WATCH/2008/5
Annex 1

Asbestos : Revising the overall summary analysis of cohorts – "Approach 2"

Introduction and summary

This annex sets out the results of work on "Approach 2" as set out in *The risks of lung cancer and mesothelioma from relatively low-level exposures to different forms of asbestos - proposal for progressing this issue* (WATCH/2008/3). It is set out in the following sections:

> Section 1: A reminder of the approach used for developing quantitative risk models in the original Hodgson and Darnton 2000[1] paper (referred to subsequently as HD2000).
>
> Section 2: An analysis of the influence of each data point in HD2000 to determine whether different decisions about the values of model parameters would be made in the absence of each point.
>
> Section 3: A summary of updated information available in the literature not included in HD2000
>
> Section 4: An assessment of the impact on the models when updated and additional information (from section 4) is included in the analysis.
>
> Section 5: An assessment of the impact on the models by excluding studies where the exposure data is likely to be less reliable.

The main focus will be on the 11 'pure fibre' cohorts in HD2000 plus 5 additional relevant cohorts identified from the literature. These are listed in Table 1 below using the cohort names and numbers adopted in HD2000 as well as the labels for the 3 main fibre types ('o', 'a', and 'y' for crocidolite, amosite and chrysotile respectively). An additional short label for each cohort is introduced here which will be used in various tables and charts in this annex. More detail on the additional 5 cohorts is given in section 4.

The final column of Table 1 gives a rating for each cohort (1=more reliable; 2=less reliable) which is based on the assessment of exposure data carried out in Approach 1 by Garry Burdett (see Annex 2) and the uncertainty factors assigned to each cohort by Berman and Crump to take account of the reliability of the exposure data. More details are given in section 4 but it is provided in the Table at the outset as part of the summary of which are the key cohorts underlying the HD2000 risk models and which are likely to be most reliable.

Table 1: Summary of original 11 and 5 additional ‘pure fibre’ cohorts

	HD number	Short label	HD name	Fibre type	Reliability rating
Original 11 pure fibre cohorts	1	Wit	Witttenoom	o	1
	13o	SA-o	SA crocidolite mine	o	2
	14	Mas	Massachusetts	o	2
	12	Pat	Paterson	a	2
	13a	SA-a	SA amosite mine	a	2
	2f	Car-f	Carolina (women)	y	1
	2m	Car-m	Carolina (men)	y	1
	5y	NOr	New Orleans (chrysotile sub-cohort)	y	2
	6	Que	Quebec	y	1
	10	Bal	Balangero	y	1
	16	Con	Connecticut	y	2
Additional pure fibre cohorts (described in more detail in section 4)	26	Tyl	Tyler amosite insulators	o	2
	27	Lib	Libby vermiculite miners	t*	1
	28	Wit-e	Wittenoom environs	o	1
	29	Que-e	Quebec environs	y	1
	30	Lib2	Libby miners and other workers	t*	1

*t=tremolite

Summary

- The HD2000 analysis used a single measure of risk per unit of cumulative exposure for total (ie pleural+peritoneal) mesothelioma (R_M) and lung cancer (R_L) for each cohort and compared the consistency of these values within groups of cohorts for each of the pure fibre types.

(Note R_M and R_L are thus equivalent to the proportionality constants in a linear dose response model: Risk = $R_{M \text{ or } L}$ x [Cumulative exposure])

Table 2: Original summary values of R_M and R_L for each fibre type were:

Fibre type	% mesothelioma risk per unit exposure (R_M)	% excess lung cancer risk per unit exposure (R_L)
Crocidolite (o)	0.5	5
Amosite (a)	0.1	
Chrysotile (y)	0.001	0.1

- Although the total mesothelioma risk within the range of exposures considered looks broadly linear, separate consideration of the risk of pleural and peritoneal mesothelioma led to the investigation of non-linear models for each type of the form: Risk (denoted 'P_M') = Constant x [Cum. Exp.] ^{x}
- In the best fitting model for pleural mesothelioma x=0.75 and for peritoneal mesothelioma x=2.1 with separate constants for the fibre types (zero in the case of peritoneal mesothelioma due to chrysotile).

- For lung cancer, a model of the same form was considered and the best fitting value of the slope (ie the power of cumulative exposure) was x=1.3 with separate constants for amphibole (crocidolite and amosite taken together) and chrysotile.

- Consideration of the impact of each data point on the fitted models suggests that similar decisions about the most plausible values of the model coefficients would have been made in the absence of any one of the data points.

- Extended follow-up has now been reported for three of the cohorts (Wit, Car-m and Car-f) and using updated data had minimal impact the summary values of R_M and R_L or on the estimated non-linear model coefficients.

- Five additional cohorts not included in HD2000 were available with data suitable for inclusion in the analysis. Two of these were of particular value (the Wittenoom and Quebec environs cohorts) and the Libby cohorts also had relatively good quality data. However, the type of fibre at Libby was different to the crocidolite / amosite considered in the other studies.

- Though no one particular data point can be considered to stand out in terms of underlying data reliability, and therefore to give a more precise estimate of the risk at a given cumulative exposure, the inclusion of the additional data points in the analysis does tend to corroborate the original picture provided by HD2000, particularly for mesothelioma.

Section 1. Summary of approach for developing original quantitative risk models by Hodgson and Darnton 2000

1.1 Deriving values for risk per unit exposure for pure fibre cohorts

Having calculated the summary measures for mesothelioma risk (P_M) and lung cancer risk (P_L), and the average cumulative exposure (X) for each cohort, we started by considering the consistency of the risk per unit exposure for each disease (ie R_M=P_M/X and R_L=P_L/X) within the groups of pure fibre cohorts and mixed fibre cohorts. The results for mesothelioma are in Table 1 and Fig 2 of HD2000 and those for lung cancer are in Table 2 and Fig3. The average values or R_M and R_L for these groupings are thus equivalent to the proportionality coefficients for a linear dose model with separately slopes for each fibre type (ie P=R*X).

Table 3: Summary of consistency in R_M and R_L values

Summary	**Total mesothelioma** **(HD2000 Tab 1 Fig 2):** R_M values are statistically consistent among the three groups of pure fibre cohorts – though less so for chrysotile, and mixed cohorts not consistent.	**Lung cancer** **(HD2000 Tab 2 Fig 3):** Less consistency – particularly for pure chrysotile cohorts. This is mainly due to risk at Carolina being 2 orders of magnitude higher than mine cohorts
Crocidolite (o) cohorts	3 cohorts (Mas, Wit and SA-o) closely grouped around the mean (mean R_M=0.51). We note that if the exposure for Wit is increased by x4 – as some have suggested – the statistical consistency is lost.	R_L for 5 amphibole cohorts not statistically consistent – mainly due to lower risk for SA-a. Remaining 4 are consistent but not if the Wit exposure is increased by x4.
Amosite (a) cohorts	2 cohorts (Pat, SA-a) close to mean R_M (=0.10)	
Chrysotile (y) cohorts	6 cohorts (Car-m, Bal, Que, Car-f, NOr, Con). Only first 3 have any mesotheliomas. R_M similar for Bal and Que (~0.0015) but an order of magnitude higher for Car-m (=0.013). However, small numbers mean that cohorts are statistically consistent – but consistency improved when Car-m excluded (which gives mean R_M=0.001)	6 cohorts fall into two groups: Car-m and Car-f similar (R_L=6%). Other 4 cohorts are statistically consistent, dominated by Queb with R_L=0.06% - though NOr and Con substantially higher than the mine cohorts with R_L at about 1%
Mixed cohorts	R_M covers the whole range of values – and no obvious pattern with industry process or particular fibre mix	Substantial heterogeneity due to high values for Ontario and low values for Johns Manville, with US/Canada insulators in the middle

We go on to conclude that for mesothelioma, the reasonably consistent picture for the pure fibre cohorts suggests that R_M values for the o, a, and y cohorts are broadly in the ratio 500:100:1.

We suggest that a value of R_L=5% is reasonable for the amphibole cohorts, but it is not obvious what value should be chosen for chrysotile because of the inconsistency. We note various potential explanations for the discrepancy between the chrysotile mines (Que and Bal) and the Carolina cohorts (Car-m and Car-f):

1. The mineral oil hypothesis? Case-control analyses by Dement show some suggestion that mineral oil may enhance the asbestos effect – and this may be consistent with Rochdale data.
2. Longer fibres in textile processing? We concluded that this doesn't appear to be supported by analysis of lung fibre burdens by Sebastien et al (though Berman and Crump interpret these analyses as supporting this hypothesis). However, there is some evidence that longer fibres were present at Carolina – and experimental studies have shown longer fibres to be more carcinogenic.
3. Contamination with amphibole? Crocidolite was used in small quantities after 1950 at Carolina – but Sebastien found amphibole fibres only in the lungs of those exposed before 1940. Green found higher levels of amphibole than among local population controls – but only in 1 of the 10 lung cancers examined had amphibole fibres. If amphibole contamination is the explanation it is not consistent with the other two textile cohorts with mixed fibre exposures (Roc and Pen) which both have lower values of R_L than Carolina.
4. Might the cohort average approach to exposures overestimate the risk? Internal analyses of the Carolina cohort by Dement suggest R_L estimates of 1 for women and 3 for men (compared with 6.7 and 4.6 based on our approach).
5. Is the mppcf-f/ml conversion factor too low? If this was 6 instead of 3 (as suggested by McDonald etal 1983a) then our values of R_L for Carolina would be halved.

The value of R_L=0.1% chosen for chrysotile is based on the following argument:

Setting aside the possibility that amphibole presents a higher risk of lung cancer, the mixed cohorts can be used to indicate what sort of level might be typical for chrysotile. Median R_L=0.5 for the 16 cohorts with some chrysotile exposure (an order of magnitude low than Car-m (4.5) and Car-f (6.7)). But given that amphibole is likely to have larger effect within the mixed cohorts the summary value should be set lower than this – probably substantially given the difference between the amphibole risk (5%) and the risk due to the (consistent) mixed cohorts (0.32%) suggest that amphibole could account for most of the risk. The risk for "commercial" chrysotile based on the mining cohorts is 0.06% so the chrysotile risk must be at least as high as this – and a value of 0.1% would allow for some additional risk due to processing of chrysotile and this is taken to be the best estimate. (We take 0.5% to be a "cautious" estimate of R_L).

