HSE ASSESSMENT OF RECENTLY UPDATED INFORMATION RELATING TO COHORTS WITH CHRYSOTILE EXPOSURE
(produced by Andy Darnton)

In mid-September, three additional papers were brought to the attention of the WATCH chair by a member as likely to be relevant to the asbestos discussion. The papers provide updated information about two of the cohorts included in the H&D analysis and one additional cohort. All these cohorts involved predominantly chrysotile exposure.

This assessment made by HSE (Andy Darnton) provides a short discussion about each of the papers, plus some further details about the additional cohort. Copies of each of the papers are also attached. It then presents updated summary estimates for mesothelioma risk per unit of cumulative exposure and the results of refitting the H&D-type models for pleural mesothelioma.

1. Finkelstein and Meisenkothen[1] – Connecticut friction products plant

This paper is primarily focussed on the incidence of mesothelioma among employees of the Connecticut factory that manufactured friction products using chrysotile. The data used in the H&D analysis for this cohort were extracted from the most recent analysis available at the time[2] in which there were no cases of mesothelioma.

Finkelstein and Meisenkothen discuss information about six individuals with mesothelioma subsequently extracted from litigation case files, and two additional cases identified in a separate study by Teta *et al*.[3] They conclude that two of these 8 cases meet the criteria for inclusion in the original cohort mortality study, but the mesotheliomas occurred after the cut-off date for follow up. Based on these two cases and an estimate of the expected all cause mortality to include further follow-up, they then derive an H&D-type mesothelioma risk estimate of 0.002 per cent of total expected mortality per f/ml.yr (95% CI 0.0002-0.006). They also give estimates for three other cohorts – one of which (North Carolina) was not included in the H&D analysis (this cohort is discussed later).

Unfortunately, because the information about the two cases that apparently meet the criteria for inclusion in the cohort study was taken from a separate source, it is not clear whether the individuals were actually among the original cohort members. There is thus the potential for the risk estimate to be biased in the upward direction (since it is more likely that any eligible individuals that weren't included in the original study for some reason would be subsequently identified if they were cases than if they were not). Nevertheless, in assessing the potential impact this new data has on the H&D analysis I have assumed that the estimate of 0.002% per f/ml.yr is credible.

2, Mirabelli *et al*.[4] and 3. Pira *et al*.[5] – Balangero mine

Mirabelli and colleagues discuss a number of cases of mesothelioma among workers exposed to chrysotile (and also possibly the amphibole “balangeroite” – see below) at the Italian Balangero mine, or subsequently exposed to asbestos that originated from the mine. The Mirabelli paper uses information from the Piedmont mesothelioma registry to identify cases with an occupational history which included work at the mine. It is not clear from this paper how many of the cases that apparently fulfilled the inclusion criteria of the original Balangero miners cohort[6] actually were among the original members of that cohort. Pira and colleagues present an updated analysis of that original cohort which extends follow-up from the end of 1987 to the end of 2003. They found 5 mesothelioma deaths (1 peritoneal) and conclude that the data assessed by Mirabelli *et al*. suggest one additional death among those eligible for the cohort analysis. The peritoneal case was not identified by Mirabelli *et al*. since it occurred prior to the establishment of the Piedmont registry. Using a "best evidence" approach therefore suggests six mesothelioma cases in total, one of which was a peritoneal case, and leads to an updated H&D-type mesothelioma risk estimate of 0.0043% per f/ml.yr (95% CI: 0.0016-0.0093) which compares with 0.0025% per f/ml.yr (95% CI: 0.0003-0.0090) in the original H&D analysis.

There is continuing debate about the role of "balangeroite" – a mineral which may have similar properties to amphibole asbestos, and present in small quantities in the Italian mine – in the causation of mesothelioma within this cohort[7,8]. Asbestos lung content analyses of the Italian miners might help to resolve this issue, but so far none have been published.

The calculated percentage excess lung cancer risk per unit chrysotile exposure, using data reported by Pira *et al*. based on comparisons with the external reference population, is 0.09% per f/ml.yr. The internal analyses of lung cancer in relation to cumulative exposure are suggestive of a somewhat lower risk estimate – perhaps half this value. Nevertheless, these results are broadly consistent with the previously suggested H&D summary estimate of 0.1% per f/ml.yr (whereas the earlier data for the Balangero miners had shown the lowest lung cancer estimate of all the chrysotile cohorts we considered – i.e. 0.03% per f/ml.yr).

