Ann. Occup. Hyg., Vol. 56, No. 8, pp. 879–887, 2012

doi:10.1093/annhyg/mes065

Quality of Evidence Must Guide Risk Assessment of Asbestos

VIRISSA LENTERS†[1], ALEX BURDORF†*[2], ROEL VERMEULEN[1], LESLIE STAYNER[3] and DICK HEEDERIK[1]

[1]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands; [2]Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands; [3]Department of Epidemiology and Biostatistics, University of Chicago, Chicago, IL, USA

Received 15 April 2012; in final form 23 July 2012; published online 20 September 2012

In 2011, we reported on the sensitivity of lung cancer potency estimates for asbestos to the quality of the exposure assessment component of underlying evidence. Both this meta-analysis and a separate reassessment of standards published by the Health Council of the Netherlands (Gezondheidsraad) have been commented on by Berman and Case. A criticism is that we used a truncated data set. We incrementally excluded poorer-quality studies to evaluate trends in meta-analyzed lung cancer potency estimates (meta-K_L values). This was one of three analysis approaches we presented. The other two used the full set of studies: a meta-analysis stratified by covariates and dichotomized by poorer and better exposure assessment aspects; and a meta-regression modeling both asbestos fiber type and these covariates. They also state that our results are not robust to removal of one study. We disagree with this claim and present additional sensitivity analyses underpinning our earlier conclusion that inclusion of studies with higher-quality asbestos-exposure assessment yield higher meta-estimates of the lung cancer risk per unit of exposure. We reiterate that potency differences for predominantly chrysotile- versus amphibole-asbestos-exposed cohorts are difficult to ascertain when meta-analyses are restricted to studies with fewer exposure assessment limitations. We strongly argue that the existence of any uncertainty related to potency issues should not hamper the development of appropriate evidence-based guidelines and stringent policies in order to protect the public from hazardous environmental and occupational exposures.

Keywords: asbestos; amphiboles; chrysotile; epidemiology; exposure assessment; lung cancer; meta-analysis; potency; risk assessment; study quality

INTRODUCTION

In 2011, we published a study on the sensitivity of lung cancer potency estimates for asbestos to the quality of the exposure assessment component of underlying evidence (Lenters *et al.*, 2011). This meta-analysis informed the approach taken by the Health Council of the Netherlands to obtain updated exposure standards (Gezondheidsraad, 2010). Their risk assessment also included mesothelioma. Two of the authors reported on the new exposure standards for occupational and environmental exposure to asbestos in the Netherlands and the underlying risk assessment procedures in a commentary in the *Annals of Occupational Hygiene* (Burdorf and Heederik, 2011). It was also reported how restriction to higher-quality studies has been used in a re-evaluation of the health risks from asbestos by the Health Council of the Netherlands.

Two central messages were discussed in the original commentary. First, quality of the exposure

*Author to whom correspondence should be addressed.
Tel: +31-10-7038469; fax: +31-10-7038451;
e-mail: a.burdorf@erasmusmc.nl
†These two authors contributed equally to this publication.

assessment strategies in occupational cohort studies on asbestos differs considerably between studies, and a poor exposure assessment might introduce bias toward a lower risk. Evaluation of this potential bias showed that a meta-analysis of studies with more limitations in the exposure assessment component of the study generally yielded lower meta-risk estimates for lung cancer than a meta-analysis of studies with fewer limitations (Lenters *et al*., 2011), in line with theory that misclassification of exposure often attenuates exposure–response estimates. Second, the quality of evidence should have implications for risk assessment practice and the meta-analyses upon which risk assessments are based.

In their commentary, Berman and Case (2012) put forward why they disagree with our main messages. We take this opportunity to respond to their arguments.

COMMENTS MADE BY BERMAN AND CASE

The disagreement with our message regarding bias in exposure–response relations focuses on the evidence of the influence of exposure assessment quality on the estimates of the exposure–response relationship. Berman and Case express several comments:

1. We selectively excluded epidemiological studies not satisfying predefined quality criteria and then applied a meta-analysis to the resulting, truncated data set while the meta-exposure response slope from the truncated data sets was not statistically significantly different from the overall meta-exposure–response slope;
2. As the evidence of bias presented by us does not appear to be statistically significant, additional sensitivity analyses seem warranted, according to Berman and Case, before it can be concluded that study quality affects exposure–response slopes. They present their own analyses to try to illustrate that the effects we describe are not robust to removal of a single study [South Carolina (Hein *et al*., 2007)] from the analysis.
3. They were surprised by the discrepancies in meta-analysis results between our sensitivity analyses and theirs.