1.2. Extrapolation to low doses

We go on to suggest that if the relationship between exposure and response was non-linear then the impact on low dose extrapolations could be dramatic. We discuss evidence for non-linearity in the mesothelioma dose-response based on comparisons of pleural and peritoneal mesotheliomas. Plotting percent peritoneal mortality against percent pleural mortality (ie P_M for peritoneal mesothelioma against P_M for pleural) doesn’t require quantitative exposure data and this allowed an additional 8 cohorts to be considered. The plot (HD2000 Fig 5) suggests two alignments – one for amosite and one for croc – both with a similar slope – implying that the peritoneal rate is proportional to at least the square and perhaps even the cube of the pleural rate. (If the two anomalous points – Canadian and Leyland gas masks – are left out the ratio is 3.2; if left in it is 2.4.) Whatever the physical/biological explanation, these observations suggest that at least one of the outcomes has a non-linear relationship with exposure. We suggest that support for a slope <1 relationship for pleural meso is also supported by the Wittenoom dose-specific analyses by Berry 1991.

1.3. Developing the dose-response model

Separate fits to the pleural and peritoneal mesothelioma data for which quantitative exposure estimates *are* available suggests separate lines with a common slope for all three fibre types for pleural mesothelioma, and separate lines with a (different) common slope for amosite and croc for peritoneal mesothelioma. Since a range of slopes are consistent with the data, the ratio of peritoneal to pleural slopes from the analysis which doesn’t depend on quantitative exposure data (between 2.4 and 3.2) is then used to inform the final choice of slopes for pleural and peritoneal meso (0.75 and 2.1 – ratio=2.8).

For lung cancer, the full chrysotile dataset suggests a negative slope – this is due to Carolina. Without this point the slope is fairly flat. For amphibole the Mas and SA-a cohorts are influential in the slope being >1. Excluding these gives a best slope of 1.4 with a CI that includes 1. We take the best model to have a slope of 1.3 (the mid point of the plausible range of slopes 1.0-1.6) based on the amphibole cohorts. Given that the chrysotile cohorts alone don’t provide sufficient basis for estimating the slope we take the same slope for chrysotile – and determine the scaling constant (A_L) by fixing the predicted excess mortality at the median exposure for chrysotile cohorts (70 f/ml.yr) to 0.1% (best estimate) or 0.5% (cautious estimate).

Finally to reiterate the point that the Mas cohort has a strange effect – it tends to force the pleural meso slope below 1 and force the lung slope above 1. This means that if the exposure estimate is wrong it will make one of these slopes depart from 1 even more. For example, if the exposure is overestimated it will make the lung cancer slope even steeper above 1 (and the pleural slope steeper but closer to 1 from below). If the exposure is underestimated it will make the lung slope closer to 1 from above, but flatten the pleural slope moving it further away from 1 from below.

Section 2. Assessment of how sensitive the original models are to key data points

The process described above uses makes use of all 20 cohorts selected – plus an additional 8 cohorts for which no quantitative exposure data was available. However, those that are most important in the development of the risk models are the 11 pure fibre cohorts described in Table 1 as these provide the data points used in the actual model fitting.

As a starting point for considering how robust the quantitative risk models are, the influence of each data point on the fitted parameters was assessed by refitting the model excluding each in turn. The relevance of this exercise is to assess whether different decisions about the value of the slope parameters are likely to have been made in the absence of each data point.

2.1 Mesothelioma

Table 4 shows the fitted parameter values for the common slope model for pleural mesothelioma ($P_M = A_{(fib)}.X^r$ where, P_M=% excess mesothelioma mortality, X=cumulative asbestos exposure, $A_{(o)}$, $A_{(a)}$ and $A_{(y)}$ are the regression coefficients for crocidolite, amosite and chrysotile, and r is the fitted slope), peritoneal mesothelioma (same model form but with coefficients $A'_{(o)}$, $A'_{(a)}$, and slope t), and the ratio of pleural to peritoneal slopes, t/r.

Table 4: Parameter estimates for original mesothelioma risk models fitted with each data point excluded

		Pleural mesothelioma					Peritoneal mesothelioma				
Model		slope, r	$A_{(o)}$	$A_{(a)}$	$A_{(y)}$	Cooks distance	Slope, t	$A'_{(o)}$	$A'_{(a)}$	Cooks distance	t/r
Including all cohorts original cohorts		0.75	0.93	0.13	0.0047	-	2.1	0.0022	0.00060		
Amphibole only		0.77	0.87	0.12	-	-					
Excluding....											
1	Wit	0.76	1.02	0.13	0.0045	0.28	2.05	0.0028	0.00073	0.05	2.71
13o	SA-o	0.79	0.79	0.11	0.0036	0.04	2.14	0.0019	0.00052	0.01	2.69
14	Mas	0.76	0.92	0.13	0.0045	0.00	2.25	0.0014	0.00033	0.07	2.97
12	Pat	0.69	1.13	0.12	0.0069	0.28	2.06	0.0025	0.00053	0.26	2.99
13a	SA-a	0.69	1.13	0.20	0.0069	0.11	2.06	0.0025	0.00075	0.01	2.99
2m	Car-m	0.87	0.65	0.09	0.0022	0.07					2.42
2f	Car-f	0.71	1.05	0.15	0.0060	0.01					2.95
6	Que	0.87	0.65	0.09	0.0039	4.07					2.42
10	Bal	0.78	0.85	0.12	0.0038	0.01					2.69
16	Con	0.69	1.12	0.17	0.0069	0.02					3.04
5	NOr	0.71	1.07	0.16	0.0062	0.01					2.97

The values for the pleural slope (r) range from 0.69 to 0.87. Excluding the Quebec or Carolina men cohorts has the largest effect – in both cases tending to increase r to 0.87. Values for the peritoneal slope (t) range from 2.05 (if Wittenoom is excluded) to

2.25 (if Massachusetts is excluded). The ratio of slopes range from 2.42 (excluding Quebec or Carolina men) to 3.04 (excluding Connecticut) which is contained with the plausible range of slopes derived from considering pleural and peritoneal risk for cohorts without quantitative exposure information in the original analysis (see Table 3 and Fig 5 of HD2000).

Table 5 shows the resulting slopes from a simultaneous fit to the pleural and peritoneal mesothelioma data for amphibole cohorts (fitting the model $P_M=A_{(fib)}.X^r+A'_{(fib)}.X^t$) under two constraints on the ratio of slopes (t/r=2.4 and 3.2) as in the original analysis, again excluding each data point in turn.

Table 5: Slopes for simultaneous fit to original amphibole data under two constraints for t/r

	Constraint:	t/r=3.2		t/r=2.4	
		r	t	r	t
Including all 5 amphibole cohorts		0.67	2.1	0.86	2.1
Excluding....					
1	Wit	0.67	2.1	0.82	2.0
13o	SA-o	0.68	2.2	0.84	2.0
14	Mas	0.66	2.1	0.81	2.0
12	Pat	0.62	2.0	0.76	1.8
13a	SA-a	0.68	2.2	0.84	2.0

Based on this exercise the overall plausible range of slopes is r=0.62-0.86 and t=1.8-2.2. The largest effect on the values of r and t results from excluding the Paterson amosite cohort.

2.2 Lung cancer

Table 6 shows the value of r and A_L in the lung cancer model $P_L=A_L.X^r$ fitted to the original amphibole data if each data point is excluded in turn.

Table 6: Parameter estimates for original lung cancer risk models fitted with each data point excluded

Model		slope, r	A_L	Cooks distance
Including all amphibole cohorts		1.6	0.49	-
Excluding 14 (Mass.) and 13a (SA amos.)		1.4	1.1	-
Excluding....				
1	Wit	1.56	0.57	0.02
13o	SA-o	1.64	0.40	0.15
14	Mas	1.49	0.73	0.33
12	Pat	1.58	0.55	0.33
13a	SA-a	1.44	0.92	0.05

2.3 Conclusion

An overall feature of these results is the fact that in the common slope models no one particular point dominates the choice of r and t – particularly for mesothelioma. For lung cancer the combined effect of the Massachusetts and SA amosite cohorts does lead to a high value of r=1.6. However, overall the results suggest that similar conclusions would be drawn for the value of r and t in the absence of data from any one of the original cohorts.

Unfortunately, the scope for testing the impact of excluding multiple data points is somewhat limited, given the small number of points overall, but this is considered to some extent as part of the assessment of the impact of various updates to existing cohort data and data from additional cohorts.

Section 3. Summary of additional information now available from the literature

Additional information from the literature can be grouped into two broad categories: i) updates to cohorts already included in HD2000 and ii) cohorts not included in the original HD analysis which provide important additional data points relevant to the risk models. The second category could be subdivided into those which carry more weight – since they yield more reliable information and thus potentially give valuable new insight into the dose response – and those that carry less weight – since they yield less reliable information and thus only contribute to the overall picture in a more general way.

A literature search identified two recent papers which fall into the first category and provide updated follow-up covering three of the cohorts included in the original analysis: Wittenoom, Carolina (men) and Carolina (women).

Five additional cohorts were identified that were not included in the original analysis and therefore fall into the second category: a cohort of individuals living in the environs of Wittenoom, a cohort of women living in the environs of Quebec, two overlapping cohorts of vermiculite miners and associated workers at Libby, Montana, and a cohort of amosite insulation product manufacturers at Tyler, Texas. The Wittenoom and Quebec environs cohorts could be considered to carry more weight than the other three since it is at least arguable that average cumulative exposures for groups of individuals not directly working with asbestos in occupational settings might better reflect the actual exposure experience of the majority, whereas substantial excursions to very high levels of exposure are more likely for some individuals in groups in occupational settings. In addition, the exposure levels for these cohorts will typically be lower than in the corresponding occupational settings and so are valuable additional points lower down the dose response curves.

i) Updates to cohorts already considered

Wittenoom (Musk et al., 2007)

Musk and co-workers recently published an update of mortality among the Wittenoom crocidolite miners[2]. Improved tracing led to a slightly expanded cohort of 6500 male workers with follow-up extended to the end of 2000. By this date, there had been over 2400 deaths (overall survival=63%) including 190 mesotheliomas (158 pleural, 32 peritoneal) and 281 lung cancers.

