exposures are associated with all kind of occupations if duration of exposure is short. However, low cumulative exposures have been particularly observed in the general population due to downstream use of asbestos [7]. Like other meta-analyses, we could not determine whether risks might differ by exposure intensities, since intensities could mostly not be distinguished from reported cumulative exposures. Information on intensities is especially important if a threshold exists for asbestos-related lung cancer. However, no threshold of exposure intensity has been delineated for asbestos-related lung cancer. Moreover, a study by Frost et al. [21] showed that long-term asbestos removal workers had a significant increased risk of lung cancer compared to short-term workers indicating that cumulative exposure is an important measure if persons are exposed to low intensities.

The degree to which different types of asbestos have different potencies is a topic of ongoing debate [2, 22]. Berman and Crump showed a nine times higher increased risk for long amphiboles compared to long chrysotile fibers of all widths, and had even higher estimates for specific diameters (a ratio of 16:1 for long amosite versus long chrysotile for fibers with widths <4 μm) [2, 11]. Hodgson and Darnton estimated the risk difference between chrysotile and amphibole fibers for lung cancer to be between 10 and 50 [3]. In the study of Lenters et al., a difference in risk ratio of a factor 8 was observed when all 19 studies were included (i.e., without adjusting for quality) [4]. In our analyses, we observed a non-significant three- to fourfold difference in potency between chrysotile and amphibole fibers.

Various explanations exist for the higher potency differences observed in previous meta-analyses compared to our results. Firstly, we used nonlinear regressions and estimated the overall slope from a distribution of study slopes. This resulted in shrinkage of study-specific slopes to the overall combined slope as well as less weight of point estimates at high exposures, and therefore, our analyses are less influenced by extreme results. Secondly, among the amphibole studies, we observed very high intercepts for the Wittenoom and New Jersey studies (i.e., intercepts of 2.8 and 3.8, respectively). These high intercepts were partly due to very high risks observed at relatively low exposures: the Wittenoom study observed a risk of 2.6 for 0.11 f-y/ml and the New Jersey study a risk of 2.8 for 3 f-y/ml. In the meta-analysis by Berman and Crump, these high intercepts were truncated at 2 [2, 12]. Therefore, our estimated risk for amphiboles is likely to be lower compared to risks estimated by Berman and Crump. When we fitted a natural spline without intercept, we observed a significant increased risk for amphiboles. In this case, the ratio of potency for amphobiles versus chrysotile was estimated to lie between 8:1 and 12:1, which was comparable to the ratios observed in the analyses of Berman and Crump for long fibers. However, the observed exposure–response relationship for amphiboles based on the spline without intercept was uncertain at higher cumulative exposure levels. Thirdly, Berman and Crump controlled for different fiber sizes in their meta-analysis [2]. Several studies showed that relatively longer and thinner fibers are stronger associated with lung cancer [2, 23, 24]. Since chrysotile fibers are generally longer and thinner than amphiboles, this might also explain the higher potency ratio between fibers types observed by Berman and Crump. Finally, Hodgson and Darnton used a different methodology to estimate the asbestos-related lung cancer risk [3]. They derived exposure-risk relationships across cohorts by calculating an average exposure and an excess risk for each cohort to avoid the effect of random measurement error. However, when for example, misclassification is more severe in lower exposure categories, the method applied does not necessarily completely eliminate the effect of exposure misclassification. Furthermore, mean levels do not reflect actual exposure levels accurately when observations are skewed. Also, it is expected that extraneous risk factors are differential distributed across study cohorts, which can have influenced their results.

From our results, it was apparent that the Quebec mine study and South Caroline textile study had a significant impact on the risk estimates for chrysotile. Upon removing the Quebec study, the RR for chrysotile increased considerably, whereas the exclusion of the South Carolina resulted in lower risks for chrysotile. The combined estimate of the three other studies involving chrysotile exposure also showed relatively low risks. The differences between the Quebec mine and South Carolina textile studies have been discussed extensively. A recent study by Berman concluded that the characteristics of the fiber can potentially explain the differences in lung cancer potency observed between these cohorts [25]. In that study, it was shown that the South Carolina textile workers were exposed to longer asbestos structures compared to the

Quebec miners and millers. The PCM-counted structures in textile factory dusts were virtually 100 % asbestos and 100 % asbestiform. In contrast, at least one-third of the structures counted by PCM in chrysotile mine and mill dusts were not asbestos. Additional limitations of PCM measurements have been discussed elsewhere [26]. Interestingly, the South Carolina study was classified as one with no limitations and the Quebec study as one with several limitations in the exposure assessment component as assessed by Lenters et al. [4] They showed that better quality studies yielded higher meta-estimates. This pattern was also observed with our spline regression model suggesting that observed fiber-specific potency differences at low cumulative exposure might also be partly due to differences in quality. Moreover, Lenters et al. showed that when analysis is restricted to only studies with few quality limitations of the exposure assessment component, the epidemiological evidence base is too sparse to draw deductions about potency differences per fiber type. Therefore, in light of the quality, we could not easily ascertain the magnitude of the potency differences between different fibers at low cumulative exposure.

