increase in time ratios observed across categories of duration at the univariate analysis (Table 2).

Noteworthy, as the information on asbestosis was available only from 1978, Frost restricted the follow-up window even though information on mesothelioma deaths was available from 1972. This choice determined both a loss of cases and an exacerbation of the bias due to left censoring. Remarkably, asbestosis was only weakly associated with the outcome; hence, this variable is not likely to induce substantial confounding. Thus, Frost should have considered the entire follow-up period to study the other variables. Estimates restricted to 1978 and 2005 and adjusted by asbestosis could have served as a sensitivity analysis.

We would invite Frost to perform a simple and quick reanalysis. She should (i) include only cases exposed for the first time between 1950 and 1969 to limit left and right censoring (she would still retain 56% of the cases); (ii) analyse the entire follow-up period (1972–2005) to limit left censoring and increase the number of cases; (iii) avoid adjustment for the year of first exposure. If confounding by the latter is a strong concern, Frost could conduct stratum-specific analysis. The number of deaths that occurred among subjects exposed for the first time between 1950 and 1959 (216 or more after the addition of the years from 1972 to 1977 to the follow-up), and 1960 and 1969 (145 or more) is large enough to fit regression models with a reasonable number of covariates. We believe that this supplemental analysis could add an important piece of knowledge.

REFERENCES

Consonni D, Barone-Adesi F, Mensi C (2014) Comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978-2005)': methodological problems with case-only survival analysis. *Br J Cancer* **111**: 1674.

Frost G (2013) The latency period of mesothelioma among a cohort of British asbestos workers (1978-2005). *Br J Cancer*.

Lanphear BP, Buncher CR (1992) Latent period for malignant mesotheliomaof occupational origin. *J Occup Med* **34**: 718–721.

Mirabelli D, Zugna D (2014) Comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978-2005)'. *Br J Cancer* **111**: 1675.

*Correspondence: Dr A Farioli; E-mail: andrea_farioli@yahoo.it
Published online 5 August 2014

BJC

British Journal of Cancer (2014) 111, 2198–2199 | doi:10.1038/bjc.2014.441

Response to comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)'

G Frost*,[1]

[1]Mathematical Sciences Unit, Health & Safety Laboratory, Harpur Hill, Buxton, Derbyshire SK17 9JN, UK

Sir,

I read with interest the comments by Farioli *et al* (2014) on the recent publication investigating the latency period of mesothelioma (Frost, 2013). They raised important points regarding the decisions made during analysis—in particular, adjusting for year of first exposure, and restricting follow-up to 1978 onwards—and their potential effects on the results. These were touched on in the paper, but perhaps not to the detail that was warranted. Farioli *et al* (2014) requested additional analysis, which has been completed and is presented here.

Table 1 shows the results of a multivariable generalised gamma accelerated failure-time model that includes only cases first exposed to asbestos between 1950 and 1969 to limit left and right censoring, and analysing the entire follow-up period (1971–2005) rather than restricting it to post 1978. In addition, results are also presented for the same multivariable model but avoiding adjustment for the year of first exposure, as requested by Farioli *et al* (2014). Unfortunately, it was not possible to undertake the stratum-specific analysis as suggested by Farioli *et al* (2014), owing to the relatively small number of cases in each stratum.

Only including cases exposed for the first time between 1950 and 1969, and analysing the entire follow-up period (1971–2005) did not greatly influence the results in comparison to those presented in the original paper (Table 1). However, avoiding adjustment for the year of first exposure resulted in three notable differences: the latency period for women was no longer statistically significantly longer than that for men; asbestos removal workers now observed a statistically significantly shorter latency period than insulation workers; and there was now a statistically significant association between duration of exposure and latency, with latency tending to increase with duration (Table 1).

It is well known, and intuitive, that estimates of latency are related to the duration of follow-up. If a cohort has been followed up for just 20 years since their first exposure to asbestos, then only shorter mesothelioma latencies of 20 years or less would be possible within the follow-up period and so any estimate of median latency would be an underestimate (given the long latency for mesothelioma). Peto highlighted this, and the relationship between latency and both age at exposure and mortality due to other causes, in his 1985 paper (Peto, 1985). It was therefore expected that there would be a strong association between latency and the year of first exposure, with latency decreasing as the year of first exposure increases. In fact, this was one of the main reasons for including this variable in the final multivariable model that was presented in the paper.