4. Loomis *et al*.[9] – North Carolina textiles factories

A fourth paper, cited by Finkelstein and Meisenkothen, documents an analysis of workers at four textile plants in North Carolina. This was not available at the time of the original H&D analysis, though we did write to the relevant journal shortly after publication to comment on implications of this new data[10].

Three of the four North Carolina plants converted raw asbestos – mostly from Quebec – and cotton fibres into yarn and woven materials. Small quantities of amosite were used in one of the three plants. The forth plant manufactured friction products.

The cohort consists of 3975 men and 1795 women employed for at least 1 day between 1950 and 1973 at one of the 4 plants and followed up until the end of 2003.

Exposure samples were available for the period 1935-1986 for three of the plants. Air samples before 1964 used particle counts and these were converted to fibre counts using conversion factors derived from parallel sampling (conversion factors ranged from 1.60 to 8.04).

The reported overall average cumulative exposure was 17.1 f/ml.yr (for workers included in the exposure-response analysis). The reported H&D-type mesothelioma risk estimate was 0.0098% per f/ml.yr. This was based on 8 cases of pleural mesothelioma among the subgroup with 20 or more years of follow-up. An average cumulative exposure is not reported for this group in the paper, but using the reported risk estimate of 0.0098%, the number of mesotheliomas, and the expected all cause mortality (reported in the online appendix), the calculated average exposure is 68 f/ml.yr – considerably higher than the overall cohort average of 17.1 f/ml.yr. The risk estimate is of a similar order to that based on the South Carolina textiles plant (0.016%, although based on only 3 cases), and an order of magnitude higher than that based on the Quebec study (0.0010%).

The reported H&D-type risk estimate for lung cancer in the North Carolina cohort is 1.67% per f/ml.yr for the subgroup with 20 or more years of follow-up. This is between the higher estimate of 4.8% per f/ml.yr from the South Carolina cohort and the much lower suggested summary estimate of 0.1% per f/ml.yr in the original H&D paper. However, the internal analysis of lung cancer in relation to cumulative exposure in the North Carolina cohort suggests a relative risk of 1.102 per 100 f/ml.yr which translates almost exactly into an excess risk of 0.1% per f/ml.yr.

Summary estimates of mesothelioma risk per unit of cumulative exposure

Table 1 shows an updated summary of the pure fibre cohorts included in the original H&D analysis and the additional cohorts considered since (those considered to inform previous WATCH discussions, as well as the North Carolina cohort) in a similar format to that presented in Appendix 1 of the October 2008 WATCH meeting. The updated and new information about chrysotile cohorts is shown in the second half of the table.

The original data for cohorts that have now been updated is shown in italics for completeness (this information is not included in the pooled estimates of mesothelioma risk per unit of cumulative exposure).

The mesothelioma risk estimates for the 8 chrysotile cohorts shown in Table 1 are not statistically consistent (P<<0.001) so the pooled estimate of 0.0013% per f/ml.yr does not represent a valid summary. Three cohorts stand out as having considerably higher risks per f/ml.yr: North and South Carolina (men), and the Balangero mine (referred to subsequently as “high-risk chrysotile” cohorts). If the two Carolina cohorts are excluded, the remaining estimates (including Balangero) are statistically consistent with a summary estimate of 0.0011 (very close to the original H&D summary estimate). The consistency is improved if Balangero is also excluded and the summary estimate drops very slightly to 0.0010. The pooled estimate based on the three high-risk chrysotile cohorts is a factor a 7 higher than this at 0.0070.

Figure 1 shows the overall mesothelioma risk for each cohort plotted against average cumulative exposure. Those cohorts included in the H&D model are labelled in bold with and colour coded by fibre type – cohorts not included are labelled with text in brackets. The fitted lines based on the original H&D pleural mesothelioma model are shown with broken lines (common slope with separate coefficients for crocidolite, amosite and chrysotile).

The position of the data points for the three high-risk chrysotile cohorts suggest there might be a case for fitting a model with a separate high-risk chrysotile coefficient but again assuming a common slope (although whether the Balangero cohort should be included in this group is likely to be open to debate since the reasons it has a higher risk estimate may well be different than those for the Carolina cohorts). The solid lines are the fitted lines based on such a model. The estimate of the slope parameter (0.68) is consistent with that of the original H&D model.

Table 2 shows the fitted coefficients for various models with the same form as the original H&D model: separate lines for each fibre type (defined by the coefficients, A) but with a common slope (defined by the parameter r).

