Review of "Eliminating occupational cancer in Europe and globally" by J. Takala

There primary concerns of this manuscript are outlined below. More detail discussion of these points is presented on the following pages.

1. The author makes no distinction at all between chrysotile and amphibole asbestos and instead groups all asbestos findings together.

2. The first 12 pages of the manuscript use selective data to establish the cancers at work and the associated burden of occupational cancer.

3. The author selectively chooses his references to obtain high estimates and ignores more recent studies which show lower estimates.

4. In the subsequent discussion on "Asbestos exposure is the biggest killer", the author 'blends' data on past exposures in implying that they are current exposures causing cancer without presenting the time course of use or differentiating between effects from chrysotile in comparison to amphibole asbestos.

5. Takala then proceeds to explain that the ratio between mesothelioma and work-related lung cancer commonly used in the past was 1:1 citing as an example, Rushton (Rushton et al. 2012). He states that this estimate may be underestimate the realted lung cancer as identification of asbestos related cancers in populations in each country is not very feasible.

6. Takala uses the McCormack et al. 2012 to state that the lung cancer – mesothelioma ratio is much higher than previously estimated and as a result the number of asbestos related deaths is much greater than WHO had originally stated. The author relies on the McCormack et al. 2012 publication to make extrapolation from mesothelioma cases to lung cancer cases, however, the McCormack et al. 2012 paper clearly states that *"For chrysotile, widely consumed today, asbestos-related lung cancers cannot be robustly estimated from few mesothelioma deaths and the latter cannot be used to infer no excess risk of lung or other cancers."*

7. Takala then proceeds to extrapolate the incorrect ratio of lung cancer to mesothelioma derived from McCormack et al. 2012 world wide by using as a proxy for asbestos exposure the asbestos consumption in tonnes of asbestos used in a country or region. In doing so he uses estimates from Tossavainen 2004 which are based upon "asbestos" consumption Australia, Europe and the Unites States in the early 1970's. In addition, the Tossavainen 2004 paper does not present asbestos use by fiber type (chrysotile vs amphibole asbestos) or differentiate mesothelioma incidence by fiber type.

8. As stated by McComack et al, 2012, "For chrysotile, widely consumed today, asbestos-related lung cancers cannot be robustly estimated from few mesothelioma deaths and the latter cannot be used to infer no excess risk of lung or other cancers."

1. **The author makes no distinction at all between chrysotile and amphibole asbestos and instead groups all asbestos findings together.**

   Nearly all the references included by Takala refer only to "asbestos" and do not differentiate between effects from pure chrysotile and those from amphibole asbestos. Takala references himself 4 times only one of which is a peer-reviewed publication. In all these references, there is no mention of chrysotile and no distinction between effects from pure chrysotile and amphibole asbestos.

   He cites Straif (2008 and 2012) in the introduction on estimates of occupational cancer, however, Straif also makes no mention of chrysotile and only uses the term "asbestos" with no distinction between the types.

   In addition, he cites Rushton et al., 2008 and 2012 who present estimates on the burden of occupational cancer in the UK. Rushton et al., 2008 and 2012 do not mention the word chrysotile in their papers and refer only to "asbestos". There is no mention in these articles that the UK was the largest importer of amphibole asbestos in Europe

2. **The first 12 pages of the manuscript use selective data to establish the cancers at work and the associated burden of occupational cancer.**

   Takala selectively cites the scientific literature in order to provide the highest estimates of occupation cancer. In doing so he relies predominately on the estimates proposed for the UK by Rushton et al., 2008 and 2012.

3. **The author selectively chooses his references to obtain high estimates and ignores more recent studies which show lower estimates.**

   The publication by Purdue et al., 2015 entitled "The proportion of cancer attributable to occupational exposures" which appeared in the journal Annals of Epidemiology has not been cites by Takala. The Purdue et al. publication takes into account studies from the United States, Denmark, Finland, Iceland, Norway, Sweden, and Great Britain. From these studies they reported that "The estimated occupation-attributable fraction for total cancer generally ranged between 2% and 8% (men, 3%-14%; women, 1%-2%)". These estimates are lower than those cited by Takala.

4. **In the subsequent discussion on "Asbestos exposure is the biggest killer", the author 'blend' data on past exposures in implying that they are current exposures causing cancer without presenting the time course of use or differentiating between effects from chrysotile in comparison to amphibole asbestos.**

Takala focuses on the UK largely through the Rushton study as this study provides the highest estimates of cancer. Yet, he does not clearly explain that the exposures which potentially could cause these cancers occurred 30 – 60 years ago due to the latency for lung cancer and mesothelioma to develop. He does state in the middle of page 11 that "Current estimates of occupationally related cancers result from exposures to hazardous agents many decades ago, but hazardous substances continue to be found in the workplace and pose a risk of future disease." *However, he does not state that UK importation of amphibole asbestos was the highest in Europe and that importation of amosite asbestos was eliminated in the 1980 and chrysotile in 2000.*

Takala continues by stating that "One way to estimate exposures is to investigate the current prevalence of occupational exposure to carcinogens by interviewing a random population of working age men and women in a geographical area such as the Australian Work Exposures Study (Carey et al. 2014)."

In Figure 4 Most frequent carcinogens and exposures at work in the United Kingdom, even if one were to accept these estimates, there is no time line of when these exposures took place, whether they are past exposures or current exposures and again pure chrysotile use as occurs today is not differentiated from mixed or pure amphibole asbestos use.

Takala implies that the past exposures that may account from the cancers are also current exposures. This is seen on Page 12 were he states:
"Occupational carcinogens affect 1 in 5 workers in the EU, based on EU CAREX (Carcinogen exposure database), or 23 per cent of those employed are exposed to carcinogens (Kauppinen 2000)."