Farioli *et al* (2014) commented that the time since first exposure to asbestos should not be adjusted for because of its spurious association with latency. However, I propose that this is precisely why it should be included. For example, asbestos removal work only started to become prominent in Great Britain in the 1980s with asbestos insulation work being much earlier, and so this group will tend to have shorter follow-up times and hence a spuriously shorter average latency than they would if they had the same follow-up time as insulation workers. Therefore, without attempting to adjust for differences in follow-up through variables such as time since first asbestos exposure, the true effect of occupation (if any) could be distorted. However, this is not an issue in the analysis presented in Table 1, which restricts cases to only those that were first exposed between 1950 and 1969.

Not adjusting for time since first asbestos exposure results in a trend of increasing latency with increasing duration of exposure (Table 1). As touched upon in the original paper and in the comment by Farioli *et al* (2014), this is not unexpected given what we know about latency—for example, in order to have experienced >30 years of exposure to asbestos, an individual could not have died with mesothelioma within 30 years of their first exposure to asbestos. Latency, year of first exposure and duration of exposure are all closely related, and so adjusting for time since first exposure removed this spurious association between duration and latency (Table 1).

Finally, Farioli *et al* (2014) commented on the choice to restrict follow-up to when information on asbestosis was available (from 1978 onwards), rather than including the full follow-up period. This choice was made because having asbestosis is an important indicator of the intensity of exposure to asbestos and so was of interest in its own right, rather than being included purely to adjust for potential confounding. A sensitivity analysis conducted at the time, and now the results presented here, confirmed that including all follow-up rather than restricting this to 1978 onwards made little difference to the results. Hence I presented the results using the restricted follow-up and including death with asbestosis, with an analysis of the full follow-up time serving as a sensitivity analysis.

There were three main indicators of intensity of asbestos exposure specified in the original paper that were used to judge the strength of support for the intensity hypothesis: sex, presence of asbestosis and occupation. The additional analysis presented here did not allow presence of asbestosis to be included, and so the judgement here relies on sex and occupation. The difference in mesothelioma latency with sex was in the direction expected if the intensity hypothesis was true, but it was not statistically significant when not adjusted for year of first exposure. In addition, the difference in latency between insulation workers and removal workers was in the opposite direction to that expected if the hypothesis was true. Hence my conclusion from the original paper remains unchanged; this study found no evidence that greater intensity asbestos exposure would lead to shorter mesothelioma latencies.

I would also like to take this opportunity to remark on the comment mentioned by Farioli *et al* (2014) and made by Consonni *et al* (2014) and Mirabelli and Zugna (2014), that the analysis should have included all individuals in the cohort and not just those who died with mesothelioma. This is a point that was considered before undertaking the analysis, but a number of problems arise if all individuals are included. First, $<1\%$ of individuals in the cohort died from mesothelioma during follow-up. Therefore, if individuals who died from other causes or were alive at the end of follow-up were treated as censored observations, then the median latency would not be estimable using classical methods. In addition, any median latency predicted from survival analysis would be longer than the life expectancy of individuals in the cohort—the predicted median latency from an empty generalised gamma accelerated failure-time model using data from the full cohort was 115 years.

Table 1. Adjusted time ratios for mesothelioma latency among British asbestos workers (1971–2005)

			Including year of first exposure			Excluding year of first exposure		
Characteristic	**No. of deaths**	**Person-years at risk**	**Time ratio**	**95% CI**	**LR test**	**Time ratio**	**95% CI**	**LR test**
Sex					$P=0.015$			$P=0.154$
Male	359	6427	1.00	Ref.		1.00	Ref.	
Female	8	169	1.12	1.01–1.25		1.08	0.96–1.23	
Main smoking status					$P=0.258$			$P=0.146$
Current	199	3684	1.00	Ref.		1.00	Ref.	
Former	103	1753	1.03	0.99–1.07		1.04	1.00–1.09	
Never	65	1159	1.01	0.97–1.06		1.02	0.97–1.07	
Main occupation					$P=0.483$			$P=0.034$
Manufacturing	121	2436	0.98	0.93–1.02		0.96	0.91–1.02	
Removal	117	1856	0.98	0.93–1.03		0.93	0.87–0.98	
Other	53	980	1.01	0.96–1.06		1.00	0.94–1.06	
Insulation	76	1324	1.00	Ref.		1.00	Ref.	
Year of first exposure					$P<0.001$			NA
1950–1959	220	3745	1.00	Ref.		NA	NA	
1960–1969	147	2851	0.86	0.83–0.90		NA	NA	
Age at first exposure (years)					$P<0.001$			$P<0.001$
<20	148	2599	1.00	Ref.		1.00	Ref.	
20–	112	2129	0.96	0.92–0.99		0.97	0.93–1.01	
30–	66	1171	0.91	0.87–0.96		0.90	0.85–0.95	
40–	30	535	0.80	0.74–0.86		0.77	0.71–0.84	
50+	11	162	0.84	0.76–0.92		0.77	0.69–0.86	
Duration of exposure (years)					$P=0.237$			$P=0.001$
<10	13	372	1.00	Ref.		1.00	Ref.	
10–	83	2048	1.09	1.00–1.19		1.13	1.02–1.25	
20–	155	2800	1.08	0.99–1.18		1.18	1.07–1.30	
30–	101	1302	1.11	1.01–1.23		1.27	1.15–1.42	
40+	15	75	1.08	0.97–1.21		1.21	1.07–1.38	
Mesothelioma type					$P=0.020$			$P=0.025$
Pleural	184	3450	1.00	Ref.		1.00	Ref.	
Peritoneal	80	1378	0.97	0.93–1.01		0.97	0.93–1.02	
Pleural + peritoneal	4	56	0.75	0.65–0.86		0.76	0.64–0.89	
Not specified	99	1712	0.98	0.94–1.02		0.96	0.92–1.00	

