Ann. Occup. Hyg., Vol. 57, No. 5, pp. 675–677, 2013

Reply

Received 11 March 2013; in final form 12 March 2013

RESPONSE TO THE LETTER BY DRS BERMAN AND CASE

In 2011, we published in *Environmental Health Perspectives* a meta-analysis of the association between occupational asbestos exposure and lung cancer, exploring how aspects of the exposure assessment strategy influenced heterogeneity in exposure–response associations (Lenters *et al.*, 2011). In a separate commentary in this journal, we discussed that some elements of this meta-analysis were used by the Health Council of the Netherlands in their re-evaluation of exposure standards for asbestos, both for occupationally exposed and non-occupationally exposed (Burdorf and Heederik, 2011). Our commentary and our meta-analysis were criticized in a commentary by Berman and Case (2012). We replied to their arguments one by one in great detail and concluded that we remained confident about the conclusions we reached earlier (Lenters *et al.*, 2012). Berman and Case (2013) now continue the discussion by reiterating their opinion that in whatever way study quality is considered, observed effects are better attributed to fibre type than study quality. They thus argue that fibre type is the strongest determinant of risk for lung cancer.

In our meta-analysis, we clearly demonstrate that the variability in exposure–response slopes is influenced by fibre type and quality of exposure assessment. We argue that ignoring the latter may result in a biased estimate of the difference in carcinogenic potency of different fibre types. We see no need to change these conclusions on the basis of their most recent (repeated) comments.

A crucial point in the discussion is that one may question whether all evidence should be included in risk assessments for protecting the workforce and general population. Some studies cannot be interpreted because basic documentation is (sometimes completely) lacking, whereas others have major limitations. These are serious omissions and especially against the background of progress in methodologies in occupational epidemiology; some studies would not be included under current practices in meta-analyses. Many regulatory agencies follow the practice that studies must meet minimum documentation and quality criteria before they are included in evaluations. The problem with regard to risks associated with exposure to asbestos is that some questions will be answered better and with less uncertainty only by conducting new studies with a rigorous design and high quality exposure assessment than by (re-)evaluating the available evidence across all studies with its limitations in new meta-analyses. New studies like the recently published study among Chinese textile workers exposed to chrysotile asbestos are of more potential relevance (Wang *et al.*, 2013). The quality of this study needs to be established, but it is of interest that this study has a relatively steep exposure–response relation. Similarly, a large pooled analysis of case–control studies on joint effects of occupational carcinogens, including asbestos, and smoking in relation to lung cancer will hopefully also produce informative evidence, which may contribute to the discussion on fibre type and lung cancer risk (Olsson *et al.*, 2011).

We agree with the concluding sentences by Dr Hodgson (this issue) on study quality and fibre type that no statistical conclusion can be as clear and robust as we would like them to be on such an important question (Hodgson, 2013). Scientists in the public health field have to consider the limitations of the available evidence and translate these into conservative exposure standards to protect our workers and the general public. This goes beyond answers to questions on the role of fibre type versus study quality and which association is stronger. We concur that fibre type is important—especially as most of the asbestos mined is chrysotile asbestos—but reiterate that in evaluations of exposure–response associations, quality of exposure assessment should

be considered. This point has been shown in several recent papers on this topic (e.g. Karami *et al.*, 2012; Vlaanderen *et al.*, 2012).

RESPONSE TO THE LETTER BY DR HODGSON

Hodgson (2013) performed additional analyses in response to our meta-analysis and commentary as well as the discussion with Berman and Case (2012). We welcome this additional piece of work that includes permutation tests to explore the effects of including and excluding individual studies from the sensitivity analysis we published earlier. The results indicate a somewhat stronger effect of fibre type versus study quality. An important final conclusion by Dr Hodgson is that study quality should in principle be taken into account. More importantly, the analysis also further illuminates how limited the available data is, and as a result, how difficult it is, if not impossible, to draw strong and statistically robust conclusions on one of the carcinogens most often studied. We agree with the concluding sentences by Dr Hodgson on study quality and fibre type in which he states that no statistical conclusion can be as clear and robust as we would like them to be on such an important question.