The high proportion of untraced individuals in the Wittenoom cohort and the fact that ascertainment of deaths in Australia is substantially complete means that truncating the person-years at the date last known to be alive will tend to lead to an overestimation of the SMRs. The measures of excess mesothelioma and lung cancer mortality we used in the HD2000 analysis (based on mortality truncated at subjects' 65th birthdays as reported by Berry in 1991 [3]) will tend to overcome this bias. However, updated mortality on this basis was not reported by Musk et al. Instead, SMRs were calculated in two ways (as in previous analyses) in order to illustrate the minimum and maximum extent of this bias: SMR1 is based on the assumption that those lost to follow up were alive until age 85 and SMR2 was based on person years truncated at the date subjects were last known to be alive.

For the purpose of the updating the HD2000 analysis, expected all cause and lung cancer mortality was calculated using the mid point of the two SMR values. This implies expected all cause mortality of 1589 deaths and, using the original cumulative exposure estimate of 23 f/ml.yr, R_M=0.49 (almost identical to the value derived for the HD2000 analysis.) On this basis the 281 lung cancers represent an excess of 144.3 deaths and R_L=4.6 (compared to 3.4 as derived in HD2000).

Carolina cohorts (Hein et al., 2007)

This update slightly expanded the number of subjects in the white male and white female cohorts and extends follow up to the end of 2001 [4]. The large lung cancer excesses in these two cohorts have persisted with the extra follow-up – particularly among males and 1 additional pleural mesothelioma death has been observed.

The male cohort (Car-m) now includes 868 deaths from all causes (overall survival=30%) against 571.1 expected, including 3 mesotheliomas (2 pleural, 1 peritoneal) and 116 lung cancers against 49.6 expected. Updated mesothelioma and lung cancer excesses per unit cumulative exposure were similar to the original values derived in HD2000 (Updated R_M=0.016; original R_M=0.013; updated R_L=4.8; original R_L=4.6).

The female cohort (Car-f) now includes 709 deaths from all causes (overall survival=32%) against 549.6 expected, including no mesotheliomas and 61 lung cancers against 27.5 expected. Updated lung cancer excess per unit cumulative exposure was slightly lower than the original value derived in HD2000 and more in line with that for males (updated R_L=4.7; original R_L=6.7).

ii) Additional cohorts not included in the original HD2000 analysis

Wittenoom environs (Hansen et al., 1993 and 1998; Reid et al., 2007)

Hansen and colleagues report follow up of a cohort of 4659 individuals resident at Wittenoom between 1943 and 1993 for at least 1 month and who were not directly employed in the crocidolite industry [5,6]. Based on follow-up to the end of 1993, 31 mesothelioma deaths (30 pleural, 1 peritoneal) were observed (Reid personal communication) and 377 deaths due to all causes were expected. As in the Wittenoom occupational cohort, expected mortality was calculated using two different censoring schemes: firstly by censoring at date of death, date lost to follow up or end of follow-up and secondly, date of deaths, the end of study date or age 85 (ie assuming that those lost to follow up are still alive until the end of the study or age 85). The expected all cause mortality corresponding to the mid-point of the two SMRs was used in the mesothelioma risk calculation. The reported average cumulative exposure for the cohort was 5.5 f/ml.yrs. Given the relative young age of first exposure (15 years) and average follow-up period of 29.5 years, adjusting for age first exposed at 30 years has a relatively large effect on the risk per unit exposure, reducing R_M by a factor of 3.8 from 1.495 to 0.393. No information about lung cancer mortality was reported.

Reid and colleagues recently reported an update of this cohort [7]. With increased follow-up to the end of 2002, 64 mesothelioma deaths have been observed. The expected number of deaths due to all causes was not reported. However, based on follow up to the end of 1999 using the first censoring approach, 715 deaths were observed against 486.3 expected, and up to this point 55 pleural and 2 peritoneal mesothelioma deaths had been observed (A Reid, personal communication). This gives an SMR for all causes of 1.47 – very close to that based on follow up to the end of 1993. On the assumption that the increased follow-up leads to no excess mortality using the second censoring method (as was the case based on follow-up to 1993), the expected all cause deaths corresponding to the mid point of the two SMRs is approximately 580. This value was used as the denominator in the mesothelioma risk calculation. The additional six years of follow-up leads to a slightly smaller reduction factor of 3.6 to allow for age of first exposure, which then gives R_M=0.50, almost identical to that based on the Wittenoom occupational cohort (R_M=0.49).

Quebec environs (Camus et al., 1998)

Camus and colleagues report mortality during 1970-1989 in a cohort of women aged at least 30 who were resident in 2 asbestos-mining areas in Quebec [8]. During this period there was a deficit of deaths from all causes based on comparisons with reference areas within Quebec (2242 deaths observed; 2464 expected) 11 mesothelioma deaths (10 pleural; 1 peritoneal) and no excess due to lung cancer (71 deaths observed; 71.7 expected). Average cumulative exposure (adjusted from a working time basis) was estimated to be 105 f/ml.yr with the plausible range of cumulative exposures estimated to be within a factor of 5 either side of this value.

The average age at first exposure and the period of exposure were not reported for this cohort and this prevents direct adjustment of R_M for age first exposed at 30 years. These values are being sought from Dr Camus. The typical period of follow-up is likely to be substantially longer than in the Wittenoom environs cohort on the assumption that mining operations have been taking place in Quebec since the late 1800s. If exposures first occurred around 1920, typical follow up could be around 50 years. If this were the case, then the effect of the average age at first exposure being below 30 years will be less extreme than for the Wittenoom environs cohort. Taking the exposure period to be from 1920 and the average age at first exposure to be 15 years (as for Wittenoom environs) suggests the value of R_M should be reduced by a factor of 2.7 to allow for age at first exposure (adjusted R_M=0.002).

Vermiculite miners and associated workers, Libby, Montana (McDonald et al., 2004; Sullivan 2007)

McDonald and colleagues report mortality among a cohort of 406 mine workers exposed to fibrous amphibole material (predominantly tremolite) as a contaminant of the mined vermiculite [9]. Based on follow-up to 1999 there were 285 deaths from all causes (overall survival=30%) against 224.4 expected, and 44 lung cancers against 18.3 expected. There was some uncertainty in the number of mesotheliomas due to the way the deaths were coded, however, there may have been 12 mesotheliomas in total, 2 of which were peritoneal. The reported average duration of employment (9 years) and fibre concentration (18 f/ml) implies an average cumulative exposure of about 160 f/ml.yr. This is corroborated by lung cancer mortality data reported by

McDonald and colleagues in an earlier report of this cohort [10] where the mid points of the tabulated exposure categories weighted by the expected lung cancer mortality suggest an average cumulative exposure of about 150 f/ml.yr. Based on this latter value, the calculated values of R_M (adjusted) and R_L are 0.041 and 0.93 respectively.

Sullivan reported mortality among a larger cohort of 1672 vermiculite miners, millers and processors at Libby [11]. Based on follow-up to 2001 there were 711 deaths from all causes (overall survival=57%) against 574 expected, 15 mesotheliomas (14 pleural; 1 peritoneal), and 89 lung cancer deaths against 52.5 expected. An average of exposure category mid-points weighted by the expected lung cancer deaths and expected NMRD deaths (Table 3) implies an average cumulative exposure of about 85 f/ml.yr leading to values of R_M (adjusted) and R_L of 0.030 and 0.82 respectively – slightly lower than those derived from McDonald's results.

Tyler amosite insulation product manufacturers (Levin et al., 1998)

Levin and coworkers reported mortality among 753 white males who had worked at the Tyler plant between 1954 and 1972 [12]. Based on follow-up to the end of 1993 there were 222 deaths from all causes (overall survival=71%) against 133.6 expected, 6 mesotheliomas (4 pleural, 2 peritoneal), and 35 lung cancers against 12.6 expected. No overall average cumulative exposure estimate was given, but average fibre concentrations of between 15.9 f/ml and 91.4 f/ml were obtained from three surveys carried out between 1967 and 1971. The average length of employment was 12.7 months. Taken together these data suggest an overall average of about 50 f/ml.yr may not be an unreasonable cumulative exposure estimate. The mean age at first exposure was not reported (median=25 years). Calculated values of R_M and R_L were 0.09 and 3.54 respectively.

Section 4: Basis for rating the reliability of cohorts

Berman and Crump [13] reviewed the quality of exposure and mortality outcome data in the various historic cohorts and assigned numerical values for the following factors:

Table 7: Berman and Crump uncertainty factors

Factor	**Issues considered in assignment of values**	
F1: uncertainty due to exposure concentrations estimates	1) Were measurements collected at the locations and times that the worker exposures actually occurred? 2) Personal sampling or area monitoring?	Range of values assigned: 1.5-4.0 (to the nearest 0.5). Most typical value 2.0 due to use of area samplers, lack of measurements representative of episodic but high-exposure jobs (usually associated with cleanup), and lack of measurements from earliest periods of exposure (when dust control equipment / procedures absent). Value of 2.0 assigned only if 1) authors had access to substantial numbers of samples representative of the majority of local operations of interest, 2) described systematic procedure for extrapolating exposure estimates to less well studied local operations, 3) systematic procedure for extrapolating exposure estimates to earlier exposure periods.
F2: uncertainty due to derivation of conversion factors for exposure indices	1) Were conversion factors used to convert Midget Impinger exposure measures to membrane filter/PCM? 2) If so were factors developed from parallel sampling, expert judgement or other studies?	Range of values assigned: 1.0-3.0 1.0 assigned only if no conversions 1.5 assigned if study wide conversion factor developed based on paired measurements 2.0-3.0 assigned otherwise.
F3: uncertainty due to manner in which JEMs were constructed	Were detailed work histories available to be used to identify the complete set of specific jobs that each worker performed over their working life and the duration of time spent on each job? Or were crude estimates of average duration was applied to all members of the cohort? The factor, F3, is used to account for conditions in which less than optimal job histories were used to identify the set of jobs performed by each worker and the duration that each worker spent performing each such job.	
F4L/F4M: uncertainty in lung cancer/ mesothelioma mortality data	Was diagnosis uncertain for any of the cases? Was the data presented in a form that allowed the Berman and Crump models to be fitted without making additional approximations or assumptions?	