Different aims lead to methodological differences between meta-analyses

To fully appreciate our response, a specific point needs clarification. The meta-analysis on asbestos and lung cancer by Lenters *et al*. (2011) considered the role of quality of the exposure assessment to potentially explain heterogeneity in exposure–response slope estimates and it was not aimed at deriving a specific risk estimate to be used in standard setting procedures. A separate analysis was conducted for the Health Council of the Netherlands, specifically to inform policy decisions, via a formal risk assessment, and propose updates for existing exposure limits. Different aims of the two exercises influenced the methodology. However, we cannot comment on behalf of the Health Council or defend choices made in the recommendations for new standards for asbestos. Thus, we will not explicitly address Berman and Case's comments on the mesothelioma meta-estimates (K_M). Mesothelioma was not addressed in the meta-analysis published in the peer-reviewed research article by Lenters *et al*. (2011).

A major difference in methodology was that slopes in the Health Council report are assumed to start with zero excess risk at zero occupational exposure as is common for regulatory processes in the Netherlands and the European Union, when no threshold is observed. The analyses by Lenters *et al*. (2011) were based on K_L [lung cancer potency factor of asbestos (US Environmental Protection Agency, 1986)] values with unrestricted intercepts for the linear exposure–response relationships. The intercept was not restricted on purpose. Exposure misclassification can influence slope, intercept, and standard error of an exposure–response relation (Armstrong, 1998). Simple random measurement error would lead to attenuation of the slope while, at the same time, resulting in higher intercept (pivoting around the mean). Restriction of the intercept would restrict the potential influence of measurement error and change the exposure–response slopes, which in turn might obscure associations with factors that influence the slope of an exposure–response relation. We explored associations between quality and exposure–response slopes using restricted K_L values published by others in a sensitivity analysis. This approach allowed a more accurate assessment of the influence of exposure assessment quality on heterogeneity and exposure–response slopes and it is thus not surprising that the K_L values presented in the study by Lenters *et al*. (2011) (their Supplementary table 5, available at *Annals of Occupational Hygiene* online) showed the strongest associations with exposure assessment quality parameters in comparison with the sensitivity analysis in which all K_L values with fixed intercept ($\alpha = 1$) were used (meta-K_L ratios for best and all studies were 4.2 and 1.3, respectively). The comparison of trends with our K_L values and those of Berman and Crump (2008a,b) in the commentary by Berman

and Case reflect this as well, but this was already explicitly discussed in the analysis by Lenters *et al.* (2011). Adjustment for effect of quality of a study, by increasing the standard error of the exposure–response slope of that particular study on the basis of a quality score, as done by Berman and Crump (2008a,b), involves scaling problems, leads to arbitrary adjustments, and ignores the fact that exposure misclassification not only reduces the power of a study but also introduces bias in exposure–response slopes.

Selective removal of studies

Berman and Case argue that we 'selectively exclude epidemiological studies . . . and then apply a meta-analysis to . . . truncated data' and suggest that we 'more rigorously conduct these sensitivity analyses', implying that our approach is biased and invalid. We do not arbitrarily exclude studies. In our work (Lenters *et al*., 2011), we explored whether five *a priori* defined quality criteria influence the meta-analytic risk estimates, using several different analytical approaches. First, we explored associations in a subgroup meta-analysis, stratifying all studies by these five exposure assessment covariates. In the next step, we evaluated an important determinant of risk differences, asbestos fiber type, in conjunction with these quality criteria, in univariate and multivariate meta-regression analyses. In this analysis, we observed that quality covariates were associated (for only a few, statistically significantly) with the meta-K_L, even when fiber was included in the model. An additional step would be to include more variables in the regression analysis, as suggested by Berman and Case. However, with 19 available data points, this is problematic and the models would be too unstable. Finally, in order to capture the influence of increasing quality, the meta-analysis was incrementally limited to those studies that satisfied the exposure assessment quality criteria. All different approaches clearly show that risk estimates increase with increasing quality. Detailed sensitivity analyses were provided in the supplementary material (available at *Annals of Occupational Hygiene* online) to demonstrate that using different sets of K_L values produced by different authors (Hodgson and Darnton, 2000; Berman and Crump, 2008a,b) and using K_L values derived with the upper cumulative exposure category excluded or with an intercept fixed to one did not affect our main conclusion (Lenters *et al*., 2011).

