Ann. Occup. Hyg., Vol. 55, No. 6, pp. 565–568, 2011

doi:10.1093/annhyg/mer042

Commentary

Applying Quality Criteria to Exposure in Asbestos Epidemiology Increases the Estimated Risk

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Received 29 May 2011; in final form 6 June 2011

Mesothelioma deaths due to environmental exposure to asbestos in The Netherlands led to parliamentary concern that exposure guidelines were not strict enough. The Health Council of the Netherlands was asked for advice. Its report has recently been published. The question of quality of the exposure estimates was studied more systematically than in previous asbestos meta-analyses. Five criteria of quality of exposure information were applied, and cohort studies that failed to meet these were excluded. For lung cancer, this decreased the number of cohorts included from 19 to 3 and increased the risk estimate 3- to 6-fold, with the requirements for good historical data on exposure and job history having the largest effects. It also suggested that the apparent differences in lung cancer potency between amphiboles and chrysotile may be produced by lower quality studies. A similar pattern was seen for mesothelioma. As a result, the Health Council has proposed that the occupational exposure limit be reduced from 10 000 fibres m^{-3} (all types) to 250 f m^{-3} (amphiboles), 1300 f m^{-3} (mixed fibres), and 2000 f m^{-3} (chrysotile). The process illustrates the importance of evaluating quality of exposure in epidemiology since poor quality of exposure data will lead to underestimated risk.

Keywords: asbestos; exposure assessment; guidelines; risk assessment

THE CONTINUING DEBATE ON HEALTH CONSEQUENCES OF ASBESTOS

Asbestos is a well-known carcinogen responsible for cancer of the pleura and peritoneum (mesothelioma) and lung cancer. The profound consequence of historical exposure to asbestos is well documented in many countries (Lin *et al.*, 2007). In all Western countries, the pleural mesothelioma incidence among men has increased dramatically in the past 40 years. In recent years, in some countries, a leveling off of mesothelioma rates has been observed, whereas in most countries, the mesothelioma incidence is still expected to rise in the next few years (Montanaro *et al.*, 2003; Burdorf *et al.*, 2005). Asbestos is most likely the occupational risk with the highest burden of disease. For example, The Netherlands has one of the highest mesothelioma-related mortality rates that is expected to peak around 2014, and in the period 2000–2028, at least 13 000 mesothelioma deaths and another 13 000 deaths due to asbestos-related lung cancer are expected (Segura *et al.*, 2003). In the UK, mesothelioma mortality is predicted to peak at 2400 deaths in the year 2016 and from 2007 to 2050 will contribute to at least 60 000 deaths (Tan *et al.*, 2010).

The effects of asbestos on health are one of the best documented, yet most controversial, topics in occupational health. Although many thousands of articles are available on the health effects of asbestos, considerable debate remains on the differences in carcinogenicity among different fibre types and the exact shape of the exposure–response relationship (Ogden, 2009). This debate rages also on the pages of the *Annals of Occupational Hygiene*, as illustrated by recent publications whereby one author stated

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firmly that amphiboles are responsible for almost all cases of mesothelioma (McDonald, 2010), and other authors showed that mesothelioma cases also occurred among workers in a plant using only chrysotile (Finkelstein and Meisenkothen, 2010).

Other ongoing asbestos debates relate to the derivation of occupational exposure limits and to the risk to public health posed by typically low levels of environmental exposure. Two authoritative meta-analyses of epidemiological studies on exposure–response relationships show an order of magnitude agreement in excess risk expressed per fibre year (Hodgson and Darnton, 2000; Berman and Crump, 2008a,b). However, small differences in estimated risk may easily amplify in formal risk assessments procedures that rely on extrapolation towards very low levels of exposure to asbestos that were not encountered in the epidemiological studies included in the meta-analyses. Studies in the cities of Casale Monferrato and Bari in Italy (Magnani *et al.*, 2001) and Amagasaki City in Japan (Kurumatani and Kumagai, 2008) have demonstrated that environmental exposure to asbestos in the vicinity of asbestos-cement plants, at levels much lower than typically seen in occupational situations, may cause mesothelioma.

