I thank Dr. Boffetta and co-authors1 for taking the trouble to answer my critique of their study on lung cancer among man-made vitreous fibers (MMVF) workers,2 a critique that I e-mailed to each one of them as early as September–October 2001. (Regrettably, I never received any response to this attempt to engage Dr. Boffetta and co-workers in an informal scientific discussion of their study.)

In their letter to the editor,1 Dr. Boffetta and co-authors declare their surprise that my critique3 was published in the present journal. Some background information is needed to elucidate why things happened that way:

When Dr. Boffetta and co-workers first published their study in December 2000, it was in the form of an internal IARC report2 (available to people who asked for it). By the same time, the mass media were notified about the results that seemed to acquit rock and slag wool of being carcinogenic. Later, in October 2001, their report2 formed the basis on which IARC decided to downgrade rock and slag wool fibers from class 2B (possibly carcinogenic to humans) to class 3 (not classifiable as to carcinogenicity in humans).4 During this process of mass-media promotion and IARC decision making, the study on lung cancer among MMVF workers2 was de facto not open for a customary discussion within the scientific community.

In July 2002, the MMVF study2 was published in Epidemiology,5 and about the same time my critique of the IARC report2 was published in the present journal.3 Subsequently, I submitted a critical letter to the editor of Epidemiology, but the editor rejected my letter with the argument that my critique had already been published elsewhere. Accepting that, I submitted a new, ultra-short letter (a few lines only) to Epidemiology to provide the readers of that journal with a reference to my critique.3 However, the editor of Epidemiology refused to publish even that very short letter.

Now to the substantial comments put forward by Dr. Boffetta and co-authors:

Asbestos

In their letter,1 Dr. Boffetta and co-authors try to play down the remarkable fact that their study failed to demonstrate an association between asbestos and lung cancer.2 However, the observation of four cases of mesothelioma among the MMVF workers2 strongly indicates that asbestos exposure had not been negligible. Failing to demonstrate an asbestos–lung cancer association,2 the investigators ought to admit that their study performs poorly in terms of detecting existing relations.

Ascertainment of the Case Diagnosis

Non-differential misclassification of non-cases as “cases” produces a strong bias towards null-results in case–control studies.6 In the nested case–control study by Dr. Boffetta and co-workers,2 a great part of the “lung cancer” diagnoses came from death certificates only. In total, histology was lacking for 55 (41%) of the “lung cancer” cases,2 and at least some of these people are likely not to have had lung cancer. Comparing results for all cases with results based on histologically verified cases only, I found a consistent difference5 suggesting that the case series actually did contain some false cases. In that context, the authors declare that I did ignore “...the fact that the number of histologically verified cases we reported refers to workers employed more than one year...”1, a statement that lacks sound basis: From the IARC report,2 it is possible to extract comparable data for analyses based on all cases and analyses based on histologically verified cases only.3

Selection of the Control Series

Dr. Boffetta and co-authors will have that I have stated that they “...did not consider cases of lung cancer before they develop the disease as candidates for the control series.”1 I never made any statement of that kind. I did, however, notice the fact that the control series contained no subjects that became cases after enrolment as controls, and I mentioned that I would have expected the control series to contain at least a few (later) cases, in particular as the match-stratification made the data so sparse that each one of 44 subjects had to serve as control for more than one case.3

As regards the exclusion of people with tobacco-related diseases from the control series,2 this peculiarity of the MMVF study has created a control series that consistently underrates the prevalence of heavy smokers in the base population, i.e., the population from which the lung cancer cases emerged. The effect of employing such a smoking-biased control series is that the influence of (heavy) smoking is overrated in the case series, from which heavy smokers were not excluded. Dr. Boffetta and co-authors state that “...the lack of evidence of confounding of tobacco smoking on MMVF-associated lung cancer risk within the case–control study further invalidates Dr. Hansen’s argument,”1 a statement that makes no sense.
because the invalidity of their control series has to do with the fact that this series does not represent the study base with regard to smoking history.

Procurement of Exposure Data

Regarding the presence of truly unexposed jobs in MMVF production plants, I find it hard to believe that these jobs have not been affected by the overall fiber pollution of the indoor and outdoor areas of these plants.

As regards the dubious blinding of the expert panels, the net effect of a possible information bias cannot be stated. However, the problem needs to be considered, in particular as the expert panels not only reconstructed job and smoking histories, but also provided information about job- and period-specific exposures.

Time from Exposure to Disease

Dr. Boffetta and co-authors state that they did ignore lung cancer cases occurring within the first 15 years since the beginning of exposure. Contrary to that statement, the IARC report leaves one with the impression that they rather employed a lagging procedure in which they ignored exposure occurring within the last 15 years prior to diagnosis/enrolment into the control series.

Documentation

In my critique I mentioned that the IARC report was insufficiently documented and that the documentation available contained a considerable number of errors and miscalculations. (In September-October 2001 I e-mailed to Dr. Boffetta and co-workers a long list of documentation errors that I had encountered in their report.) In their letter to the editor, the authors have chosen not to comment on that part of my critique.

Conclusion

The comments by Dr. Boffetta and co-authors do not provide any important new arguments. Thus, I have to maintain that due to bias towards null-results, the study by Dr. Boffetta and co-workers does not add to our knowledge about a possible MMVF–lung cancer relation. Unfortunately, the IARC has based a downgrading on this non-informative study, a development that might have been prevented had Dr. Boffetta and co-workers been willing to engage in a scientific discussion at an earlier stage.

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References