Given the low number of (observational) studies, we are not surprised that inclusion of quality covariates does not substantially reduce heterogeneity (I^2) or improve model fit (Akaike Information Criterion or AIC) associated with the meta-analyses.

For the separate, formal risk assessment exercise, the Health Council of the Netherlands has derived its proposed exposure standards for air levels of asbestos based on a subset of studies meeting certain quality criteria (Gezondheidsraad, 2010), as is common practice in regulatory settings and recommended by, for example, the Cochrane Collaboration.

Nonsignificant associations

Berman and Case also state that the observed differences were not significant, i.e. the *P* value was not below 0.05. This is a common misinterpretation of the *P* value in statistical analysis: A *P* value that exceeds 0.05 alone has no bearing on the issue of whether or not the effect parameter is equal to the null value (Ahlbom *et al*., 1990). In a recent statement from the Cochrane Collaboration: 'A moderate *P* value is often misinterpreted as evidence that there is no effect, whereas the correct interpretation is that there is not strong evidence for an effect' (Schünemann *et al*., 2009). The reader has to bear in mind that the body of evidence available for a meta-analysis of asbestos and lung cancer involved only 19 risk estimates—epidemiological studies with quantitative estimates of asbestos exposure and risk—and that heterogeneity among studies in occupational epidemiology is often larger than in other fields of epidemiology.

For all five quality criteria, we consistently find a difference varying from 1.3- to 6.3-fold in the univariate analyses, although several criteria were well above the significance threshold of 0.10 (Lenters *et al*., 2011) and could have arisen by chance. Based on the consistency of higher quality being linked with higher risk and the relevant magnitude of the observed difference, we deem it unlikely that this pattern was observed due to chance and propose that quality really does matter, as expressed in our publications (Burdorf and Heederik, 2011; Lenters *et al*., 2011) and illustrated again in the tables presented in this response.

Results of the sensitivity analyses are robust

Berman and Case (2012) are surprised that our sensitivity analysis, using the K_L values of Berman and Crump (2008b), leads to a meta-K_L of 0.06, where they presented a value of 0.30 using their modeling approach. We have been completely transparent in how our calculations were made, but differences can occur between meta-analyses depending on the way exposure–response slopes have been calculated, models have been chosen and specified, and

effects have been estimated. We derived K_L values by fitting Poisson regression models (with SAS PROC NLMIXED) and performed meta-analyses with untransformed K_L values and corresponding variances (derived from standard errors) using restricted maximum likelihood (REML) estimation methods in a random effects model [with SAS PROC MIXED (Thompson and Sharp 1999; van Houwelingen *et al*., 2002)]. In our elimination strategy, the between-study variance (determining the weight each study receives in the meta-analysis) varies when fewer studies are included in the meta-analysis. Berman and Case used log(K_L) values and corresponding standard deviations and applied a model 'identical to a random effect model', which was not made fully transparent. In modeling the study-specific K_L values, they also forced the K_L to be positive and the intercept to be <2, whereas for our primary analyses (Lenters *et al*., 2011), the K_L values were unrestricted (as described above). We can nearly reproduce their meta-estimates, and it seems their approach results in much less variability in the study weights in the random effects meta-analysis model than in our approach. In analyses with considerable heterogeneity, restricted maximum likelihood estimators are more appropriate to obtain unbiased estimates than maximum likelihood estimators (van Houwelingen *et al*., 2002). Thus, we are not surprised that these different input and modeling choices have led to discrepancies between the results of meta-analyses conducted by Berman and Case and us. However, when we repeated the analyses with our set of K_L values and the modeling approach applied by Berman and Case (2012), similar trends were observed between the study quality parameters and meta-K_L values.

Berman and Case (2012) present their alternative sensitivity analysis to demonstrate that 'there appears to be little to no evidence from the indicated analyses to suggest that a systematic effect of study quality on K_L or K_M values'. This suggests that our primary and sensitivity analyses are incorrect and that we drew the wrong conclusion. We counter that our various analytical approaches— stratification, univariate and multivariate meta-regressions, and exclusion based on exposure assessment covariates—consistently demonstrated that quality of exposure assessment has an impact on K_L values. Increased meta-K_L values were particularly evident for two covariates: greater coverage of the exposure history by exposure measurement data, and more complete job histories. We originally provided extensive sensitivity analyses in our supplementary material to the meta-analysis, including a more 'objective' exclusion table in which studies were eliminated based on the number of criteria they failed to meet rather than in a certain order, which yielded similar results (Supplementary table 2 of Lenters *et al*., 2011, available at *Annals of Occupational Hygiene* online). In addition, the significance criteria applied by Berman and Case (2012), in which they evaluate tests for trends in their commentary, is overly conservative ($P < 0.01$: strong association; $0.01 < P < 0.03$: marginal; $0.03 < P < 0.05$: no trend) and beyond any mainstream use of statistical significance. A more transparent presentation of correlations and P values would have been preferred.