Dr Hodgson asks the question how quality should be taken into account in a meta-analysis. Berman and Crump (2008) changed the weight of a study in their meta-analysis by widening the confidence limits based on arbitrary units depending on quality. We would argue against such an approach because it does not distinguish accuracy and precision of an estimate. As such, the approach ignored that exposure assessment quality issues do have an effect on both the slope and the confidence interval of the exposure–response relation. We do advocate that meta-analyses and risk assessments should be transparent about the effect of study quality on exposure–response relations in the analysis. However, it is the responsibility of the researchers that perform the risk assessment to define *a priori* the quality criteria that they deem most appropriate (e.g. Vlaanderen *et al.*, 2010, 2011). It is a debatable practice to include studies that are not sufficiently documented and for which, as a result, crucial elements of the design and findings of these studies cannot be judged. The evaluation committee for asbestos of the Health Council of the Netherlands did make their own choices in this context.

It is good to realize that all our conclusions from this discussion are based on the assumption that associations between exposure and risk can be described by linear associations. A recent meta-analysis indicated that this might not be true (van der Bij *et al.*, 2013). Meta-analysis on the basis of flexible modelling resulted in smaller and non-significant differences between different fibre types at the low exposure range, indicating that all earlier analyses presented have also some intrinsic limitations related to assumptions made.

Dr Hodgson criticizes some aspects of our quality criteria. We would like to clarify that we do not claim to have produced the definitive set of criteria for the purpose of study quality evaluations. We were interested in a 'proof of principle' type of exercise and defined a set of criteria that we *a priori* thought covered some of the major issues in exposure assessment in the context of epidemiological studies, and for asbestos specifically. To define a comprehensive set of criteria for wider application seems an important task, which requires interdisciplinary action by occupational hygienists, epidemiologists, and occupational physicians and any such initiative is welcomed. However, we do not agree with the notion that contrast is a characteristic of a study that does not measure quality, but is merely an estimate of power. We can refer to the abundant literature on attenuation of exposure–response relations in relation to exposure variability. Underestimation of the exposure–response relation is dependent on the ratio of inter-individual variation of exposure relative to the intra-individual variation. Thus, studies with the same intra-individual variability in exposure, but different inter-individual variability in exposure, will yield different exposure–response slopes. In reality, this is not as simple as described by attenuation formulas because we use a combination of data on the individual level and categorized data, but it illustrates why we chose to consider contrast in exposure.

In addition, an underpowered study is a study that is poorly designed to answer the research questions asked. This is more than a semantic word game. Several studies on cancer risks resulting from asbestos exposure, also some of those included in the evidence base considered by us and Dr Hodgson, are small with little contrast in exposure, and could not have answered the research question they were designed for. On the other hand, this is not problematic for a meta-analysis. Such a study can be included and will in the end have limited influence.

Dr Hodgson specifically mentions the Gustavsson study (Gustavsson *et al.*, 2002): a case–control study that satisfies four of the five quality criteria, but '… produces a clearly aberrant exposure response

estimate …'. This is an intriguing statement because it is a high-quality study for which one of the quality criteria (coverage of the risk period) is difficult to assess because of its design, and not because the quality of the study for this aspect has proven to be low. Some aspects of the Gustavsson study, which differ from the cohort studies, may have contributed to the steep exposure–response slope, truly non-exposed controls, adjustment for smoking, a considerably more recently exposed population, and measurements available for many occupations. Yes, this study stands out, but whether it is aberrant, and has to be considered as a statistical outlier, is something that cannot be judged based on a high exposure–response slope alone. This study presents results in a range of exposures generally not studied by others, and needs to be corroborated by similar studies.

We agree with Dr Hodgson that only further research, but especially new independent data, will be able to answer some of the questions that we still have about health risks of asbestos. This is a crucial conclusion; only additional high-quality studies will add new information and might help to answer questions regarding potency in relation to fibre type and study quality.

We maintain that exposure assessment quality has received too little attention in evidence syntheses of asbestos and lung cancer compared with the traditional focus on fibre type. Any meta-analyses should evaluate and be transparent about the effect of quality. How this should be done is a matter of protocol development and up to regulatory agencies. We are confident that our work will contribute to this endeavour.

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doi:10.1093/annhyg/met017