Conclusion

Our results showed relative lung cancer risks for asbestos exposures of 4 and 40 f-y/ml to be between 1.013 and 1.027, and 1.13 and 1.30, respectively. Although we could not unequivocally determine potency differences between different fiber types at very low exposure levels of asbestos, the collected evidence suggests a threefold difference in risk between chrysotile and amphibole asbestos. This potency difference was not significant and lower than the generally held consensus. The flexible spline regression model we applied indicated that for low cumulative exposures, the increase in relative risk of lung cancer due to asbestos exposure may be larger than expected from previous results. This would suggest that, in general, a larger fraction of lung cancer incidence may be attributable to (many individuals having) relatively low cumulative exposure levels than previously estimated and might have important implications in developed nations. Additional research is required, in particular among removal workers and the general population in developed countries or low-exposed industrial cohorts using quantitative estimates of asbestos exposure, to further substantiate this notion.

Acknowledgments This study was supported by the Institute for Asbestos Victims, The Netherlands.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Straif K, Brahim-Tallaa L, Baan R, Grosse Y, Secretan B, El GF, Bouvard V, Guha N et al (2009) A review of human carcinogens–part C: metals, arsenic, dusts, and fibres. Lancet Oncol 10: 453–454
2. Berman DW, Crump KS (2008) A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. Crit Rev Toxicol 38(Suppl 1):49–73
3. Hodgson JT, Darnton A (2000) The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 44:565–601
4. Lenters V, Vermeulen R, Dogger S, Stayner L, Portengen L, Burdorf A, Heederik D (2011) A meta-analysis of asbestos and lung cancer: Is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? Environ Health Perspect 119:1547–1555
5. Lash TL, Crouch EA, Green LC (1997) A meta-analysis of the relation between cumulative exposure to asbestos and relative risk of lung cancer. Occup Environ Med 54:254–263
6. Virta RL (2005) Mineral commodity profiles-asbestos: U.S. Geological Survey Circular 1255-KK. p 56
7. Gustavsson P, Nyberg F, Pershagen G, Scheele P, Jakobsson R, Plato N (2002) Low-dose exposure to asbestos and lung cancer: dose-response relations and interaction with smoking in a population-based case-referent study in Stockholm, Sweden. Am J Epidemiol 155:1016–1022
8. Vlaanderen J, Portengen L, Rothman N, Lan Q, Kromhout H, Vermeulen R (2010) Flexible meta-regression to assess the shape of the benzene-leukemia exposure-response curve. Environ Health Perspect 118:526–532
9. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
10. Greenland S, Longnecker MP (1992) Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 135:1301–1309
11. Harrel FE (2001) Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis. Springer, New York
12. Berman DW, Crump KS (2008) Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol 38(Suppl 1):1–47
13. Armstrong BG (1998) Effect of measurement error on epidemiological studies of environmental and occupational exposures. Occup Environ Med 55:651–656
14. Shi JQ, Copas JB (2004) Meta-analysis for trend estimation. Stat Med 23:3–19
15. National Institute for Occupational Safety and Health (1976) Revised Recommended Asbestos Standard. National Institute for Occupational Safety and Health, Washington, DC (DHHS (NIOSH) Publication No. 77–169)
16. Occupational Safety and Health Administration Health (1995) Asbestos standard for general industry. Occupational Safety and Health Administration, Washington, DC (OSHA publication 3095 1995 (revised))
17. Rothpearl A (1989) The jackknife technique in statistical analysis. Chest 95:940
18. Stayner L, Steenland K, Dosemeci M, Hertz-Picciotto I (2003) Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. Scand J Work Environ Health 29:317–324
19. van Loon AJ, Kant IJ, Swaen GM, Goldbohm RA, Kremer AM, van den Brandt PA (1997) Occupational exposure to carcinogens and risk of lung cancer: results from The Netherlands cohort study. Occup Environ Med 54:817–824