We now supply results from additional jackknifing analyses, in which we remove each study one-by-one to explore the difference between the meta-K_L values based on all studies versus the meta-K_L values based on studies with the fewest exposure assessment quality issues (Table 1). It is clear from the results that the overall trend of increasing meta-K_L values is generally stable, although two studies are influential: the trend is weaker when Study 4, of predominantly chrysotile-exposed workers from a textile plant in South Carolina (Hein *et al*., 2007) is excluded; conversely, when Study 9, of predominantly amphibole-exposed workers from a mine near Libby, Montana (Sullivan, 2007), is excluded, differences between the overall K_L value and the K_L value based on the best studies becomes much more pronounced. This contradicts the results presented by Berman and Case (2012; in their table 2) with information about the P values of rank correlation tests, and we disagree with their statement that removal of Libby, another high-quality study, does not affect results.

We also included sensitivity analyses for the two other analytical approaches, subgroup meta-analysis (Table 2) and meta-regression analysis (Table 3), in which we present the original results based on K_L values from all 19 cohorts and new results with the K_L from the South Carolina cohort (Hein *et al*., 2007) excluded from analyses. As expected, exclusion of South Carolina, the cohort with the second largest K_L estimate [refer to figure 1 in Lenters *et al*. (2011)], influenced the results. However, the pattern that a meta-analysis of higher-quality studies yields larger meta-K_L values and that covariates capturing the quality of the exposure assessment are associated with K_L values still holds.

Finally, we included a sensitivity analysis, which demonstrates that changing the order of exclusion based on covariates does not change the overall trend (Table 4), in contrast to what Berman and Case suggest in their commentary. These sensitivity analyses show that the trend of increasing estimates (meta-K_L

Table 1. Results from the meta-analysis (meta-K_L values) in which studies were excluded stepwise with exposure assessment descriptors: a sensitivity analyses in which we leave out one study at a time.

Incremental exclusion[a]	**Original results**	**No. of studies**	**Meta-K_L × 100**[b]																		
			Study number[c] **excluded**																		
			1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
None	0.13	18	0.16	0.16	0.14	0.10	0.15	0.10	0.10	0.14	0.13	0.14	0.13	0.13	0.13	0.16	0.16	0.14	0.12	0.11	0.13
-studies with insufficient documentation	0.18	10–11	0.24	0.20	0.15	0.13	0.22	0.16	0.16	0.20	0.19	0.19	0.18	0.18	0.18	0.20	0.23	0.19	0.17	0.15	0.18
-studies with external conversion factors	0.19	8–9	0.26	0.21	0.15	0.12	0.24	0.17	0.17	0.22	0.19	0.20	0.19	0.19	0.19	0.21	0.21	0.20	0.19	0.16	0.19
-studies with insufficient job histories	0.36	4–5	0.37	0.37	0.35	0.25	0.36	0.35	0.35	0.49	0.41	0.36	0.36	0.36	0.36	0.37	0.37	0.35	0.36	0.34	0.35
-studies with cumulative exposure ratio ≤50	0.56	2–3	0.58	0.58	0.54	0.24	0.58	0.55	0.55	0.57	1.69	0.56	0.56	0.56	0.56	0.58	0.58	0.57	0.56	0.55	0.55
-studies with coverage ≤30%	0.55	1–2	0.57	0.56	0.53	0.23	0.57	0.53	0.54	0.55	1.64	0.55	0.55	0.55	0.55	0.57	0.57	0.55	0.54	0.54	0.55
Ratio of best to all studies	4.2		3.6	3.5	3.8	2.3	3.8	5.3	5.4	3.9	12.6	4.2	4.2	4.2	4.2	3.6	3.6	3.9	4.5	4.9	4.2

