The letter has not been published or simultaneously submitted for publication in whole or in part elsewhere.

Sir,

We read with interest the systematic review and meta-analysis by Dutheil et al. on occupational and residential exposure to asbestos and prostate cancer risk. We believe this study suffers from several methodological errors.

First, the search of the literature appears to be deficient. We conducted a quick search, which we do not pretend was systematic, and identified 10 studies that reported results on risk of prostate cancer among asbestos exposed workers and were not included in the review by Dutheil et al. (Table 1; outdated results were included for 4 studies). Notably, the 2 studies that included the largest number of prostate cancer deaths (Lin et al., 2015 and Ferrante et al., 2017) were not included in the meta-analysis by Dutheil et al.

Second, Dutheil et al. double-counted some observations. In particular, the papers by Reid et al. and Armstrong et al. refer to the same cohort of Australian crocidolite workers.

Third, it is debatable whether cohorts of oil refinery workers, such as that studied by Tsai et al., should be included in reviews on asbestos, since these workers are exposed to other potential carcinogens. In any case, if one particular cohort of oil refinery workers is included, it is not clear why the many other cohorts from the same industry are excluded.

Fourth, we think that it is a mistake to combine results of prostate cancer incidence and mortality. On the one hand, prostate cancer incidence is highly sensitive to the implementation of screening with prostate specific antigen. On the other hand, mortality from prostate cancer depends on access to effective treatment. These 2 factors might vary between asbestos-exposed workers and the national or regional populations that are used as reference in the studies. These sources of bias require careful consideration, and combining the 2 measures of occurrence, whose biases might act in opposite directions, generates confusion in the results.

For these reasons, we think that the results of the meta-analysis by Dutheil et al. are not interpretable and their conclusion that asbestos exposure is associated with prostate cancer is not justified. A careful review of this issue should be based on stronger methodology than the one used by Dutheil et al.

Disclosure Statement
Paolo Boffetta was involved in litigation on asbestos exposure and prostate cancer risk. Enrico Pira has acted as Court-appointed expert witness and as consultant to parties (judge, prosecutor, and defendant attorney) in asbestos litigations.

Authors’ Contributions
All authors contributed to the design of the study. Paolo Boffetta and Nicolò Franco drafted the manuscript; all authors reviewed and approved the manuscript.

Funding
No funds were obtained for the study.

How to Cite this Article

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Keywords: asbestos, bias, epidemiology, prostate cancer
In Response

To the Editor: We thank Boffetta et al. for their relevant comments concerning our recent systematic review and meta-analysis on asbestos exposure and prostate cancer.2

First, Boffetta et al.1 identified putatively missing articles in our meta-analyses (comprising 30 articles). However, we want to acknowledge that all the suggested articles are not retrieved in any databases using our search strategy. Our algorithm was (prostate cancer OR prostate neoplasm) AND (asbestos* OR crocidolite* OR chrysotile* OR amphibole* OR amosite*). All the 10 suggested articles did not describe prostate cancer within their title or their abstract. They were impossible to detect using our algorithm, as those articles did not focus at all on prostate cancer—prostate cancer is only described as one line in a table in those articles. The only way to systematically retrieve the 10 suggested articles would have been to broaden the keywords by removing the “prostate” keyword. Using our algorithm (ie, derivatives from “prostate cancer” and “asbestos”), we had a putative number of 2547 articles to include in our meta-analysis. Broadening our algorithm without “prostate” (ie, derivatives from “cancer” and “asbestos”), the number of putative articles to include would rise to more than 25,000 (10 times more), which is clearly nonmanageable. Boffetta et al.1 are experts on asbestos exposure, and we are thankful from their comments. However, articles were probably retrieved from their knowledge without using our algorithm, but this is not the way to compute a metaanalysis using a reproducible search strategy.

Lastly, we also want to point out that we included twice more articles than the preceding metaanalysis of Peng et al.3 published quite simultaneously with our metaanalyses. Second, we did not double-count the same observations. Armstrong et al.4 studied occupational asbestos exposure in miners, whereas Reid et al.5 described environmental exposure in children living around the mine. Moreover, the studies were published in 19884 and 20135 (ie, with a 25-year gap).

