Comment on 'Estimating the asbestos-related lung cancer burden from mesothelioma mortality' - IARC and Chrysotile Risks

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Comment on 'Estimating the asbestos-related lung cancer burden from mesothelioma mortality' – IARC and Chrysotile Risks

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Sir,

We have read with interest and concern the recent article in the *BJC* by McCormack *et al* (2012), *Estimating the asbestos-related lung cancer burden from mesothelioma mortality*. The article puts forth erroneous estimates and conclusions by omitting newer data, relying on incomplete and/or outdated data, omitting critiques of data relied upon, and drawing conclusions using heterogeneous data sets that are not adequately controlled for latency and/or exposure. These shortcomings undermine conclusions and recommendations in the report.

While several authors of the McCormack *et al* (2012) article are employees or affiliated with IARC, their article omits relevant data identified and published by 2009 when, during 17–24 March 2009, the IARC Working Group on the Evaluation of Carcinogenic Risks to Humans met in Lyon, France (Straif *et al*, 2009; IARC, 2012). Specific to our concerns regarding chrysotile asbestos, McCormack *et al* (2012) omit the most recent update by Mirabelli *et al* (2008) on the Italian chrysotile asbestos mining cohort and discussed in the evaluation of the 2009 IARC monograph working group. The update by Mirabelli *et al* (2008) found a total of 27 cases of mesothelioma associated with the site, including not only miners, but also relatively low-dose 'white collar' and environmental cases stemming from the mine. McCormack *et al* (2012) exclude this information resulting in attentuation of the risk estimates. Instead, they cite an older study: the 1990 cohort study by Piolatto *et al* (1990), in which only two mesothelioma cases in miners had been reported. This mine's asbestos was 'pure' chrysotile without amphiboles of any type (IARC, 2012).

McCormack *et al* (2012) also cite and rely on outdated data from IARC (1987), *Overall evaluations of carcinogenicity: an updating of IARC Monographs*, ignoring newer and more relevant data presented at the 2009 IARC meeting and included in IARC's latest monograph on asbestos pertaining to chrysotile (IARC, 2012). These newer data have important implications as both latency and dose are major factors in the aetiology of mesothelioma occurrence, neither adjusted for nor adequately addressed.

Bignon *et al* (2002) concluded 'very few studies have focused on the time-related pattern of occupational exposure as a significant factor in the occurrence of mesothelioma,' and multiple studies cited by McCormack *et al* (2012) suffer from this lack of focus. One of the McCormack *et al* (2012) authors (Boffetta) acknowledges elsewhere the importance of latency as the main determining risk factor (La Vecchia and Boffetta, 2011). The current paper includes studies having insufficient latency for mesothelioma to manifest (Zasadzinski *et al*, 2013).

McCormack *et al* (2012) also refer to studies of earlier potency estimates reported by Hodgson and Darnton (2000) while ignoring the significantly revised estimates lowering the potency differences between chrysotile and amphibole asbestos by these same authors (Hodgson and Darnton, 2009).

The authors fail to impose quality control standards to their study, as required when dealing with hetrogeneous data sets and as demonstrated by Lenters *et al* (2011) in their meta-analysis, which included only studies adequately controlled for exposure.

McCormack *et al* (2012) further state that figures showing mesotheliomas related to chrysotile asbestos exposure may be erroneously over-reported, but give no explanation for their statement that *'the lung cancer excess depends critically on the rates on which the SMR is based'*. Such an effect would be true for all asbestos types, including the amphibole and mixed exposure cohorts,

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especially given the inadequate coding scheme for mesothelioma and under-reporting due to a variety of country-to-country reporting errors (Delgermaa *et al*, 2011) over the time frames covered by the cited epidemiology studies of McCormack *et al* (2012). Until recently, the coding for mesothelioma was unspecific until the implementation of the International Classification of Diseases-10 in 1994, which gave mesothelioma its own specific codes.

The McCormack *et al* (2012) conclusion that mesothelioma occurring in chrysotile-exposed cohorts is due to other asbestos types lacks justification, as it is based on lung-burden analysis alone.