[a]See Lenters *et al*. (2011) for a description of the exposure assessment covariates. 1. Study authors insufficiently described the exposure assessment; 2. Impinger-based measurements of particles (million particles per cubic foot) were converted to fibers per milliliter with an external or generic factor (instead of an internally derived factor based on paired measurements in the department or environment under study); 3. Job history information was insufficiently complete or detailed; 4. Ratio of highest to lowest cumulative exposure category, as an indication of contrast in exposure (50 represented the median among the 19 studies); 5. Proportion of the exposure history that was temporally covered by exposure measurement data.
[b]Analyses (Tables 1–4) were performed with a random effects model (REML) and K_L values and variances extracted from Lenters *et al*. (2011).
[c]Study numbers correspond to the following industry-based cohorts: 1. Quebec, Canada, mines and mills; 2. Italy, mines and mills; 3. Connecticut, friction products plant; 4. South Carolina, textile plant; 5. North Carolina, textile plants; 6. Wittenoom, Australia, mines; 7. Paterson, NJ, insulation factory; 8. Tyler, TX, insulation factory; 9. Libby, MT, vermiculite mines and mills; 10. UK, friction products factory; 11. Ontario, Canada, cement plant; 12. New Orleans, LA, cement plants; 13. Sweden, cement plant; 14. Belgium, cement plant; 15. USA, factory retirees; 16. USA and Canada, insulation workers; 17. Pennsylvania, textile plant; 18. Rochdale, UK, textile plant; and a population-based case–control study, and 19. Stockholm County, Sweden. Refer to Lenters *et al*. (2011) for complete references.

Table 2. Univariate associations between K_L factors stratified on fiber type and different characteristics of exposure assessment.

Inclusion	**Original results (Lenters *et al.*, 2011)**			**Excluding South Carolina (Study #4)**	
	Meta-K_L × 100(95% CI)	*P* value[a]	Studies included	Meta-K_L × 100(95% CI)	*P* value[a]
All studies	0.13 (0.04, 0.22)	–	1–19	0.10 (0.02, 0.18)	
Fiber					
Chrysotile[b]	0.04 (−0.05, 0.12)		1–5	0.03 (−0.03, 0.08)	
Amphiboles	0.33 (0.09, 0.56)	0.06[c]	6–9	0.32 (0.10, 0.55)	0.02[c]
Mixed	0.13 (0.03, 0.23)		10–19	0.12 (0.03, 0.21)	
Amphiboles & mixed	0.18 (0.07, 0.29)	0.10[d]	6–19	0.17 (0.07, 0.26)	0.04[d]
Documentation					
Insufficient[b]	0.11 (–0.04, 0.26)	0.46	2, 3, 6, 7, 10, 11, 14, 16	0.09 (–0.03, 0.21)	0.66
Sufficient	0.18 (0.04, 0.33)		1, 4, 5, 8, 9, 12, 13, 15, 17–19	0.13 (0.01, 0.24)	
CE ratio (highest:lowest exposure category)					
≤50[b]	0.10 (–0.05, 0.26)	0.38	2, 3, 8, 11, 13, 15–18	0.09 (–0.03, 0.22)	0.66
>50	0.20 (0.04, 0.35)		1, 4–7, 9, 10, 12, 14, 19	0.13 (0.01, 0.25)	
Conversion factor (mppcf to f-ml/yr)					
External or never PCM[b]	0.12 (–0.07, 0.30)	0.69	3, 7, 11, 15–17	0.10 (–0.05, 0.25)	0.85
Internal or always PCM	0.16 (0.03, 0.28)		1, 2, 4–6, 8–10, 12–14, 18, 19	0.11 (0.01, 0.22)	
Coverage of exposure data					
≤30%[b]	0.08 (–0.01, 0.18)	0.08	1, 2, 3, 6–8, 10, 13–16, 19	0.07 (–0.01, 0.15)	0.17
>30%	0.27 (0.08, 0.46)		4, 5, 9, 11, 12, 17, 18	0.20 (0.03, 0.37)	
Job histories					
Insufficient[b]	0.03 (–0.10, 0.17)	0.08	1, 3, 5, 11, 12, 13	0.03 (–0.07, 0.13)	0.08
Sufficient	0.19 (0.08, 0.30)		2, 4, 6, 7, 8–10, 14–19	0.15 (0.05, 0.24)	

[a]Difference between subgroups (*F*-test).
[b]Reference category in meta-regression analyses.
[c]Test for difference between meta-K_L values for chrysotile, amphiboles, and mixed strata.
[d]Test for difference between meta-K_L values for chrysotile versus the amphiboles and mixed strata.
CE = cumulative exposure; PCM=phase contrast microscopy; mppcf=million particles per cubic foot; f-ml/yr= fibers/ml*year

values) of asbestos-lung cancer potency with increasing exposure assessment quality is robust.