The specific values assigned by Berman and Crump for each cohort are shown in Table 8 below. Berman and Crump combined the factors into two summary values for lung cancer and mesothelioma using the formulae:

$FL=\exp\{[Ln^2(F1)+Ln^2(F2)+Ln^2(F3)+Ln^2(F4L)]^{½}\}$, and

$FM=\exp\{[Ln^2(F1)+Ln^2(F2)+Ln^2(F3)+Ln^2(F4M)]^{½}\}$.

We used the combined uncertainty measure for mesothelioma (FM) to assign the cohorts to two groups as shown in the final column of the Table: Group 1= ‘more reliable’ and Group 2= ‘less reliable’. Cohorts for which FM was 3 or higher were assigned to the less reliable group with the remainder assigned to the more reliable group. Those cohorts not assessed by Berman and Crump were assigned to groups based on the qualitative descriptions of the exposure data given by Garry Burdett (see Annex 2).

Table 8: Uncertainty factors assigned by Berman and Crump

HD number	Short label	Fibre type	F1	F2	F3	F4L	F4M	FL	FM	Reliability rating
1	Wit	O	2	1	1	1	1	2.00	2.00	1
13o	SA-o	O	Not included by Berman and Crump							2
14	Mas	O	Not included by Berman and Crump							2
12	Pat	A	3.5	1	1	1	1	3.50	3.50	2
13a	SA-a	A	Not included by Berman and Crump							2
2f	Car-f	Y	1.5	1	1	1	1	1.50	1.50	1
2m	Car-m	Y	1.5	1	1	1	1	1.50	1.50	1
5y	NOr	Y	2	1.5	1	1	5	2.23	6.04	2
6	Que	Y	2	1.5	1	1	1	2.23	2.23	1
10	Bal	Y	2	1	1	1	-	2.00	2.00*	1
16	Con	Y	2	3	1	1	3	3.67	5.48	2
26	Tyl	a	3	1	1	1	-	3.00	3.00*	2
27	Lib	t*	2	1.5	1	1	-	2.23	2.23*	1
28	Wit-e	O	Not included by Berman and Crump							1
29	Que-e	Y	Not included by Berman and Crump							1
30	Lib2	t*	Not included by Berman and Crump							1

*Assuming a value of 1 for F4M
**Rated 1 for lung cancer and 2 for mesothelioma

Although this categorisation of studies may be a reasonably way of informally identifying the subset of cohorts that are likely to provide more reliable information, it is clear that no single cohort emerges as having much more reliable information than any of the others, with the possible exception of the Carolina cohorts. This seems to suggest that a “best-study approach” to estimating the risk per unit exposure is not feasible; rather, the HD approach of deriving risk estimates from the generality of the evidence over the set of cohorts is more appropriate. Furthermore, given the weight of evidence for the difference in potency between the fibre types, a best study would be required for each fibre type. Clearly this presents difficulties for amosite. The Wittenoom studies would be potential candidates in the case of crocidolite. For chrysotile, the difficulty is that the highest quality study appears – particularly in respect of lung cancer – to be the main source of the inconsistency among studies. Indeed, the lung cancer risk estimates for Carolina are among the highest of any of the studies considered here (including the amphibole studies).

Having said this, the 9 cohorts rated as 1 do provide a basis for fitting the model for pleural mesothelioma used in HD2000 with a common slope, r, and separate scaling constants for crocidolite (based on Wit and Wit-e), tremolite (based on Lib and Lib2), and chrysotile (based on 5 chrysotile cohorts). The results are described in section 5.5.

Section 5: Updating the quantitative risk models using the original cumulative exposure estimates

5.1 Total (pleural+peritoneal) mesothelioma

The first step in updating the quantitative risk models was to examine the consistency of the total mesothelioma risk per unit exposure (R_M) within the groups of cohorts of a particular fibre type.

Updated data extracted from the literature is shown in Table 9 in red. Original data is also shown for comparison. Results are also plotted in Figure 1. Briefly, the results can be summarised as follows:

- The 4 crocidolite cohorts (Massachusetts, updated Wittenoom, SA mines, and Wittenoom environs) are closely grouped around the average R_M value of 0.50, very close to the original value of 0.51.

- The three true amosite cohorts (Paterson, SA mines, and Tyler) are also statistically consistent (test for heterogeneity: p=0.43) with an average of R_M=0.10 (the same as in the original analysis) but R_M values for the two Libby cohorts are less than half this value and if these points are counted as amosite cohorts the resulting 5 points are no longer statistically consistent (test for heterogeneity: p=0.003).

- The risk per unit exposure for the Quebec environs cohort (R_M=0.0016) is somewhat higher than the Quebec miners cohort (R_M=0.0009), however this is still an order of magnitude below value for the Carolina men (R_M=0.016), and the inclusion of this point results in the chrysotile cohorts not being statistically consistent (test for heterogeneity: p=0.02). If the Carolina cohorts are excluded the risks per unity exposure are consistent with R_M=0.001 (p=0.48).

5.2 Non-linear risk estimates for pleural mesothelioma

The results of refitting the risk models for pleural mesothelioma are shown in Table 10. As in HD2000 the fitted model is $P_M=A_{(fib)}.X^r$ where, P_M=% excess mesothelioma mortality, X=cumulative asbestos exposure, $A_{(o)}$, $A_{(a)}$ and $A_{(y)}$ are the regression coefficients for crocidolite, amosite and chrysotile, and r is the fitted slope. The Table shows the fitted coefficients and deviance for the original model including the original set of 11 cohorts and the fitted coefficients and deviance[1] for the model when updated and additional cohorts are included in turn. The second part of the table shows the original and updated fits allowing each fibre type to have a different slope, $r_{(fib)}$.

The updates to the Wittenoom cohort have very little effect on the parameter estimates or the model fit, however, the Carolina updates tend to reduce the slope. If both sets of updates are included the fit is reasonable (Deviance (D)=7; degrees of freedom (df)=7) and this gives a value of r=0.65 (compared with 0.75 originally) with a 95% confidence interval which just includes 1 (linear slope). The Tyler and Libby

---

[1] One measure of whether the model fits the data well is if the deviance (D) is in the range $\nu \pm \sqrt{2\nu - 1}$, where v is the number of degrees of freedom remaining (the number of observations minus the number of fitted parameters).

cohorts again have limited impact on the model, but including the larger Libby cohort reduces the slope further (r=0.63 with a 95% confidence interval which just excludes 1) and the model again fits reasonably well (D=8.64, df=10). Inclusion of Wittenoom environs cohort tends has the effect of increasing the slope (r=0.83) whereas including the Quebec environs cohorts has less impact on the slope (r=0.69 if Wit-e is not also included). The model with all updates and additional points included fits the data well (D=10.41, df=12) with r=0.82 and a 95% confidence interval that just excludes 1 (0.66-0.99).

The independent slopes model with all updated and additional points included is somewhat different to the original fit: the crocidolite slope is higher than originally and the amosite slope substantially lower (r=0.71 compared with 1.2 originally) if the Libby cohorts are counted as amosite. Not surprisingly, excluding the Libby cohorts gives an amosite slope similar to the original.

A summary of the data for pleural mesothelioma is given in Figure 2. The chart shows the mesothelioma risk (P_M) plotted against cumulative exposure (X) for all cohorts. The (mixed fibre) cohorts not included in the model fitting are labelled on the chart with square brackets [.] and white diamonds, the original set of cohorts are labelled with blue diamonds and the data points for additional cohorts with red squares. Points labelled with red text are those rated as 1 in terms of data reliability (see Table 8). The black broken lines represent the common slopes model fitted to the original 11 cohorts (slope r=0.75) and the solid blue lines the same model fitted to the updated dataset (slope r=0.82).

5.3 Non-linear risk estimates for peritoneal mesothelioma

The results of refitting the risk models for peritoneal mesothelioma are shown in Table 11. The model form is the same as for pleural mesothelioma, but here the slope parameter is labelled as t rather than r. The Table shows the coefficients and deviance for the original model including the original set of 5 amphibole cohorts and the coefficients and deviance for the model when updated and additional cohorts are included in turn. The two chrysotile cohorts where (single) cases of peritoneal mesothelioma were observed (Carolina men and Quebec environs) are not included in the modelling.

The main feature of these results is the effect of including the Libby cohorts and counting them as amosite. It is obvious from a plot of peritoneal mesothelioma risk (P_M) against cumulative exposure (X) for peritoneal mesothelioma (Figure 3) that there are fewer peritoneal mesotheliomas at Libby than in the amosite cohorts. The model which includes both Libby cohorts fits poorly (D=27.9, df=5). Including just the other three available updates (Wittenoom, Tyler and Wittenoom environs) yields parameter estimates broadly similar to those for the original model. Including the Libby points but as a separate fibre type (last row of Table 11) results in a good fit to the data (this model is represented in Fig 3 with blue lines).

5.4 Simultaneous fits of the pleural and peritoneal mesothelioma non-linear model

Here the approach used in the original analysis of comparing the fitted slopes obtained if the ratio of slopes (t/r) is constrained to either end of the plausible range

(2.4-3.2) was adopted. The models were fitted to the amphibole data but with the Libby cohorts excluded. With t/r=2.4 the fitted slopes are r=0.87 and t=2.1, and with t/r=3.2 the fitted slopes are r=0.70 and t=2.25 (D=5.53, df=4). With t/r=2.8 (the mid-point of the plausible range) the fitted slopes are r=0.78 and t=2.2, very close to the values derived in the original analysis.

