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

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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 and left and right censoring, and analysing the entire follow-up period (1971–2005) rather than restricting it to 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). 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 asbestos was available (from 1978 onwards), rather than including the entire 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 latency 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 Zügna (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.

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.

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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) would 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 estimated 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.

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

| Characteristic | No. of deaths | Person-years at risk | Time ratio | 95% CI | LR test | Time ratio | 95% CI | LR test |
|---------------|---------------|----------------------|------------|-------|---------|------------|-------|---------|
|               |               |                      |            |       |         |            |       |         |
| Sex           |               |                      |            |       |         |            |       |         |
| Male          | 359           | 6427                 | 1.00       | Ref.  | 1.00    | 1.08       | 0.96–1.23 |
| Female        | 8             | 169                  | 1.12       | Ref.  | 0.97–1.06 |
| Main smoking status |        |                      |            |       |         |            |       |         |
| Current       | 199           | 3684                 | 1.00       | Ref.  | 0.99–1.07 |
| Former        | 103           | 1753                 | 1.03       | Ref.  | 0.97–1.06 |
| Never         | 65            | 1159                 | 1.01       | Ref.  | 0.95–1.06 |
| Main occupation |             |                      |            |       |         |            |       |         |
| Manufacturing | 121           | 2436                 | 0.98       | 0.93–1.02 |
| Removal       | 117           | 1856                 | 0.98       | 0.93–1.03 |
| Other         | 53            | 980                  | 1.01       | 0.96–1.06 |
| Insulation    | 76            | 1324                 | 1.00       | Ref.  | 0.97–1.06 |
| Year of first exposure |         |                      |            |       |         |            |       |         |
| 1950–1959     | 220           | 3745                 | 1.00       | Ref.  | NA      | NA         | NA     |
| 1960–1969     | 147           | 2851                 | 0.86       | 0.83–0.90 |
| Age at first exposure (years) |       |                      |            |       |         |            |       |         |
| <20           | 148           | 2599                 | 1.00       | Ref.  | 1.00    | 1.00       | 0.93–1.01 |
| 20–30         | 112           | 2129                 | 0.96       | 0.92–0.99 |
| 30–40         | 66            | 1171                 | 0.91       | 0.87–0.96 |
| 40–50         | 30            | 535                  | 0.80       | 0.74–0.86 |
| 50+           | 11            | 162                  | 0.84       | 0.76–0.92 |
| Duration of exposure (years) |       |                      |            |       |         |            |       |         |
| <10           | 13            | 372                  | 1.00       | Ref.  | 1.00    | 1.00       | 0.93–1.01 |
| 10–20         | 83            | 2048                 | 1.09       | 1.00–1.19 |
| 20–30         | 155           | 2800                 | 1.08       | 0.99–1.18 |
| 30–40         | 121           | 1302                 | 1.11       | 1.01–1.23 |
| 40+           | 15            | 75                   | 1.08       | 0.97–1.21 |
| Mesothelioma type |        |                      |            |       |         |            |       |         |
| Pleural       | 184           | 3420                 | 1.00       | Ref.  | 1.00    | 1.00       | 0.95–1.02 |
| Peritoneal    | 80            | 1378                 | 0.97       | 0.93–1.01 |
| Pleural + peritoneal | 4       | 56                   | 0.75       | 0.65–0.86 |
| Not specified | 99            | 1712                 | 0.98       | 0.94–1.02 |

All 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).

Supporting information is available in the online version of this article.

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

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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 0.49 (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)