How should we conduct meta-analyses and what evidence should we include?

There is a more fundamental underlying issue at stake in this exchange of arguments. Should we allow poorly documented evidence and studies that will not pass present scientific criteria for well-designed and conducted epidemiological studies to be incorporated into meta-analyses? And should we only dismiss such evidence when there are significant associations between quality and study outcome *a posteriori*? The real issue in this debate is how information on quality of a set of studies should be used in meta-analyses and, ultimately, in risk assessments. It is common practice in evidence-based medicine to draw conclusions on the most informative studies, i.e. the studies of the highest quality. The Health Council of the Netherlands has derived the new exposure standards on the basis of studies with an acceptable quality. Earlier reviews of the National Research Council and the Environmental Protection Agency (1986), the Health Effect Institute (1991) in the USA, and Doll and Peto (1985) from the Health and Safety Executive in the UK on health effects of asbestos all considered quality of the exposure assessment. Already in 1985, Doll and Peto commented, when considering which studies should be used for more detailed risk calculations '. . . *The reliability of exposure estimates is therefore crucial to any comparison either of different sectors or of different studies within a sector. This cannot be assessed until the original measurements and the basis for particle to fibre conversion have been published in detail. As this has not been done, we have*

Table 3. Univariate and multivariate meta-regression models of lung cancer potency (K_L), with fiber type and exposure assessment covariates modeled as independent variables.

Model	**Original results** (Lenters *et al*., 2011)			**Excluding South Carolina (study #4)**		
	β-Coefficient (95% CI)	*P* value	AIC	β-Coefficient (95% CI)	*P* value	AIC
Univariate						
Fiber: amphiboles/mixed	0.13 (–0.03, 0.29)	0.10	28.7	0.14 (0.005, 0.28)	0.04	14.9
Documentation: sufficient	0.07 (–0.13, 0.28)	0.46	30.6	0.04 (–0.13, 0.21)	0.66	19.0
CE ratio: >50	0.09 (–0.13, 0.31)	0.38	30.3	0.04 (–0.14, 0.21)	0.66	19.1
Conversion factor: internal	0.04 (–0.18, 0.26)	0.70	30.8	0.02 (–0.17, 0.20)	0.85	19.1
Coverage of exposure data: >30%	0.19 (–0.02, 0.40)	0.08	27.6	0.13 (–0.06, 0.31)	0.17	16.9
Job histories: sufficient	0.16 (–0.02, 0.33)	0.08	27.9	0.12 (–0.02, 0.25)	0.08	16.2
Multivariate: fiber + covariate						
Fiber: amphiboles/mixed	0.14 (–0.03, 0.32)	0.09	30.9	0.16 (0.01, 0.30)	0.04	17.6
Documentation: sufficient	0.08 (–0.09, 0.25)	0.34		0.06 (–0.09, 0.21)	0.39	
Fiber: amphiboles/mixed	0.15 (–0.04, 0.34)	0.12	30.9	0.16 (0.003, 0.32)	0.05	17.8
CE ratio: >50	0.09 (–0.10, 0.28)	0.33		0.05 (–0.11, 0.21)	0.48	
Fiber: amphiboles/mixed	0.15 (–0.02, 0.32)	0.08	31.0	0.16 (0.01, 0.32)	0.04	17.5
Conversion factor: internal	0.07 (–0.11, 0.26)	0.40		0.06 (–0.10, 0.22)	0.43	
Fiber: amphiboles/mixed	0.13 (0.00, 0.26)	0.05	27.1	0.14 (0.01, 0.26)	0.03	15.2
Coverage of exposure data: >30%	0.18 (0.01, 0.36)	0.04		0.14 (–0.03, 0.31)	0.11	
Fiber: amphiboles/mixed	0.05 (–0.22, 0.31)	0.71	30.1	0.13 (–0.10, 0.37)	0.25	17.4
Job histories: sufficient	0.13 (–0.14, 0.40)	0.31		0.03 (–0.21, 0.26)	0.82	

Fiber types amphiboles and mixed exposures were grouped. For each covariate (fiber type and five exposure assessment covariates), a reference category was chosen as denoted in Table 2.
CE=cumulative exposure

felt constrained to exclude other studies from further consideration, but we do not wish to imply that none of them can provide useful data.' Since this evaluation, for a few studies, updated documentation of the exposure assessment component has been published. Similarly, in a more recent evaluation, the Health Effect Institute considered 14 cohort studies, of which only four were deemed to have a sufficient quality of exposure data to be used in a quantitative risk assessment for asbestos. What is different in our meta-analysis is that we propose a transparent approach to evaluate how various aspects of the exposure assessment component of retrospective cohort studies affect lung cancer risk estimates for asbestos. We have not limited ourselves to the classical issues on fiber type and fiber conversion but have also incorporated more general quality aspects of the exposure assessment strategy.