5.5 Lung cancer

Updated data extracted from the literature is shown in Table 12 in red. Original data is also shown for comparison. Results are also plotted in Figure 4. Briefly, the results can be summarised as follows:

- The updated Wittenoom miners cohort improves the consistency of the crocidolite cohorts with R_L=4.7 (test for heterogeneity: p=0.22). No lung cancer data was available for the Wittenoom environs cohort.

- The values of R_L for the Libby cohorts are less than 1/5th of the original R_L value for amosite and if these cohorts are treated as amosite the statistical consistency is lost (test for heterogeneity: p<0.001).

- The amphibole cohorts are statistically consistent if the Libby and SA amosite cohorts are excluded (test for heterogeneity: p=0.165).

- As in the original analysis the chrysotile cohorts are statistically consistent (R_L=0.066) if the Carolina cohorts are excluded (test for heterogeneity: p=0.15).

The results of refitting the non-linear risk models for lung cancer are shown in Table 13 and Figure 3. The table shows the coefficients and deviance for the original model including the original set of 5 amphibole cohorts and the coefficients and deviance for the model when updated and additional cohorts are included in turn.

The scope of the modelling is more limited for lung cancer because of the smaller number of available data points. Again the inconsistency of the Libby results with the other amphibole cohorts is evident. Adding just the updated Wittenoom miners data and the Tyler data gives a model with a slope of r=1.24 (95% CI just excludes a linear slope of 1) but the fit is less than adequate (D=12.2, df=4). The degradation in the fit of this model is of borderline statistical significance if the slope is constrained to be 1 (D=16.1, df=5).

5.6 Restricting the analysis to data from cohorts rated as more reliable

As discussed in section 4, the number of cohorts rated as more reliable (group 1 – see Table 8) is somewhat limited, particularly for amphibole (Wittenoom and Libby cohorts only). Nevertheless, fitting the pleural mesothelioma model to these points yields parameter estimates very close to those for the model fitted to the full data and the fit is still acceptable (D=6.46, df=5) – as shown in Table 10 below (last two rows of first part). The 95% confidence interval for the slope just includes a linear slope (r=1).

The range of cumulative exposures for the 9 data points in the model is 5.5 f/ml.yr (Wittenoom environs) to 600 f/ml.yr (Quebec miners).

The limited number of data points means it is not feasible to fit the models for peritoneal mesothelioma and lung cancer to the subset of data for cohorts rated as more reliable.

5.7 Conclusion

Few cohorts (only the Wittenoom miners and Carolina textile workers) had reported on extended follow-up since the HD2000 analysis and it is not surprising therefore that inclusion of the updated data has a minimal impact on the average mesothelioma and lung cancer risk per unit exposure (R_M and R_L) for the pure fibre type groups or on the estimated non-linear model coefficients.

The risk estimates for the Tyler amosite cohort are consistent with the Paterson cohort – based on a fairly crude estimate of the average cumulative exposure level. While this does reinforce the results of the original analysis to some extent, too much weight should not be placed on this actual point given the quality of the exposure estimate.

Despite limitations in the exposure estimates, the Wittenoom and Quebec environs cohorts are arguably more important since they provide additional data points for lower cumulative exposures alongside their related occupational cohorts. These points could therefore arguably be seen as subsets of lower exposed individuals within the same exposure context. As such – and given that the risk estimates are in line with those from their related occupational cohorts – these points provide some additional confirmation that the HD approach of using average risks per unit exposure for cohorts – rather than within-cohort dose response relationships – is valid. (Note that this issue is also discussed in Appendix B of the HD2000 paper.)

For the purposes of this analysis, the Libby cohorts were grouped with the three pure amosite cohorts since the amphibole fibre at Libby is likely to more closely resemble amosite than crocidolite or chrysotile. However, although the results are broadly consistent for pleural mesothelioma (see Fig 2) the other results suggest that this grouping may not be appropriate. The total mesothelioma risk per unit exposure for the Libby cohorts (R_M=0.04 for Lib and R_M=0.03 for Lib2) was somewhat lower than for the three amosite cohorts (combined R_M=0.10) and this is driven by the much lower number of peritoneal mesotheliomas. The lung cancer risks for Libby were also lower than for the amosite cohorts. In fact measurements of fibre size distributions by the US EPA suggest that the type of fibre at Libby appears to be typically coarser than amosite (G Burdett, personal communication) and this would be consistent with the discrepancies observed here.

For pleural mesothelioma – which will be the dominant type of mesothelioma moving down the cumulative exposure scale – the argument for a non-linear dose-response is reinforced by this updated analysis. The estimate of the slope is 0.82 (85% CI: 0.66-0.99) based on the full updated dataset, and 0.83 (95% CI: 0.65-1.00) if restricted to cohorts which are likely to be more reliable. If this relationship holds beyond the range of exposures considered here it implies proportionately more mesotheliomas should be seen at lower exposures than predicted by a model with linear slope.

However, a further consideration about the apparent non-linearity in the dose-response is the fact that the regression models do not take into account variability in the independent variable (cumulative exposure). This means that the fitted slope parameter may to some extent reflect the effect of regression to the mean. Unfortunately the potential extent of this effect is not clear. In order to take account of the effect in a formal analysis, quantification of the uncertainty in the cumulative exposure estimates would be required, which clearly presents a challenge in the context of the data we have been considering.

Arguments about whether cumulative exposure is an adequate predictor of risk over the entire scale will also be important to any consideration of the risk at lower exposures – particularly for chrysotile which is much more rapidly cleared from the lungs than amphibole asbestos.

Table 9: Summary of mesothelioma mortality data and exposure-specific risk estimates

Cohort Number	Cohort Name	Rating	Process	Fibre	Mesothelioma Deaths		Total expected mortality	Adjustment factor for age first exposed	Average cumulative exposure (f/ml.y)	Mesothelioma risk expessed as % total expected mortality per f/ml.yr (Rm)			
					Total Number	Number Peritoneal				unadjusted	adjusted for age at first exposure	95% CI	p value for heterogeneity
14	Massachusetts	2	O	o	5	3	8.3	0.74	120	0.50	0.68	(0.22,1.6)	
1	Wittenoom	1	M	o	72	10	601.8	1.08	23	0.52	0.48	(0.38,0.60)	
1	Wittenoom updated	1	M	o	190	32	1589.4	1.06	23	0.52	0.49	(0.42,0.57)	
13o	SA crocidolite mines	2	M	o	20	2	223.2 #	0.93	16.4	0.55	0.59	(0.36,0.91)	
28	Wittenoom environs	1	E/M	o	57	2	578.9	3.61	5.5	1.79	0.50	(0.38,0.64)	
Pooled crocidolite estimates													
	Tot - original				**97**	**15**					**0.51**		**0.60**
	Tot - updated				**272**	**39**					**0.50**		**0.81**
12	Paterson	2	I	a	17	9	355.9	0.63	65	0.073	0.12	(0.068,0.19)	
13a	SA amosite mines	2	M	a	4	1	305.7 #	0.93	23.6	0.056	0.060	(0.016,0.15)	
26	Tyler	2	I	a	6	2	133.6	1.00	50.0	0.090	0.090	(0.033,0.20)	
27	Libby	1	M	t	12	2	224.4	0.87	150.0	0.036	0.041	(0.021,0.07)	
30	Libby - larger cohort	1	E/M	t	15	1	574.0	1.01	85.0	0.031	0.030	(0.017,0.05)	
Pooled amosite estimates													
	Tot - original				**21**	**10**					**0.10**		**0.20**
	Tot - updated				**54**	**15**					**0.05**		**0.003**
	Tot - updated - excl. Libby				**27**	**12**					**0.10**		**0.43**
2m	Carolina (men)	1	T	y	2	1	410.1	1.34	28	0.017	0.013	(0.0016,0.047)	
2m	Carolina (men) updated	1	T	y	3	1	571.1	1.21	28	0.019	0.016	(0.0032,0.045)	
10	Balangero	1	M	y	2	0	225.4	1.20	300	0.003	0.0025	(0.0003,0.009)	
6	Quebec	1	M	y	33	0	5912.7	1.00	600	0.001	0.0009	(0.0006,0.0013)	
2f	Carolina (women)	1	T	y	0	-	299.2	1.34	26	0	0	(0,0.035)	
2f	Carolina (women) updated	1	T	y	0	-	549.6	1.21	26	0	0	(0,0.021)	
5y	New Orleans (plant 2, y)	1	C	y	0	-	397.1 *	1.26	22	0	0	(0,0.033)	
16	Connecticut	2	F	y	0	-	550.7	0.93	46	0	0	(0,0.016)	
29	Quebec environs	1	E/M	y	11	1	2463.7	2.69	105	0.0043	0.0016	(0,0.003)	
Pooled chrysotile estimates													
	Tot - original				**37**	**1**					**0.0010**		**0.11**
	Tot - original - excl. Car-m				**35**	**0**					**0.0010**		**0.69**
	Tot - updated				**49**	**2**					**0.0011**		**0.02**
	Tot - updated - excl. Car-m				**46**	**1**					**0.0010**		**0.48**

\# Reduced by a factor of 0.67 to exclude expected deaths less than 10 years from first exposure

* Expected all cause mortality in plant 2 partitioned in proportion to share of expected lung cancer

Figure 1: Exposure-specific mesothelioma mortality (R_M) by cohort and fibre type