In particular, the study by Frank *et al* (1998) using tremolite-free UICC Chrysotile B (Canadian chrysotile) has shown all forms of asbestos to cause disease, including mesothelioma. In an inhalation study (Wagner *et al*, 1974) chrysotile, caused as many mesotheliomas as did crocidolite in an inhalation study. To suggest causal inference from amphiboles found in the lung parenchyma while ignoring the predominant finding of chrysotile in the pleura, where mesotheliomas occur, seems scientifically questionable (Stayner *et al*, 1996).

The relative lack of biopersistence of chrysotile asbestos in lung tissue can hardly be grounds for concluding that chrysotile asbestos does not cause mesothelioma, given the translocation and biopersistence of chrysotile in target sites of mesothelioma occurrence (Sebastien *et al*, 1980; Dodson *et al*, 1990; Suzuki and Yuen, 2001; Suzuki *et al*, 2005). After extensive hearings, the Royal Commission concluded that such data were lacking to implicate tremolite as the cause of mesothelioma in chrysotile asbestos-exposed miners (Dupré *et al*, 1984). To date, no more compelling data have been produced to conclude otherwise and, in fact, chrysotile's role in the aetiology of mesothelioma is continually reaffirmed (IPCS, 1998; Straif *et al*, 2009; IARC, 2012).

The McCormack *et al* (2012) article omits criticisms regarding the Quebec industry-sponsored research, which they refer to and where the 'amphibole hypothesis' originated. In the study by Lenters *et al* (2011), this research did not meet their quality of exposure assessment standard and was excluded for that reason. In fact, a major international epidemiology organisation has also raised criticisms of this same Quebec research in their Position Statement on Asbestos (JPC-SE, 2012).

The McCormack *et al* (2012) study minimises the health risks posed by chrysotile asbestos and suggests that 'strict regulation' in lieu of eliminating all asbestos use is acceptable. The suggestion that continuing 'controlled use' of asbestos is realistic is the asbestos industry's position and is contradictory to the World Health Organization's recommendation that all use of asbestos should stop (WHO, 2006).

Finally, the authors' inexplicable encouragement of a smoking cessation programme only for workers formerly exposed, and not for current asbestos workers, is an inconsistent public health position. The suggestion that 'controlled use' is effective has never been justified.

CONFLICT OF INTEREST

All authors are health professionals whose mandate is to advocate for health. Individually, and as part of his professional or academic duties, SHW serves as Chair of the Joint Policy Committee of the Societies of Epidemiology (JPC-SE), a consortium of 13 organisations described at www.jpc-se.org, which prepares evidence-based materials that are vetted through the individual societies for comment and possible endorsement. Both SHW and CLS played a role in the 2012 JPC-SE position statement on asbestos. RAL, BC, CLS and ALF are elected Fellows in the Collegium Ramazzini that advocates the banning of both asbestos products and mining, worldwide. BC and RAL have been advisors to the World Health Organization, which advocates against asbestos use worldwide. ALF, RAL and BC are members of the Science Advisory Board to the Asbestos Disease Awareness Organization, which advocates a worldwide ban on asbestos. RAL is retired from the National Institute for Occupational Safety and Health of the United States that recommended a ban on asbestos in the workplace as early as 1976. RAL was a Working Group member and primary author of the first International Agency for Research on Cancer (IARC) Monograph solely devoted to asbestos (Monograph 14, 1976), which determined that all forms of asbestos are carcinogenic. All authors have been retained and/or testified as expert witnesses in asbestos personal injury compensation claims, usually at the request of plaintiffs. Remuneration for such work has been donated by ALF and CLS to their respective employing institutions.

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Reply: Comment on 'Estimating the asbestos-related lung cancer burden from mesothelioma mortality'

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Sir,

In response to the comments of Lemen *et al* (2013) on our article (McCormack *et al*, 2012), we welcome the opportunity to endorse the original article and to demonstrate that none of the concerns raised are substantiated.