Third, concerning the inclusion of several type of workers (eg, miners, shipyard workers, firefighters, textile industry) and particularly oil refinery workers (ie, maintenance workers exposed to asbestos contained in insulation materials), all of these occupations were exposed to several

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Table 1. Selected studies reporting results on risk of prostate cancer among asbestos exposed workers that were not included in the review by Dutheil et al.1

<table>
<thead>
<tr>
<th>Study</th>
<th>Industry</th>
<th>Asbestos type</th>
<th>Country</th>
<th>Outcome</th>
<th>Sex</th>
<th>N</th>
<th>Obs</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acheson et al., 1984a,b</td>
<td>Insulation product mft</td>
<td>Am</td>
<td>UK</td>
<td>Mo</td>
<td>M</td>
<td>4820</td>
<td>2</td>
<td>0.94</td>
<td>0.11-3.40</td>
</tr>
<tr>
<td>Selikoff and Seidman, 1991*</td>
<td>Insulation workers</td>
<td>Mix</td>
<td>US, Canada</td>
<td>Mo</td>
<td>M</td>
<td>17800</td>
<td>59</td>
<td>1.12</td>
<td>0.85-1.45</td>
</tr>
<tr>
<td>Sanden et al., 1992*</td>
<td>Shipyard workers</td>
<td>P Ch</td>
<td>Sweden</td>
<td>Mo</td>
<td>M</td>
<td>3893</td>
<td>22</td>
<td>0.80</td>
<td>0.50-1.21</td>
</tr>
<tr>
<td>Ulvestad et al., 2002*</td>
<td>Cement workers</td>
<td>P Ch</td>
<td>Norway</td>
<td>In</td>
<td>M</td>
<td>541</td>
<td>8</td>
<td>0.6</td>
<td>0.3-1.1</td>
</tr>
<tr>
<td>Lin et al., 2015*</td>
<td>Mixed</td>
<td>Mix</td>
<td>Taiwan</td>
<td>In</td>
<td>M</td>
<td>121883</td>
<td>307</td>
<td>0.67</td>
<td>0.59-0.75</td>
</tr>
<tr>
<td>Levin et al., 2016*</td>
<td>Insulation product mft</td>
<td>Am</td>
<td>USA</td>
<td>Mo</td>
<td>PM</td>
<td>1130</td>
<td>6</td>
<td>0.78</td>
<td>0.29-1.70</td>
</tr>
<tr>
<td>Pira et al., 2016*</td>
<td>Textile product mft</td>
<td>Mix</td>
<td>Italy</td>
<td>Mo</td>
<td>M</td>
<td>894</td>
<td>7</td>
<td>0.74</td>
<td>0.38-1.94</td>
</tr>
<tr>
<td>Ferrante et al., 2017*</td>
<td>Mixed</td>
<td>Mix</td>
<td>Italy</td>
<td>Mo</td>
<td>M</td>
<td>40600</td>
<td>352</td>
<td>0.97</td>
<td>0.87-1.08</td>
</tr>
<tr>
<td>Pira et al., 2017*</td>
<td>Miners</td>
<td>Ch</td>
<td>Italy</td>
<td>Mo</td>
<td>M</td>
<td>1056</td>
<td>9</td>
<td>0.91</td>
<td>0.42-1.74</td>
</tr>
<tr>
<td>Rusiecki et al., 2018*</td>
<td>Shipyard workers</td>
<td>NA</td>
<td>USA</td>
<td>Mo</td>
<td>PM</td>
<td>4702</td>
<td>281</td>
<td>0.85</td>
<td>0.57-1.23</td>
</tr>
</tbody>
</table>

Results in italics are derived from raw data reported in the original publications.

pollutants and toxics (benzenes, metal fumes, petroleum derived, radiations, smokes, and carbon residues), rendering difficult robust conclusions on the specific link between the asbestos exposure and prostate cancer. To avoid exposition bias, we chose to include all workers or residents exposed to asbestos particles. There is a whole section discussing this limitation in the dedicated section of our article.

Fourth, we totally agree that it might be a bias to mix incidence data and mortality. This is why we computed a sensitivity analyses by type of risk (distinguishing mortality and incidence data): “Stratified results by type of risk demonstrated an increased risk of prostate cancer with standardized incidence ratio (effect size = 1.16, 95% CI = 1.04-1.27) and with standardized rate ratio (1.06, 1.04-1.27), whereas there was no evidence of an increased risk with standard mortality ratio and hazard ratio (1.09, 0.98-1.19; and 0.79, 0.45-1.13, respectively).”

In total, we understand the comments from Boffetta et al.1 even if answers were already within the articles. Metaanalysis follows a very logical methodology and has its own rules that some less-experienced readers might not be accustomed to. Our conclusions seem perfectly salient and careful; that is, “Asbestos exposure “seems to” increase the risk of prostate cancer.”

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Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Funding
This study was funded by the University Hospital of Clermont-Ferrand, France.

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