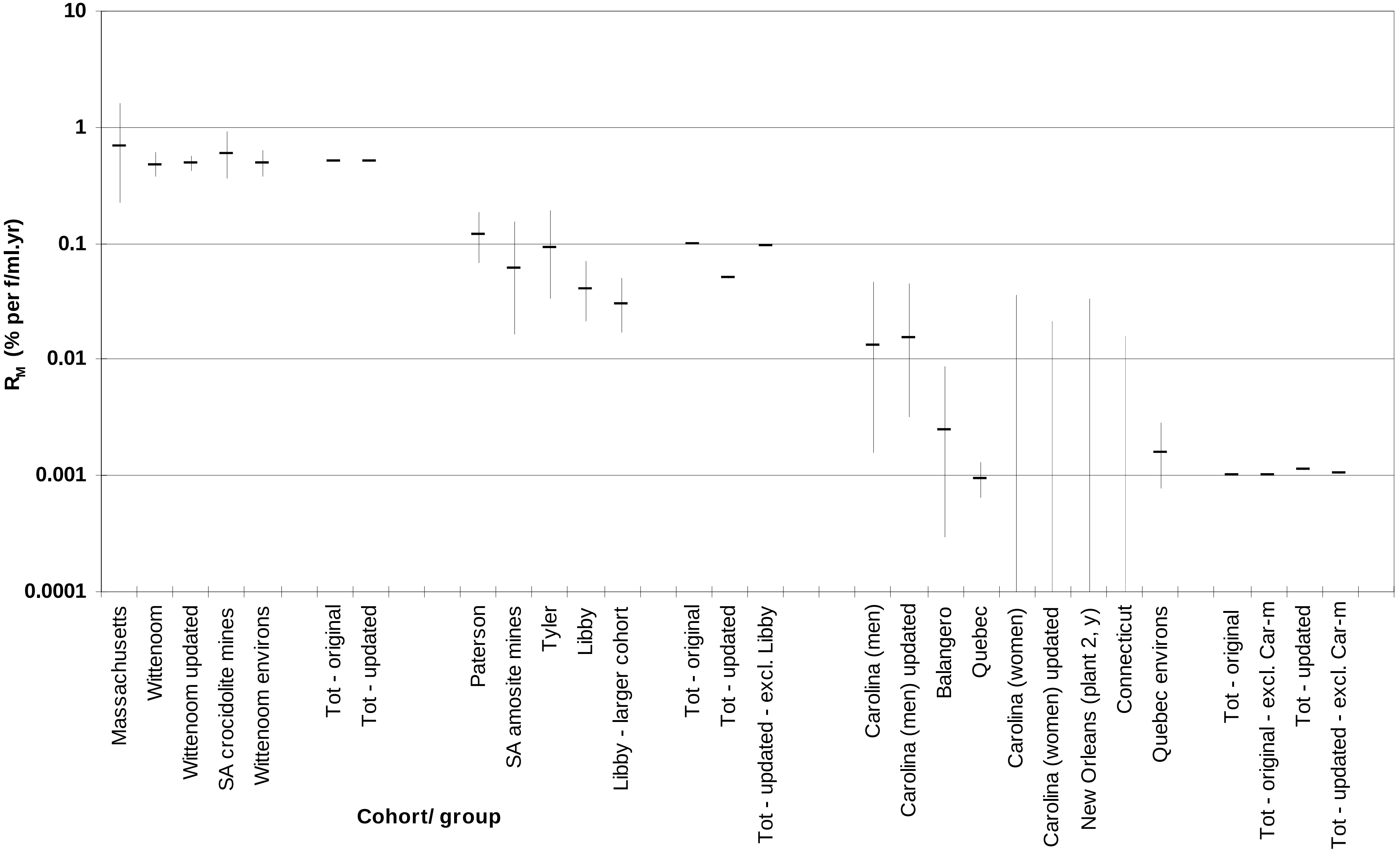


Table 10: Pleural mesothelioma – results of model fitting to updated data

Model	slope, r	(95% CI)	A(o)	A(a)	A(y)	Deviance	df
Original data common slope:	0.75	(0.32 , 1.2)	0.94	0.14	0.0048	4.52	7
+updated Wit	0.75	(0.31 , 1.2)	0.92	0.14	0.0048	4.63	7
+updated Car	0.65	(0.27 , 1)	1.3	0.19	0.0087	6.91	7
+updated Wit and Car	0.65	(0.27 , 1)	1.2	0.2	0.0089	7	7
+updated Wit and Car +Tyl	0.65	(0.27 , 1)	1.2	0.2	0.0087	7.09	8
+updated Wit and Car +Lib	0.65	(0.31 , 0.99)	1.2	0.2	0.0089	7	8
+updated Wit and Car +Lib2	0.6	(0.24 , 0.96)	1.5	0.19	0.012	7.8	8
+updated Wit and Car +Tyl+Lib+Lib2	0.63	(0.29 , 0.96)	1.3	0.19	0.01	8.64	10
+updated Wit and Car +Tyl+Lib+Lib2 +Wit-e	0.83	(0.65 , 1)	0.69	0.077	0.0029	10.36	11
+updated Wit and Car +Tyl+Lib+Lib2 +Que-e	0.69	(0.42 , 0.96)	1.1	0.15	0.0069	8.92	11
+all updates	0.82	(0.66 , 0.99)	0.7	0.08	0.0031	10.41	12
+all updates, more reliable cohorts (group 1) only	0.83	(0.65 , 1)	0.68	0.067	0.003	6.46	5

Model	slope, r(o)	r(a)	r(y)	A(o)	A(a)	A(y)	Deviance	df
Original data indep slope	0.62	1.2	0.72	1.4	0.024	0.0055	3.92	5
Updated indep slope	0.88	0.71	0.69	0.6	0.13	0.0067	9.1	10
Updated indep slope -Lib-Lib2	0.88	1.2	0.69	0.6	0.0067	0.024	7.11	8

Figure 2:

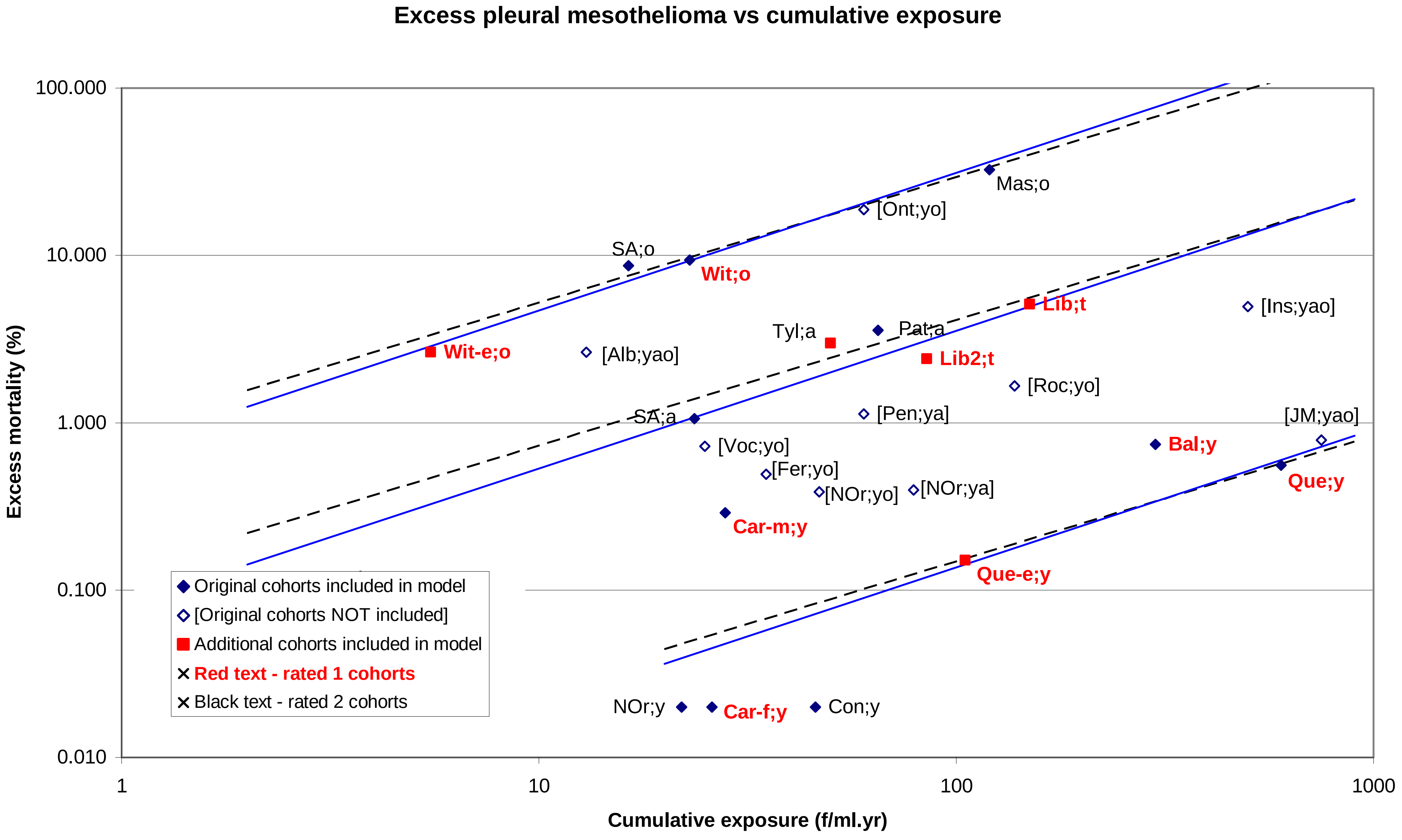

Excess pleural mesothelioma vs cumulative exposure
Excess mortality (%)
Cumulative exposure (f/ml.yr)
100.000
10.000
1.000
0.100
0.010
1
10
100
1000
SA;o
Wit;o
Mas;o
[Ont;yo]
Wit-e;o
[Alb;yao]
Tyl;a
Pat;a
Lib;t
Lib2;t
[Ins;yao]
[Roc;yo]
SA;a
[Pen;ya]
[JM;yao]
[Voc;yo]
[Fer;yo]
[NOr;yo]
[NOr;ya]
Bal;y
Que;y
Car-m;y
Que-e;y
NOr;y
Car-f;y
Con;y
◆ Original cohorts included in model
◇ [Original cohorts NOT included]
■ Additional cohorts included in model
× Red text - rated 1 cohorts
× Black text - rated 2 cohorts