We also think that this approach will contribute to methodological improvements in risk assessment and will also help occupational hygienists and epidemiologists to design better studies. Application of these concepts, involving benzene exposure, also clearly shows that study quality is associated with higher meta-risks (Vlaanderen *et al*., 2011). Unfortunately, most studies on asbestos involve the pre- and post-World War II period, the early stages of development of occupational epidemiology. Major methodological developments in occupational epidemiology, especially in exposure assessment, started in the 1970s and have continued into this century. Many of the asbestos cohort studies would have been conducted differently with present knowledge on exposure assessment in occupational epidemiology. The only way the historical asbestos studies can be informative for current risk assessment is to select those studies that have been performed according to minimal quality standards. This approach is also in line with the precautionary principle in risk assessment, as adopted in the European Union. We acknowledge that there is not yet a scientific consensus on what the quality threshold for inclusion of (observational) studies should be, although some efforts have been made to tackle this issue (e.g. Swaen 2006; Vlaanderen *et al*., 2008).

Both in our commentary as in the meta-analysis (Burdorf and Heederik, 2011; Lenters *et al*., 2011), we leave open the possibility that differences between studies in potency estimates per unit of exposure can be explained by other factors

Table 4. Results from the meta-analysis (meta-K_L values) in which studies were excluded stepwise with exposure assessment descriptors: a sensitivity analyses in which we vary the order of exclusion.

Sequence of incremental exclusion	No. of studies	Meta-K_L × 100
0. None (all 19 studies)	19	0.13
1. Studies with insufficient documentation	11	0.18
2. Studies with external conversion factors	9	0.19
3. Studies with insufficient job histories	5	0.36
4. Studies with CE ratio ≤50	3	0.56
5. Studies with coverage ≤30%	2	0.56
0. None (all 19 studies)	19	0.13
5. Studies with coverage ≤30%	7	0.27
4. Studies with CE ratio ≤50	4	0.25
1. Studies with insufficient documentation	4	0.25
2. Studies with external conversion factors	4	0.25
3. Studies with insufficient job histories	2	0.55
0. None (all 19 studies)	19	0.13
3. Studies with insufficient job histories	13	0.19
2. Studies with external conversion factors	9	0.19
1. Studies with insufficient documentation	5	0.35
4. Studies with CE ratio ≤50	3	0.56
5. Studies with coverage ≤30%	2	0.55
0. None (all 19 studies)	19	0.13
5. Studies with coverage ≤30%	7	0.27
3. Studies with insufficient job histories	4	0.52
4. Studies with CE ratio ≤50	2	0.55
1. Studies with insufficient documentation	2	0.55
2. Studies with external conversion factors	2	0.55
0. None (all 19 studies)	19	0.13
2. Studies with external conversion factors	13	0.16
1. Studies with insufficient documentation	9	0.19
4. Studies with CE ratio ≤50	6	0.18
5. Studies with coverage ≤30%	4	0.25
3. Studies with insufficient job histories	2	0.55

CE=cumulative exposure

than quality alone. These other factors include misclassification of the endpoint, average age at first exposure, residual confounding due to smoking, fiber type, and differences in distributions of fiber dimensions between industries. The recent reanalysis with contemporary technology of the dust samples from the South Carolina cohort study are of great interest (Dement *et al*., 2011; Loomis *et al*., 2012). Further studies that examine these other factors are welcomed. On the basis of our meta-analysis, we concluded that for lung cancer potency, differences between chrysotile versus amphibole asbestos-exposed cohorts become difficult to ascertain when the analysis is restricted to studies with fewer exposure assessment limitations (Lenters *et al*., 2011).

In conclusion, we remain confident that we have demonstrated in our meta-analysis that quality of exposure assessment influences the magnitude of the asbestos-lung cancer exposure–response slope. Although asbestos is one of the best studied occupational risk factors, there still remains uncertainty as to the relative importance of specific exposure characteristics. We strongly argue that the existence of this uncertainty should not hamper the development of appropriate evidence-based guidelines and stringent policies in order to protect the public from environmental and occupational exposures. We cannot agree more that there is a need for sound science when evaluating the health risks of asbestos to support risk assessments.