Model 1 is the original H&D model fitted to the original data (also shown in Figure 1 – broken lines). Model 2 the same model fitted to the updated data. This is not a good fitting model (high deviance in relation to number of degrees of freedom (DF) – see final two columns of Table 2) and the slope is substantially reduced from 0.75 to 0.48.

Introducing a separate coefficient for the three high-risk chrysotile cohorts (model 3) improves the fit substantially – and results in very similar values for the other parameters as in the original H&D model (model 3 is also shown in Figure 1 – solid lines). With only the North and South Carolina cohorts classed as high-risk chrysotile (model 4) the fit is still good.

Models 5-9 do not have the additional high-risk chrysotile coefficient, but exclude various combinations of the high-risk chrysotile cohorts to test their impact. Unsurprisingly, excluding all three (model 5) gives parameter estimates very close to model 1 and a good fit. Model 7 shows that the North Carolina cohort has the largest impact on the fit and is the main reason for the reduction in the value of the slope parameter in model 2.

Summary

The new data on chrysotile do appear to strengthen the evidence that the mesothelioma risk per unit of exposure is higher in the context of the particular processing environments at the North and South Carolina plants. The reasons for this are still unclear but may be to do with exposures involving a relatively high proportion of longer fibres. A modification to the H&D model that allows for a separate dose-response line for these cohorts still provides a good fit to the data, with values of the other parameters consistent with those from the original model. The extent to which the predictions based on this "high-risk chrysotile" dose-response can be generalised to other settings is unclear. New data for the Connecticut friction products plant (based on 2 cases) put this point very close to the original chrysotile dose-response line (i.e. consistent with Quebec). The reasons why the risk also now appears to be higher for the Balangero cohort, and whether this too provides evidence for a high-risk chrysotile scenario – or whether this point is higher for other reasons – are not clear.

Table 1: Summary of mesothelioma mortality data and exposure-specific risk estimates

Cohort Number	Cohort Name	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
14	Massachusetts	O	o	5	3	8.3	0.74	120	0.50	0.68	(0.22,1.6)
1	Wittenoom updated	M	o	190	32	1589.4	1.06	23	0.52	0.49	(0.42,0.57)
13o	SA crocidolite mines	M	o	20	2	223.2	0.93	16.4	0.55	0.59	(0.36,0.91)
28	Wittenoom environs	E/M	o	57	2	578.9	3.61	5.5	1.79	0.50	(0.38,0.64)
1	*Wittenoom*	*M*	*o*	*72*	*10*	*601.8*	*1.08*	*23*	*0.52*	*0.48*	*(0.38,0.60)*
Pooled crocidolite estimates											
	Total crocidolite			**272**	**39**					**0.50**	
12	Paterson	I	a	17	9	355.9	0.63	65	0.073	0.12	(0.068,0.19)
13a	SA amosite mines	M	a	4	1	305.7	0.93	23.6	0.056	0.060	(0.016,0.15)
26	Tyler	I	a	6	2	133.6	1.00	50.0	0.090	0.090	(0.033,0.20)
30	Libby - larger cohort	E/M	t	15	1	574.0	1.01	85.0	0.031	0.030	(0.017,0.05)
27	*Libby*	*M*	*t*	*12*	*2*	*224.4*	*0.87*	*150.0*	*0.036*	*0.041*	*(0.021,0.07)*
Pooled amosite estimates											
	Total amosite			**42**	**13**					**0.054****	
	Total exc Libby			**27**	**12**					**0.097**	
2m	S Carolina (men) updated	T	y	3	1	571.1	1.21	28	0.019	0.016	(0.0032,0.045)
2f	S Carolina (women) updated	T	y	0	0	549.6	1.21	26	0	0	(0,0.021)
5y	New Orleans (plant 2, y)	C	y	0	0	397.1	1.26	22	0	0	(0,0.033)
6	Quebec	M	y	33	0	5912.7	1.00	600	0.0009	0.0009	(0.0006,0.0013)
10	**Balangero updated**	**M**	**y**	**6**	**1**	**412.9**	**1.13**	**300**	**0.0048**	**0.0043**	**(0.0016,0.0093)**
16	**Connecticut updated**	**F**	**y**	**2**	**0**	**2800.0**	**1.00**	**46**	**0.0016**	**0.0016**	**(0.0002,0.0056)**
29	Quebec environs	E/M	y	11	1	2463.7	2.69	105	0.0043	0.0016	(0.0008,0.0028)
31	**North Carolina**	**T**	**y**	**8**	**0**	**1275.3**	**0.94**	**68**	**0.0092**	**0.0098**	**(0.0042,0.0193)**
2m	*S Carolina (men)*	*T*	*y*	*2*	*1*	*410.1*	*1.34*	*28*	*0.017*	*0.013*	*(0.0016,0.047)*
2f	*S Carolina (women)*	*T*	*y*	*0*	*0*	*299.2*	*1.34*	*26*	*0*	*0*	*(0,0.035)*
16	*Connecticut*	*F*	*y*	*0*	*0*	*550.7*	*0.93*	*46*	*0*	*0*	*(0,0.016)*
10	*Balangero*	*M*	*y*	*2*	*0*	*225.4*	*1.20*	*300*	*0.003*	*0.0025*	*(0.0003,0.009)*
Pooled chrysotile estimates											
	Total chrysotile			**63**	**3**					**0.0013****	
	Total exc N Car, S Car (men)			**52**	**2**					**0.0011**	
	Total exc N Car, S Car (men), Bal			**46**	**1**					**0.0010**	
	Total high risk chrystile: N Car, S Car (men), Bal			**17**	**2**					**0.0070**	