Table 11: Peritoneal mesothelioma – results of model fitting to updated data

Model	slope, t	(95% CI)	A'(o)	A'(a)	A'(t)	Deviance	df
Original common slope	2.1	(1.4 , 2.8)	0.0022	0.0006		0.19	2
+updated Wit	2	(1.4 , 2.6)	0.0034	0.00085		0.17	2
+updated Wit +Tyl	2	(1.4 , 2.7)	0.0033	0.00075		0.48	3
+updated Wit +Lib	1.1	(0.36 , 1.8)	0.064	0.015		16.2	3
+updated Wit +Lib2	1.6	(0.73 , 2.4)	0.014	0.0014		24.1	3
+updated Wit +Tyl+Lib+Lib2	1.1	(0.26 , 1.9)	0.064	0.0092		27.9	5
+updated Wit +Wit-e	2	(1.5 , 2.5)	0.0032	0.00078		0.18	3
+all updates	1.6	(1.1 , 2.1)	0.013	0.001		30.7	6
+updated Wit +Tyl+Wit-e	2	(1.5 , 2.6)	0.0031	0.0007		0.49	4
+all updates (tremolite separate)	2.1	(1.6 , 2.6)	0.0029	0.00066	0.000026	0.76	5

Figure 3:

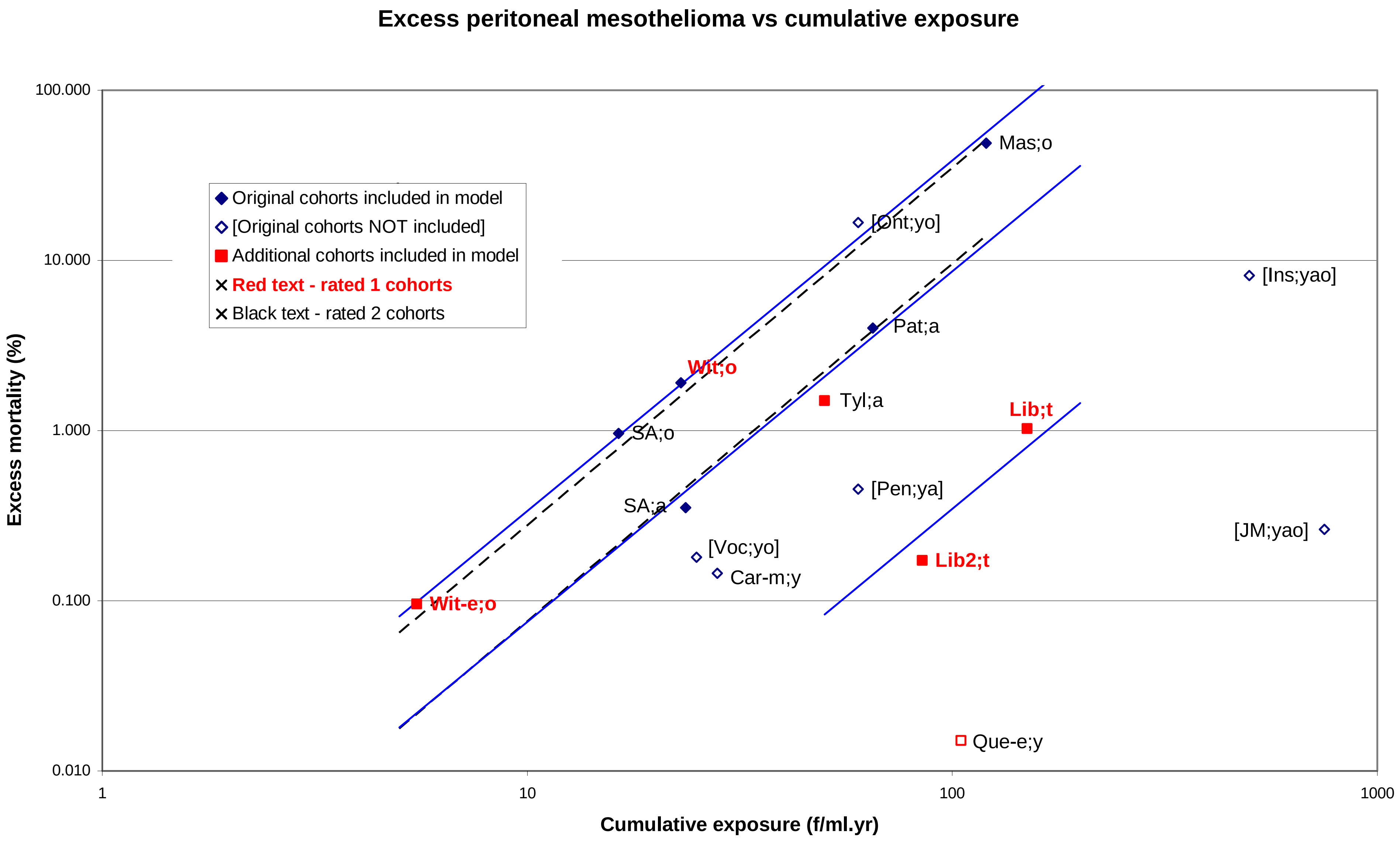

Excess peritoneal mesothelioma vs cumulative exposure
100.000
10.000
1.000
0.100
0.010
1
10
100
1000
Excess mortality (%)
Cumulative exposure (f/ml.yr)
◆ Original cohorts included in model
◇ [Original cohorts NOT included]
■ Additional cohorts included in model
× Red text - rated 1 cohorts
× Black text - rated 2 cohorts
Mas;o
[Ont;yo]
[Ins;yao]
Pat;a
Wit;o
Tyl;a
Lib;t
SA;o
[Pen;ya]
SA;a
[JM;yao]
[Voc;yo]
Car-m;y
Lib2;t
Wit-e;o
Que-e;y

Table 12: Summary of lung cancer mortality data and exposure-specific risk estimates

					Lung Cancer Deaths						Lung cancer risk expressed as % expected lung cancer per f/ml.yr		
Cohort Number	Cohort Name	Rating	Process	Fibre	Observed	Expected	SMR	Excess	% Excess	Average cumulative exposure (f/ml.y)	RI	(95% CI)	p value for heterogeneity
14	Massachusetts	2	O	o	8	0.6	13.1	7.4	1210	120	10	(3.9,21)	
13o	SA crocidolite mines	2	M	o	19	10.2	1.86	8.8	85.5	16.4	5.2	(0.71,12)	
1	Wittenoom	1	M	o	87	48.7	1.79	38.3	78.6	23	3.4	(1.9,5.2)	
1	Wittenoom updated	1	M	o	281	136.7	2.06	144.3	105.5	23	4.6	(3.6,5.7)	
	Total croc										**4.0**		**0.090**
	Total croc updated										**4.7**		**0.218**
	Total o+a										**4.6**		**0.024**
	Total o+a - SA-a										**4.9**		**0.067**
	Total o+a updated										**2.5**		**p<0.001**
	Total o+a updated - Excl. Lib & SA-a										**4.9**		**0.165**
12	Paterson	2	I	a	98	20.5	4.78	77.5	378	65	5.8	(4.4,7.4)	
13a	SA amosite mines	2	M	a	21	14.5	1.45	6.5	44.8	23.6	1.9	(-0.44,5.1)	
26	Tyler	2	I	a	35	12.6	2.77	22.4	177.0	50.0	3.5	(1.87,5.7)	
27	Libby	1	M	t	44	18.3	2.40	25.7	140.0	150.0	0.9	(0.50,1.5)	
30	Libby - larger cohort	1	E/M	t	89	52.5	1.69	36.5	69.4	85.0	0.8	(0.43,1.3)	
	Total amos										**5.0**		**0.021**
	Total amos updated										**1.8**		**p<0.001**
	Total amos updated - Excl. Lib & SA-a										**5.1**		
2f	Carolina (women)	1	T	y	38	13.8	2.75	24.2	175	26	6.7	(3.6,11)	
2f	Carolina (women) updated	1	T	y	61	27.5	2.22	33.5	122	26	4.7	(2.7,7)	
2m	Carolina (men)	1	T	y	74	32.2	2.30	41.8	130	28	4.6	(2.9,6.7)	
2m	Carolina (men) updated	1	T	y	116	49.6	2.34	66.4	134	28	4.8	(3.3,6.5)	
5y	New Orleans (plant 2, y)	1	C	y	42	32.4	1.30	9.6	29.6	22	1.3	(-0.29,3.4)	
16	Connecticut	2	F	y	49	35.8	1.37	13.2	36.9	46	0.80	(0.029,1.8)	
6	Quebec	1	M	y	587	431.6	1.36	155	36.0	600	0.06	(0.042,0.079)	
10	Balangero	1	M	y	19	17.3	1.10	1.7	9.8	300	0.03	(-0.11,0.24)	
29	Quebec environs	1	E/M	y	71	71.0	1.00	0.0	0.0	105	0.00	(-0.21,0.25)	
	Total chrys										**0.092**		**p<0.001**
	Total chrys updated										**0.101**		**p<0.001**
	Total chrys - Excl. Car										**0.067**		**0.08**
	Total chrys updated - Excl. Car										**0.066**		**0.15**