RENEWED DISCUSSION OF ASBESTOS IN THE NETHERLANDS

In the Netherlands, the use of asbestos was prohibited in 1993, but relevant occupational exposure may still occur during demolition activities. Prevailing occupational exposure limits and environmental standards were regarded as sufficient to protect the population against unacceptable risks in the future. All seemed well and settled.

Around 2000, a few women died of mesothelioma, who had lived in the direct vicinity of a factory that produced asbestos-cement in the past. This plant had distributed asbestos waste (friable and non-friable waste products containing asbestos types: chrysotile, crocidolite, and amosite) for free to local residents for private and public use in order to harden dirt tracks, yards, and driveways during 1935–1974. Therefore, the soil in this area was polluted with friable and non-friable waste materials (Driece *et al.*, 2010). Based on records of a compensation claim lawyer, at least five women with mesothelioma were identified with as only possible source of exposure the asbestos waste material on dirt tracks or yards around their homes (Burdorf *et al.*, 2004). Questions were asked in the Dutch Parliament and a full investigation was initiated, demonstrating that environmental exposure to asbestos had led to 14 female deaths from pleural mesothelioma, accounting for 64% of the extra incidence of mesothelioma among women in the area at risk (Sinninghe Damste *et al.*, 2007). The average cumulative exposure was estimated to be ~0.11 fibre-years ml^{-1}. These findings again raised the question in Parliament that whether the current guidelines were sufficiently strict to protect the general population. The Health Council of the Netherlands was asked for advice by the Ministries of the Environment and of Social Affairs and Employment to provide scientific evidence on risks of environmental and occupational exposure to asbestos.

NEW META-ANALYSIS ON EPIDEMIOLOGICAL STUDIES

The full report of the Health Council Committee was published recently (Gezondheidsraad, 2010). In this report, the Committee presents detailed arguments that not all epidemiological studies are equally suitable to be used in a risk analysis. It has become common practice in a meta-analysis to evaluate the influence of quality of the study on the overall pooled effect, whereby studies with better quality should contribute more to the evidence than studies with poor quality. Although quality aspects have been mentioned in earlier reviews on asbestos studies, quality was never systematically evaluated. This is a surprising finding, given the crucial role of epidemiological evidence in the guidelines for occupational and environmental exposure to asbestos. Since a poor quality of exposure estimates will inevitably lead to exposure misclassification and, thus, underestimation or misspecification of exposure–response relationships, the Committee decided to conduct a systematic review with quality appraisal and to analyse the influence of quality of the different studies on average effect estimates for asbestos and cancer.

QUALITY OF EXPOSURE ASSESSMENT

A generic framework for appraisal of the quality of exposure information in observational studies for risk assessment has recently been proposed (Vlaanderen *et al.*, 2008) and was adapted to epidemiological studies on asbestos. For the detailed appraisal of the scientific aspects on asbestos and lung cancer, we refer to the publication of Lenters *et al.* (2011). The full interpretation of the findings on both mesothelioma and lung cancer can be found in the original report of the Health Council (Gezondheidsraad, 2010). Five quality criteria were applied to selected cohort studies on asbestos-related disease in occupationally exposed workers. The first criterion was quality and transparancy of the descriptive documentation on the exposure assessment strategy in terms of number of measurements available, analytical procedures applied, and insight into variability in exposure within and between exposure categories. The second criterion was the use of internal or external conversion factors for changes over time in analytical and measurement techniques, most notably the conversion of particles into fibre counts. Studies with internal conversion factors across different departments in different time periods were given the highest quality. The third criterion evaluated the exposure contrast in the cohort study by the ratio in average exposure of the highest and lowest cumulative exposure category and a ratio of $\geq$50 was arbitrarily considered as a high and informative contrast. The fourth criterion related to the coverage of the accumulated work history of the cohort by exposure measurements. All selected cohort studies had used procedures for back extrapolation and those studies for which measurements were available during at least 30% of the follow-up period were regarded as of better quality. The fifth criterion stipulated that the job history information should be sufficiently detailed to capture changes in job titles or tasks over time in order to assign exposure correctly to individual workers.

