

Response to Tomenson's comment on the Short report by Guseva Canu et al. Lung cancer mortality in the French cohort of titanium dioxide workers: some aetiological insights.

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We thank the editor for the giving us the opportunity to respond to the points raised by Tomenson. Further, we would like to thank Tomenson for making publicly available parts of the so far unpublished report to the sponsors (the Titanium Dioxide Manufacturers Association, for which he provides consultancy services), including particularly the positive dose-response data for the French sub-cohort (re-analysed in our paper).¹

As clearly described in Methods and in Results of our short report, the cumulative exposure to TiO₂ was lagged by 10 years. Obviously, this also affects the number of unexposed and exposed workers as reported in the supplemental Table S3.² We recognize that we should have specified this also in the footnotes of that table.

Regarding tobacco smoking, data were available for 201 (not only 33) workers at the second French plant and the combined crude smoking prevalence for the two French plants was 34%, compatible with the age-standardized prevalence of 42% reported by Boffetta et al.¹ As discussed in our paper,² we recognize that the reported prevalence of smoking was low, and lower than that estimated on the national level.

As one part of our re-analysis, we used the available smoking data to explore potential confounding via multiple imputation for missing data, though we had to assume that data were missing at random. Given the relatively small number of cases, a complete case analysis (as suggested by Tomenson) would be much less informative.

In our re-analysis we found no evidence for confounding by smoking. Further, indirect methods support the notion that the observed positive dose-response relationship cannot be entirely explained by confounding due to smoking.³

Finally, we do not think that the increased risk among workers exposed to TiO₂ or the positive dose-response relationship would be due to a low mortality rate in the unexposed workers. Using the low exposure group as reference would still result in the same pattern and in an increased risk in the highest exposure group. We note that a dose-response relationship was also apparent in the original report from Boffetta et al.,¹ who used different cut-points for exposure categories. Because of methodological limitations of the published TiO₂ cohorts⁴ we cannot support Tomenson's statement that there is "considerable weight of evidence from 3 large cohorts of no exposure-response".

We agree that our results need to be confirmed using a different analytical approach. We propose to reanalyse the available European TiO₂ worker data using G methods⁵ to assess a potential health worker survivor effect and provide an unbiased estimation of the dose-response relationship.

References

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