Figure 4: Exposure-specific lung cancer risk by cohort and fibre type

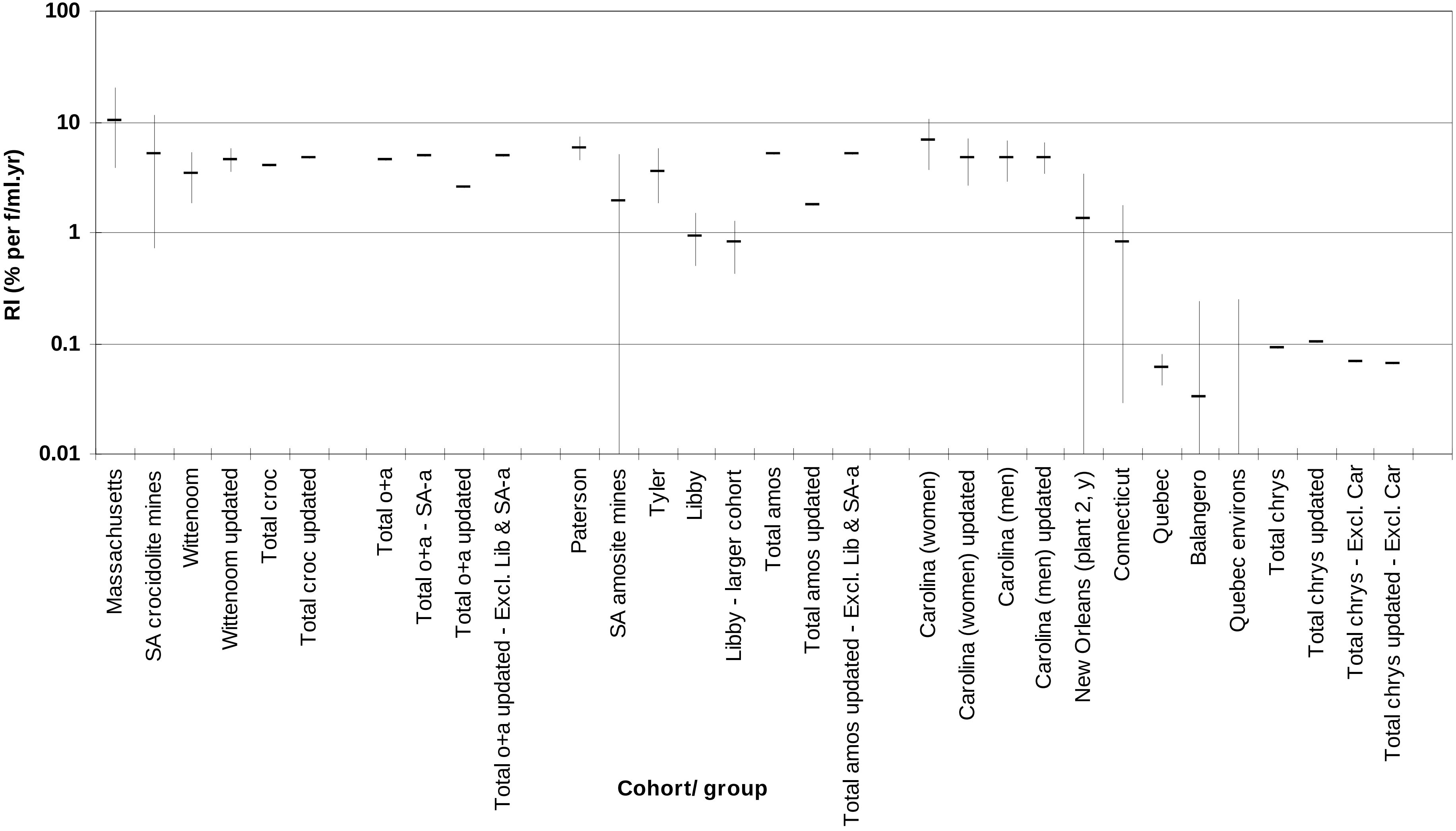
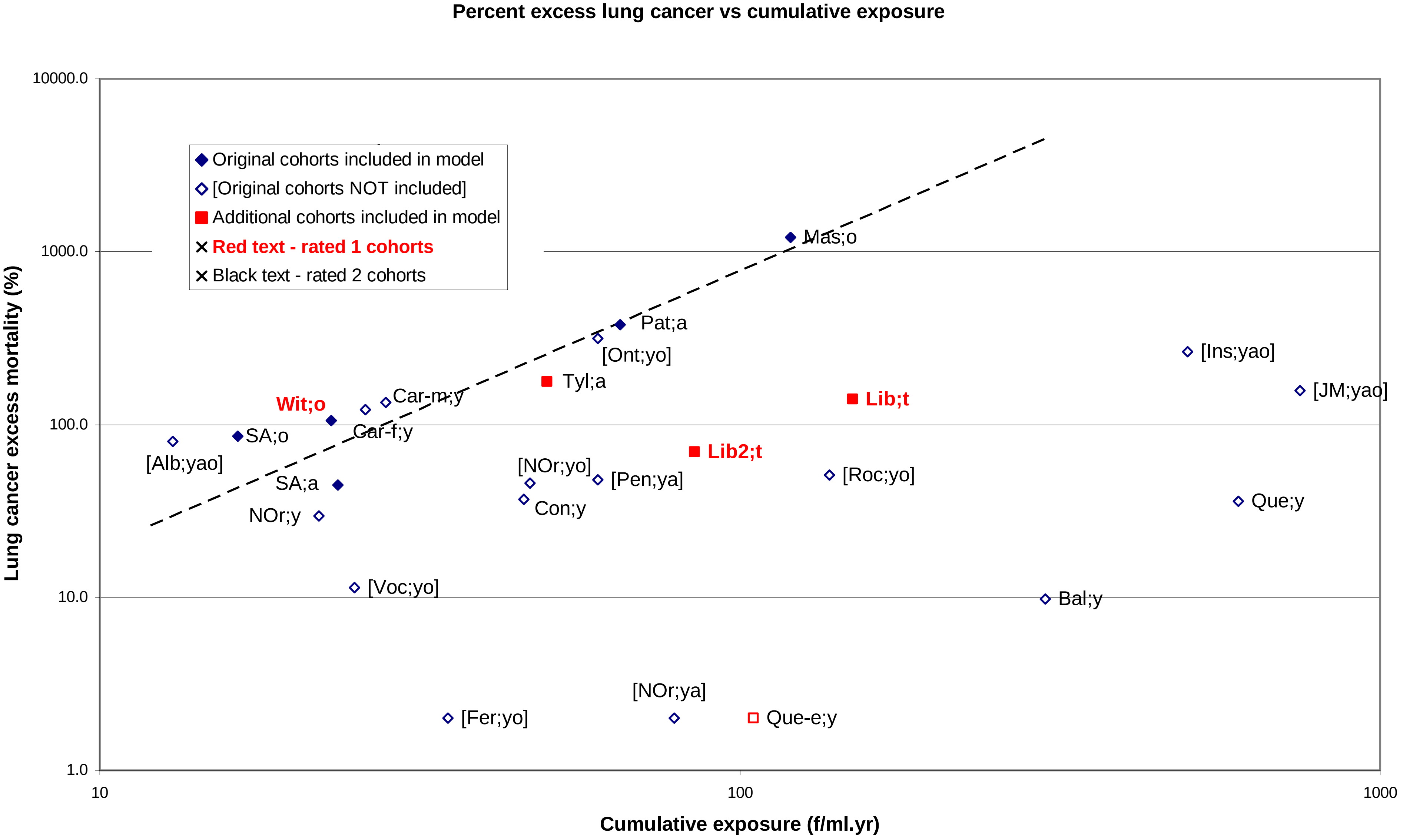


Table 13: Lung cancer – results of model fitting to updated data

Model	slope, r	(95% CI)	A	Deviance	df
Original common slope	1.5	(1.2 , 1.8)	0.63	5.8	3
+updated Wit	1.3	(1.1 , 1.5)	1.7	8	3
+updated Wit +Tyl	1.2	(1 , 1.5)	2	12.2	4
+updated Wit +Lib	0.51	(0.35 , 0.66)	23	66.7	4
+updated Wit +Lib2	0.31	(0.13 , 0.5)	39	108.2	4
+updated Wit +Tyl (slope=1)	1		4.7	16.1	5

Figure 5:


Percent excess lung cancer vs cumulative exposure
Lung cancer excess mortality (%)
10000.0
1000.0
100.0
10.0
1.0
10
100
1000
Cumulative exposure (f/ml.yr)
◆ Original cohorts included in model
◇ [Original cohorts NOT included]
■ Additional cohorts included in model
× Red text - rated 1 cohorts
× Black text - rated 2 cohorts
Mas;o
Pat;a
[Ont;yo]
Tyl;a
Lib;t
[Ins;yao]
[JM;yao]
Wit;o
Car-m;y
Car-f;y
SA;o
[Alb;yao]
SA;a
NOr;y
[NOr;yo]
[Pen;ya]
Con;y
Lib2;t
[Roc;yo]
Que;y
[Voc;yo]
Bal;y
[NOr;ya]
[Fer;yo]
Que-e;y

References

1. Hodgson, J.T., Darnton, A., 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann. Occup. Hyg. 44, 565–601.

2. Musk A, de Klerk N, Reid A, Ambrosini G, Fritschi L, Olsen N, Merler E, Hobbs M, Berry G (2007) Mortality Of Former Crocidolite (Blue Asbestos) Miners And Millers At Wittenoom. Occup. Environ. Med., Published online 28 Nov 2007

3. Berry G. (1991) Prediction of mesothelioma, lung cancer, and asbestosis in former Wittenoom asbestos workers. British Journal of Industrial Medicine. 48, 793–802.

4. Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure-response. Occup Environ Med. 2007 Sep;64(9):616-25.

5. Hansen J, de Klerk NH, Eccles JL, et al. Malignant mesothelioma after environmental exposure to blue asbestos. Int. J Cancer 1993; 54:578–581.

6. Hansen J, de Klerk NH, Musk AW, Hobbs MS. Environmental exposure to crocidolite and mesothelioma: exposure-response relationships. Am J Respir Crit Care Med. 1998 Jan;157(1):69-75.

7. Reid A, Berry G, de Klerk N, et al. Age and Sex Differences in Malignant Mesothelioma After Residential Exposure to Blue Asbestos (Crocidolite) Chest 2007; 131:376–382

8. Camus, M., Siemiatycki, J., Meek, B., 1998. Non-occupational exposure to chrysotile asbestos and the risk of lung cancer. N. Engl. J. Med. 338, 1565–1571.

9. McDonald, J.C., Harris, J., Armstrong, B., 2004. Mortality in a cohort of vermiculite miners exposed to fibrous amphibole in Libby, Montana. Occup. Environ. Med. 61, 363–366.

10. McDonald JC, McDonald AD, Armstrong B, Sebastien P. Cohort study of mortality of vermiculite miners exposed to tremolite. Br J Ind Med. 1986 Jul;43(7):436-44.

11. Sullivan PA (2007) Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: update of a cohort mortality study. Environ Health Perspect. 2007 Apr;115(4):579-85.

12. Levin, J.L., McLarty, J.W., Hurst, G.A., et al., 1998. Tyler asbestos workers: mortality experience in a cohort exposed to amosite. Occup. Environ. Med. 55, 155–160.

13. Berman, D.W., Crump, K.S., 2004. Final draft: Technical support document for a protocol to assess asbestos related risk. Prepared for the Office of Solid Waste and Emergency Response. US Environmental Protection Agency, Washington.