** Test for heterogeneity significant at 1%

Data in bold are for updated or new cohorts

Data in italics shown for completeness and not included in summary estimates

Figure 1: Excess pleural mesothelioma vs cumulative exposure with fitted lines based on original and updated H&D model, $P_M=A.X^r$

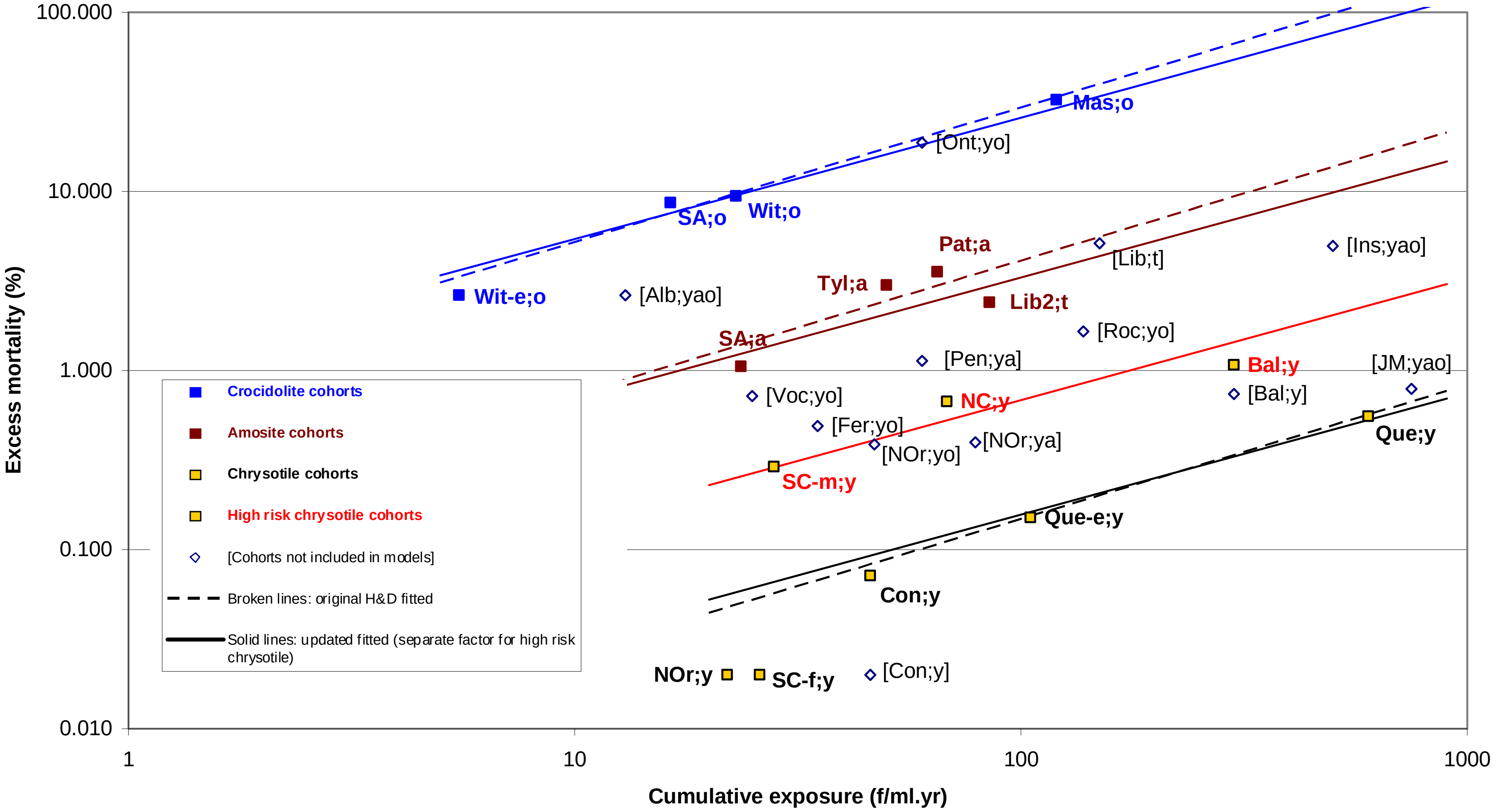

Table 2: original and refitted H&D model for pleural mesothelioma

	Model	slope, r (95% CI)	A(o)	A(a)	A(y)	A(y hi)	Deviance	DF
1	original	0.75 (0.32, 1.2)	0.94	0.14	0.0048		4.52	7
2	updated: all data	0.48 (0.24, 0.72)	2.1	0.33	0.027		20.8	10
3	updated: with factor for high risk chrys={SC,NC,Bal}	0.68 (0.41, 0.95)	1.1	0.15	0.0069	0.03	4.97	9
4	updated: with factor for high risk chrys={SC,NC}	0.73 (0.43, 1)	0.97	0.12	0.0055	0.03	8.61	9
5	updated: excl SC,NC,Bal	0.74 (0.43, 1.1)	0.93	0.11	0.0048		8.55	8
6	updated: excl NC and Bal	0.65 (0.36, 0.94)	1.2	0.16	0.0085		6.79	8
7	updated: excl SC and Bal	0.53 (0.26, 0.79)	1.8	0.28	0.019		16.09	8
8	updated: excl SC and NC	0.72 (0.42, 1)	0.99	0.12	0.0058		8.55	8
9	updated: excl NC only	0.64 (0.36, 0.92)	1.3	0.17	0.0097		11.09	9

Note: Models 1 and 3 are shown in Figure 1.

References

[1] Finkelstein M, Meisenkothen C. (2010) Malignant mesothelioma among employees of a Connecticut factory that manufactured friction materials using chrysotile asbestos. *Ann Occup Hyg* 54:692-696.

[2] McDonald A, Fry J, Woolley A, McDonald J. (1984) Dust exposure and mortality in an American chrysotile asbestos friction products plant. *British Journal of Industrial Medicine* 46:151-157.