Our research was designed specifically to address the relationship between mesothelioma and asbestos-related lung cancer (ARLC) mortality, primarily in the form of a ARLC:mesothelioma ratio. This point is critical to interpreting our design and results.

Lemen *et al* (2013) express concerns pertaining to four issues: (i) studies included and omitted; (ii) a lack of consideration of further factors that affect asbestos-related cancer risks; (iii) discussions of the carcinogenicity of chrysotile; and (iv) risk mitigation. We address each of these in turn.

Our study included 68 risk estimates drawn from 55 studies. To estimate the ARLC:mesothelioma ratio, each study was required to have examined both cancer outcomes during the same follow-up period (see inclusion criteria). Thus, the recent update of the Balangero cohort (Mirabelli *et al*, 2008) was intentionally omitted having assessed only one of the two cancer end points. We are not aware of any studies that were incorrectly omitted; all eligible studies referenced by the two Hodgson and Darnton (2000, 2010) articles were included, including the North Carolina cohort (Loomis *et al*, 2009) that prompted the risk updates. It is not appropriate to compare the studies we included to those included in a meta-analysis with a completely different aim. In our analysis, excess cancer deaths were calculated for each cohort based on observed minus expected deaths, the latter based on national/regional age- and sex-specific rates. Thus, neither the number of excess deaths nor the ratio for each cohort, as a whole, is influenced by the quality or even availability of exposure data. Hence, we had no reasons to exclude the Quebec cohort (Liddell *et al*, 1997).

Our paper emphasises that the estimated fibre-specific ratios 'characterise the overall ARLC–mesothelioma relationship across

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exposure circumstances and over a long period of time, and do not serve to precisely quantify lung cancer excess in a short time period.' Such ratios are also the most relevant when applied externally to estimate ARLCs from observed mesotheliomas, as the latter usually arise from a combination of different, often unknown, exposure histories. As pointed out by Lemen *et al* (2013) and in the devoted Discussion section ('Heterogeneity in ratio estimates within and between cohorts'), variations in the ARLC:mesothelioma ratios between cohorts or between subsets of workers within cohorts may indeed occur due to outcome misclassification, latency, exposure levels, potential confounding. Nevertheless, the best estimates of the average ratios across exposure circumstances are the ones we presented, being based on the most complete evidence-base possible.

On the carcinogenicity of chrysotile, our article clearly shows that there are both excesses of mesothelioma (four mesothelioma deaths per 1000 deaths) and lung cancer (SMR 1.7, table 3) associated with chrysotile. This is entirely consistent with the IARC classification of chrysotile as a Group 1 carcinogen to humans (IARC, 2012). At no point do we conclude that 'mesothelioma occurring in chrysotile-exposed cohorts is due to other asbestos types'; rather we considered it valid to discuss that when multiple carcinogenic fibres are present, the relevant contribution of each is more difficult to disentangle. This is particularly the case for chrysotile in the presence of amphiboles because, as concluded by the most recent meeting of the IARC Monographs, the latter appears to have a greater potency for the induction of mesothelioma than does chrysotile (IARC, 2012).

Lemen *et al* (2013) misinterpret our paper suggesting that it 'minimises the health risks posed by chrysotile'. On the contrary, we concluded the paper by emphasising the cancer risks posed by this asbestos fibre, risks that are often overlooked because they are lung cancers typically occurring in smokers. Finally, on the potential for the reduction of asbestos-related cancers, we focussed on relevant actions in two exposure groups. In currently exposed workers, removing exposure is a priority, which is consistent with WHO's position that the most efficient way to eliminate asbestos-related diseases is to stop the use of all types of asbestos (World Health Organization, 2010). Because this is not an option for formerly exposed workers, we highlighted the benefits of smoking cessation for this group. Unquestionably smoking cessation has multiple benefits for all smokers, regardless of their current or past asbestos exposure, and at no point do we suggest otherwise.

We trust that the concerns of Lemen *et al* (2013) are sufficiently addressed herein and that the important public health message of the extent of both the mesothelioma and lung cancer burdens due to all types of asbestos fibres is clear.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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