QUALITY HAS A PROFOUND IMPACT ON RISK ESTIMATES

In total, 19 cohort studies were included in the analysis of asbestos and lung cancer. For each quality criterion, the pooled effect of high-quality studies was larger than the pooled effect of low-quality studies. The quality of coverage of exposure data and job history were most critical, and excluding studies that failed by these criteria increased the risk estimate 3- to 6-fold. The measure used was the slope ($K_L \times 100$) of increase in the relative risk per unit of cumulative exposure to asbestos [in fibre-years per millilitre]. Interestingly, these differences were comparable to the observed differences between amphiboles and chrysotile. With a stepwise exclusion of less informative studies, the risk estimate $100 \times K_L$ increased from 0.13 (19 studies) to 0.48 (3 studies) (Lenters *et al.*, 2011). A similar pattern was observed for the meta-analysis of asbestos and mesothelioma. The meta-analysis on 12 studies showed a striking difference in carcinogenic potency between amphiboles, mixed exposure, and chrysotile with risk estimates K_M of 7.95, 1.08, and 0.017, respectively. However, when limiting the analysis to the studies with the highest quality with regard to exposure information, this difference decreased substantially with risk estimates K_M of 1.30 for mixed exposure and 0.15 for chrysotile (Gezondheidsraad, 2010).

This approach demonstrated that disparities between observed risks of asbestos exposure in epidemiological studies may be partly explained by profound differences in quality of the exposure information. Moreover, for lung cancer, it cannot be excluded that the suggested differences in potency between chrysotile and other types of asbestos may be entirely due to quality issues since too many studies had major limitations in their exposure assessment. With regard to mesothelioma, the differences between fibre types became less prominent when adjusted for quality of exposure information since studies of the highest quality were actually those where workers had a predominant or exclusive exposure to chrysotile.

NEW PROPOSALS FOR GUIDELINES ON OCCUPATIONAL AND ENVIRONMENTAL ASBESTOS

This novel approach by the Health Council of the Netherlands resulted in estimates of the slopes of exposure–response relationships that are roughly 5–10 times higher than those published in well-cited meta-analyses of Hodgson and Darnton (2000) and Berman and Crump (2008a,b). The existing Dutch occupational exposure limit is 10 000 fibres m^{-3} (equivalent to 0.01 fibres ml^{-1}), as measured by phase contrast microscopy, and applies to all fibre types. In current procedures, for risk assessment, two risk levels have to be determined, corresponding to one extra death for every 250 deaths from all causes (1.10^{-4} per year) and one extra death for every 25 000 deaths from all causes (1.10^{-6} per year). These risk levels are calculated for 40 years of occupational exposure.

Under the assumption of an acceptable risk of one additional death due to either lung cancer or mesothelioma per 1 000 000 person-years among exposed workers, the Health Council has proposed the following occupational exposure limits: amphiboles 420 fibres m^{-3}, mixed fibre type 1300 fibres m^{-3}, and chrysotile 2000 fibres m^{-3}. The proposals are currently considered by the Dutch government and special emphasis is given to exposure assessment procedures to demonstrate compliance with these standards. These new proposals also illustrate that the occurrence of mesothelioma due to low levels of environmental exposure in the vicinity of the asbestos-cement plant was to be expected. This supports a stringent policy to clean up the polluted area from asbestos waste.

LESSONS LEARNED

The report of the Health Council of the Netherlands on risks of environmental and occupational exposure to asbestos clearly demonstrates that a thorough evaluation of the quality of exposure assessment in epidemiological studies should be incorporated in risk assessment procedures. The quantitative evaluation of the impact of quality on the overall pooled risk is a better approach than discussing in a narrative review the pros and cons why particular studies should be included in a formal meta-analysis or not, as is typical for the asbestos debate. The traditional focus on large cohort studies should be shifted towards studies with the best exposure assessment strategies since exposure misclassification will attenuate the exposure–response relationship and, thus, result in biased risk estimates. A poor exposure assessment in epidemiological studies will lead to occupational exposure limits that do not protect the workforce against harmful effects. Occupational hygienists should play a crucial role in the design of epidemiological studies in occupational populations.

Acknowledgements—Both authors were members of the committee on asbestos of the Netherlands Health Council. The findings and conclusions in this article reflect the opinions of the authors and should not be construed to represent a statement of the Dutch Health Council.

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