[3] Teta M, Lewinsohn H, Meigs J et al. (1983) Mesothellioma in Connecticut, 1955-1977. Occupational and geographic associations. *J Occup Med* 25:749-56.

[4] Mirabelli D, Calisti R, Barone-Adesi F, Fornero E, Merletti F and Magnani C (2008) Excess of mesotheliomas after exposure to chrysotile in Balangero, Italy. *Occup Environ Med* 65: 815-819.

[5] Pira E, Pelucchi C, Piolatto P, etal. (2010) Mortality from cancer and other causes in the Balangero cohort of chrysotile asbestos miners. *Occup Environ Med* 66:805-809.

[6] Piolatto G, Negri E, La Vecchia C et al. (1990) An update of cancer mortality among chrysotile asbestos miners in Balangero, Northern Italy. *British Journal of Industrial Medicine* 47:810-814.

[7] Case BW, McDonald C. (2008) Chrysotile, tremolite, balangeroite and mesothelioma: similar situations? Occup Environ Med Online 65: Letter to Editor. Available at http://oem.bmj.com/cgi/eletters/65/12/815#589 Accessed 1 October 2010.

[8] Turci F, Tomatis M, Compagnoni R, Fubini B. (2009) Role of associated mineral fibres in chrysotile asbestos health effects: the case of Balangeroite. *Ann Occup Hyg* 53:491-497.

[9] Loomis D, Dement J, Wolf S, Richardson D. Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers. *Occup Environ Med* 66:535-542.

[10] Hodgson J, Darnton A. (2010) Mesothelioma risk from chrysotile. *Occup Environ Med* 67:432