20. De Matteis S, Consonni D, Lubin JH, Tucker M, Peters S, Vermeulen RC, Kromhout H, Bertazzi PA et al (2012) Impact of occupational carcinogens on lung cancer risk in a general population. Int J Epidemiol 41:711–721
21. Frost G, Harding AH, Darnton A, McElvenny D, Morgan D (2008) Occupational exposure to asbestos and mortality among asbestos removal workers: a Poisson regression analysis. Br J Cancer 99:822–829
22. Stayner LT, Dankovic DA, Lemen RA (1996) Occupational exposure to chrysotile asbestos and cancer risk: a review of the amphibole hypothesis. Am J Public Health 86:179–186
23. Loomis D, Dement J, Richardson D, Wolf S (2010) Asbestos fibre dimensions and lung cancer mortality among workers exposed to chrysotile. Occup Environ Med 67:580–584
24. Stayner L, Kuempel E, Gilbert S, Hein M, Dement J (2008) An epidemiological study of the role of chrysotile asbestos fibre dimensions in determining respiratory disease risk in exposed workers. Occup Environ Med 65:613–619
25. Berman DW (2010) Comparing milled fiber, Quebec ore, and textile factory dust: has another piece of the asbestos puzzle fallen into place? Crit Rev Toxicol 40:151–188
26. Dement JM, Kuempel ED, Zumwalde RD, Smith RJ, Stayner LT, Loomis D (2008) Development of a fibre size-specific job-exposure matrix for airborne asbestos fibres. Occup Environ Med 65:605–612
27. Liddell FD, McDonald AD, McDonald JC (1997) The 1891–1920 birth cohort of Quebec chrysotile miners and millers: development from 1904 and mortality to 1992. Ann Occup Hyg 41:13–36
28. Pira E, Pelucchi C, Piolatto PG, Negri E, Bilei T, La VC (2009) Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners. Occup Environ Med 66:805–809
29. McDonald AD, Fry JS, Woolley AJ, McDonald JC (1984) Dust exposure and mortality in an American chrysotile asbestos friction products plant. Br J Ind Med 41:151–157
30. Hein MJ, Stayner LT, Lehman E, Dement JM (2007) Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. Occup Environ Med 64:616–625
31. Loomis D, Dement JM, Wolf SH, Richardson DB (2009) Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers. Occup Environ Med 66:535–542
32. Berry G, de Klerk NH, Reid A, Ambrosini GL, Fritschi L, Olsen NJ, Merler E, Musk AW (2004) Malignant pleural and peritoneal mesotheliomas in former miners and millers of crocidolite at Wittenoom. Western Australia. Occup Environ Med 61:e14
33. Seidman H, Selikoff IJ, Gelb SK (1986) Mortality experience of amosite asbestos factory workers: dose-response relationships 5 to 40 years after onset of short-term work exposure. Am J Ind Med 10:479–514
34. Levin JL, McLarty JW, Hurst GA, Smith AN, Frank AL (1998) Tyler asbestos workers: mortality experience in a cohort exposed to amosite. Occup Environ Med 55:155–160
35. Sullivan PA (2007) Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. Environ Health Perspect 115:579–585
36. Berry G, Newhouse ML (1983) Mortality of workers manufacturing friction materials using asbestos. Br J Ind Med 40:1–7
37. Finkelstein MM (1984) Mortality among employees of an Ontario asbestos-cement factory. Am Rev Respir Dis 129:754–761
38. Hughes JM, Weill H, Hammad YY (1987) Mortality of workers employed in two asbestos cement manufacturing plants. Br J Ind Med 44:161–174
39. Albin M, Jakobsson K, Attewell R, Johansson L, Welinder H (1990) Mortality and cancer morbidity in cohorts of asbestos cement workers and referents. Br J Ind Med 47:602–610
40. Lacquet LM, van der Linden L, Lepoutre J (1980) Roentgenographic lung changes, asbestosis and mortality in a Belgian asbestos-cement factory. IARC Sci Publ, pp 783–793
41. Enterline PE, Hartley J, Henderson V (1987) Asbestos and cancer: a cohort followed up to death. Br J Ind Med 44:396–401
42. Selikoff IJ, Seidman H (1991) Asbestos-associated deaths among insulation workers in the United States and Canada, 1967–1987. Ann N Y Acad Sci 643:1–14
43. McDonald AD, Fry JS, Woolley AJ, McDonald JC (1983) Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. Br J Ind Med 40:368–374
44. Peto J, Doll R, Hermon C, Binns W, Clayton R, Goffe T (1985) Relationship of mortality to measures of environmental asbestos pollution in an asbestos textile factory. Ann Occup Hyg 29:305–355