However, looking at the reference Kauppinen 2000, we find that this is a summary of a workshop and not published. Still in all, Kauppinen 2000 states in the conclusions that:
"The Finnish job-exposure matrix (FINJEM) provides quantitative estimates of the prevalence and level of exposure for over 80 chemical, physical, microbiological, ergonomic and psychosocial factors for many occupations (n=311) in eight time periods (1945-2009)." This clearly was not convenient for Takala to mention.

5. **Takala then proceeds to explain that the ratio between mesothelioma and work-related lung cancer commonly used in the past was 1:1 citing as an example, Rushton (Rushton et al. 2012). He states that this estimate may be underestimate the realted lung cancer as identification of asbestos related cancers in populations in each country is not very feasible.**

Takala starts this section by citing the WHO and ILO estimates of asbestos-related mortality of 107,000 and 100,000 – 112,000 deaths per year.

He then informs us that the ratio between mesothelioma and work-related lung cancer commonly used in the past was 1:1 citing as an example, Rushton (Rushton et al. 2012). He then states that that the number of asbestos induced lung cancers has been underestimated. To support this he cites the publication by McCormack et al. 2012 in order to use mesothelioma as a proxy for asbestos exposure.

6. **Takala uses the McCormack et al. 2012 to state that the lung cancer – mesothelioma ratio is much higher than previously estimated and as a result the number of asbestos related deaths is much greater than WHO had originally stated. The author relies on the McCormack et al. 2012 publication to make extrapolation from mesothelioma cases to lung cancer cases, however, the McCormack et al. 2012 paper clearly states that "For chrysotile, widely consumed today, asbestos-related lung cancers cannot be robustly estimated from few mesothelioma deaths and the latter cannot be used to infer no excess risk of lung or other cancers."**

Takala then proceeds using the McCormack et al. 2012 to state that the lung cancer – mesothelioma ratio is much higher than previously estimated and as a result the number of asbestos related deaths is much greater than WHO had originally stated.

To do this Takala relies on the McCormack et al. 2012 publication to make extrapolation from mesothelioma cases to lung cancer cases, however, the McCormack et al. 2012 paper clearly states that *"For chrysotile, widely consumed today, asbestos-related lung cancers cannot be robustly estimated from few mesothelioma deaths and the latter cannot be used to infer no excess risk of lung or other cancers."*

McCormack et al. do shown an association of lung cancer to chrysotile, however, this is based upon the Hodgson and Darton evaluation in which both pure chrysotile cohorts are mixed with “predominately chrysotile” cohorts, the latter which included some amphibole asbestos exposure. These “predominately chrysotile” cohorts have been reviewed by Bernstein et al., 2014.

Takala further inflates the numbers he cites as he does not discuss the fact that individuals with both mesothelioma and lung cancer will likely succumb from mesothelioma rather than lung cancer. He treats each as a separate event.

Takala cites the publication by Straif 2012 on estimates of occupational cancer due to asbestos. As mentioned above, Takala does not mention or differentiate chrysotile form amphibole. In addition, he states that a “ratio of 1:1 for mesothelioma to lung cancer deaths has been used for the estimation of lung cancers attributable to asbestos”. Straif is from IARC and his article was published on 19 June 2012. Yet, he did not find it convenient to reference the McCormack et al. also from IARC and on which he was a co-author. The McCormack et al article was published in the same journal on 10 January 2012 – 6 months earlier and clearly explained that his premise was without validity.

7. **Takala then proceeds to extrapolate the incorrect ratio of lung cancer to mesothelioma derived from McCormack et al. 2012 world wide by using as a proxy for asbestos exposure the asbestos consumption in tonnes of asbestos used in a country or region. In doing so he uses estimates from Tossavainen 2004 which are based upon "asbestos" consumption Australia, Europe and the Unites States in the early 1970's. In addition, the Tossavainen 2004 paper does not present asbestos use by fiber type (chrysotile vs amphibole asbestos) or differentiate mesothelioma incidence by fiber type.**

   Takala states ideally the individual cancers caused by asbestos should be investigated in each country, that "However, this cannot be realistically carried out in every country soon. A reasonable proxy for asbestos exposure will be the asbestos consumption in tonnes of asbestos used in a country or region."

   He then proposes using a mesothelioma – lung cancer ratio to adjust all deaths based on consumption stating:

   "International comparison has shown that, in average, every 170 tonnes of asbestos used in a country causes one mesothelioma death (Tossavainen 2004)."

   Consistent with Takala's approach of using non-specific references, the Tossavainen 2004 paper does not present asbestos use by fiber type (Chrysotile vs amphibole asbestos) and in addition, the consumption data dates from 1970-1975 when amphibole asbestos was heavily used and the mesothelioma incidence dates from 1995-2000, independent of which asbestos fiber type was associated with the effect. All the countries used in the Tossavainen 2004 (Australia Finland France Germany Great Britain Italy Netherlands New Zealand Norway Sweden United States) were in the 1970's using large amounts of amphibole asbestos. Tossavainen 2004 does not include Russia in this list although he states that "In Russia, the extensive use of asbestos would predict a high incidence of mesotheliom, but the smaller use of amphiboles and the lesser level of tremolite impurities in the Russian chrysotile could reduce the risk."

   These details mentioned by Tossavainen 2004 are totally ignored by Takala in his presentation.

8. **As stated by McComack et al, 2012, "For chrysotile, widely consumed today, asbestos-related lung cancers cannot be robustly estimated from few mesothelioma deaths and the latter cannot be used to infer no excess risk of lung or other cancers."**