Abbreviations: CI = confidence interval; LR = likelihood ratio; NA = not applicable; Ref. = reference. The time ratios were estimated using multivariable generalised gamma accelerated failure-time models including only cases first exposed between 1950 and 1969 and using full follow-up (1971–2005).

This is not informative and was not the quantity of interest in this study, but rather the median latency for those who died with mesothelioma. I acknowledge that the median latency of 23 years estimated in the study (30 years after excluding deaths within 10 years of first occupational exposure) will be restricted by the duration of follow-up, and so would increase as follow-up continues.

Second, if individuals who died from other causes or were alive at the end of follow-up were included as censored observations, then the estimated latency becomes dependent on the mesothelioma incidence rate. For example, if the incidence rate of mesothelioma was greater than the 37 cases per 100 000 person-years observed among the cohort, then the predicted median latency among the cohort (that is, the estimated time at which 50% of the full cohort would have died with mesothelioma) would be shorter even if the median latency for the cases were the same. This could have a great impact when comparing groups with very different incidence rates, such as asbestos insulation workers and removal workers.

The methodology employed by the study is by no means perfect, and many of the limitations are discussed here, in previous comments and in the original paper. However, I believe that it was appropriate and remains valid. I would like to thank the commenters for their thoughtful and constructive remarks, which highlight the challenges involved when latency is the outcome of interest.

REFERENCES

Consonni D, Barone-Adesi F, Mensi C (2014) Comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)': methodological problems with case-only survival analysis. *Br J Cancer* **111**: 1674.

Farioli A, Mattioli S, Curti S, Violante FS (2014) Comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)': the effect of left censoring. *Br J Cancer* **111**: 2197–2198.

Frost G (2013) The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005). *Br J Cancer* **109**: 1965–1973.

Mirabelli D, Zugna D (2014) Comment on 'The latency period of mesothelioma among a cohort of British asbestos workers (1978–2005)'. *Br J Cancer* **111**: 1675.

Peto J (1985) Some problems in dose-response estimation in cancer epidemiology. In *Methods for Estimating Risk of Chemical Injury: Human and Non-Human Biota and Ecosystems*, Vouk VB, Butler GC, Hoel DG, Peakall D (eds). pp 361–380. Wiley: New York, NY, USA.

*Correspondence: G Frost; E-mail: Gillian.Frost@hsl.gsi.gov.uk
Published online 5 August 2014

BJC

British Journal of Cancer (2014) 111, 2199–2200 | doi:10.1038/bjc.2014.334

Comment on 'Residential distance at birth from overhead high-voltage powerlines: childhood cancer risk in Britain 1962–2008'

D Jeffers*,[1]

[1]*Meadland, Three Gates Lane, Haslemere, Surrey GU27 2LD, UK*

Bunch *et al* (2014) studied the incidence of childhood leukaemia in relation to distance at birth from high-voltage powerlines over the period 1962–2008 and found that, for children born within 200 m, the relative risk fell from 4.5 (0.97–20.83) in the 1960s to 0.71 (0.49–1.03) in the 2000s.

The opening year of the study was the last in which there was insufficient capacity to meet the maximum demand for electricity (Department of Energy and Climate Change (DECC), 2013). The next decade saw a near doubling of demand which drove a frenzied programme of power station and power line construction, (National Grid Company, 2010) and, by the time that the 1973 oil crisis forced a slow down, a 50% margin of generating capacity over the peak demand had been established (Department of Energy and Climate Change (DECC), 2013).

Construction of the 400 kV supergrid did not begin until 1965 and it is noteworthy that Bunch *et al's* maximum relative risk of 4.5 (0.97–20.83)