SUPPLEMENTARY DATA

Supplementary data can be found at http://annhyg.oxfordjournals.org/.

FUNDING

Health Council of the Netherlands to Institute for Risk Assessment Sciences, Utrecht University.

Acknowledgements—A.B. and D.H. were members of the Committee on Asbestos of the Health Council.

Disclaimer—The findings and conclusions in this article reflect the opinions of the authors and should not be construed to represent a statement of the Health Council of the Netherlands.

REFERENCES

Ahlbom A, Axelson O, Støttrup Hansen ES *et al.* (1990) Interpretation of "negative" studies in occupational epidemiology. Scand J Work Environ Health; 16: 153–7.

Armstrong BG. (1998) Effect of measurement error on epidemiological studies of environmental and occupational exposures. Occup Environ Med; 55: 651–6.

Berman DW, Case BW. (2012) Overreliance on a single study: there is no real evidence that applying quality criteria to exposure in asbestos epidemiology affects the estimated risk. Ann Occup Hyg; 56: 869–78.

Berman DW, Crump KS. (2008a) A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. Crit Rev Toxicol; 38 Suppl 1: 49–73.

Berman DW, Crump KS. (2008b) Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol; 38 Suppl 1: 1–47.

Burdorf A, Heederik D. (2011) Applying quality criteria to exposure in asbestos epidemiology increases the estimated risk. Ann Occup Hyg; 55: 565–8.

Dement JM, Loomis D, Richardson D *et al.* (2011) Estimates of historical exposures by phase contrast and transmission electron microscopy for pooled exposure–response analyses of North Carolina and South Carolina, USA asbestos textile cohorts. Occup Environ Med; 68: 593–8.

Doll R, Peto J. (1985) Effects on health of exposure to asbestos. A review prepared at the request of the Health and Safety Commission. London: HMSO.

Gezondheidsraad. (2010) Asbestos— risks of environmental and occupational exposure. Report 2010/10E. The Hague: Health Council of the Netherlands, Available at www.gezondheidsraad.nl/en/publications/asbestos-risks-environmental-and-occupational-exposure. Accessed on July 18, 2012.

Health Effects Institute. (1991) Asbestos in public and commercial buildings: a literature review and synthesis of current knowledge. HEI-Asbestos Research. Cambridge, MA: HEI.

Hein MJ, Stayner LT, Lehman E *et al.* (2007) Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. Occup Environ Med; 64: 616–25.

Hodgson JT, Darnton A. (2000) The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg; 44: 565–601.

Lenters V, Vermeulen R, Dogger S *et al.* (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: 1547–55.

Loomis D, Dement JM, Elliott L *et al.* (2012) Increased lung cancer mortality among chrysotile asbestos textile workers is more strongly associated with exposure to long thin fibres. Occup Environ Med; 69: 564–8. doi:10.1136/oemed-2012–100676.

National Research Council (NRC). (1984) Asbestiform fibers: nonoccupational health risks. Washington, DC: National Academy Press.

Schünemann HJ, Oxman AD, Vist GE *et al.* (2009) Interpreting results and drawing conclusions. In Higgins JPT and Green S, editors. Cochrane handbook for systematic reviews of interventions. Chichester, United Kingdom: Wiley-Blackwell. pp. 359–87.

Sullivan PA. (2007) Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. Environ Health Perspect; 115: 579–85.

Swaen GM. (2006) A framework for using epidemiological data for risk assessment. Hum Exp Toxicol; 25: 147–55.

Thompson SG, Sharp SJ. (1999) Explaining heterogeneity in meta-analysis: a comparison of methods. Stat Med; 18: 2693–708.

U.S. Environmental Protection Agency. (1986) Airborne Asbestos Health Assessment Update. EPA 600/8–84/003F. Research Triangle Park, NC: Environmental Criteria and Assessment Office.

van Houwelingen HC, Arends LR, Stijnen T. (2002) Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med; 21: 589–624.

Vlaanderen J, Lan Q, Kromhout H *et al.* (2011) Occupational benzene exposure and the risk of lymphoma subtypes: a meta-analysis of cohort studies incorporating three study quality dimensions. Environ Health Perspect; 119: 159–67.

Vlaanderen J, Vermeulen R, Heederik D *et al.* (2008) Guidelines to evaluate human observational studies for quantitative risk assessment. Environ Health Perspect; 116: 1700–5.