

Letter commentary on: Lung cancer mortality in the French cohort of titanium dioxide workers: some aetiological insights

Dear Editor,

Guseva Canu *et al*¹ examined exposure–response in 833 workers from one of two French plants included in a European cohort of over 14 000 male TiO₂ workers.² Dose–response was reported solely for the pooled European cohort by Boffetta *et al*,² but was investigated for this small French group (see table 1).³

No adjustment for smoking was made in the original analyses, but little reliance can be placed on the multiple imputation results reported here. An implausible 43 (8.4%) of 512 workers with known smoking status were stated to be current smokers. Given that smoking status was only ascertained for 33 workers at the second French plant,³ this is clearly inconsistent with the original report that 42% of French workers were current smokers, comparable to national data (41%).² Furthermore, multiple imputation can be worse than an analysis of subjects with complete information and may have given biased results as smoking information was not missing at random (only medical records of workers present in the last 5 years were checked).⁴ It is also unclear that the imputation model had much predictive value. However, smoking adjustment made little difference to most estimates.

The authors highlighted an approximately fourfold higher risk of lung cancer mortality (statistically non-significant) among TiO₂-exposed workers. It is most likely due to reduced lung cancer mortality among the group of unexposed workers, as it is not suggested by the categorical cumulative exposure analysis in table 1, nor was it identified because of adjustment for smoking. Incidentally, Guseva Canu *et al*¹ list 297 workers as unexposed in their

table S3, but 202 never exposed in their table S1.

The dose–response results based on annual average exposure require careful interpretation. First, the measure is stated to have been calculated using cumulative respirable TiO₂ dust lagged by 10 years, but only 5 of the 14 exposed lung cancer deaths were exposed in the 10-year lag analysis. It is erroneously claimed that the shorter mean duration of exposure of workers with annual average exposure >2.4 mg/m³ suggests the presence of a healthy worker survivor effect. However, exposure levels fell sharply over time, especially after 1980 (see online supplemental table S2). Other employees with comparable exposure during early years ended in the much larger second highest average exposure group if they worked for long enough. This may explain the erratic exposure response seen in the categorical annual average exposure analysis. The continuous average exposure HR of 1.70 per mg/m³ (95% CI 1.03 to 2.79), unadjusted for smoking, is a better effect measure, but is based on the same unexposed comparison group as the implausible fourfold excess for TiO₂ exposure.

The authors conclude that their results question the current evidence on TiO₂ carcinogenicity in humans. However, the only supporting evidence of dose–response cited was a poster presentation⁵ stated to have reported a significant increase in HR for all cancer mortality in one US cohort, although it reported that no significant association between TiO₂ and all cancer mortality (or lung cancer) was indicated. The study findings add little new to the considerable weight of evidence from three large cohorts of no exposure–response.⁶

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REFERENCES

- Guseva Canu I, Gaillen-Guedy A, Wild P, *et al*. Lung cancer mortality in the French cohort of titanium dioxide workers: some aetiological insights. *Occup Environ Med* 2020;**77**:795–7.
- Boffetta P, Soutar A, Cherrie JW, *et al*. Mortality among workers employed in the titanium dioxide production industry in Europe. *Cancer Causes Control* 2004;**15**:697–706.
- Boffetta P, Soutar A, Weiderpass E. *Historical cohort study of workers employed in the titanium dioxide production industry in Europe. Results of mortality follow-up. final report*. Stockholm, Sweden: Department of Medical Epidemiology, Karolinska Institute, 2003.
- Hughes RA, Heron J, Sterne JAC, *et al*. Accounting for missing data in statistical analyses: multiple imputation is not always the answer. *Int J Epidemiol* 2019;**48**:1294–304.
- Golden A, Ellis ED, Le H. Comparison of risk estimates from COX proportional hazards and Poisson modeling for association of occupational titanium dioxide exposure and selected causes of death. *Occup Environ Med* 2017;**74**:A49.
- Le HQ, Tomenson JA, Warheit DB, *et al*. A review and meta-analysis of occupational titanium dioxide exposure and lung cancer mortality. *J Occup Environ Med* 2018;**60**:e356–67.

Table 1 Relative risk (RR) (95% CI) of mortality from lung cancer for estimated cumulative exposure to respirable TiO₂ dust

Cumulative exposure (mg/m ³ -year)	France (n=833)*		Pooled European cohort†	
	Lung cancer deaths	RR (95% CI)	Lung cancer deaths	RR (95% CI)
0–0.73	4	1.0 Reference	53	1.0 Reference
0.73–3.43	3	1.06 (0.21 to 5.30)	53	1.19 (0.80 to 1.77)
3.44–13.19	5	1.49 (0.39 to 5.67)	52	1.03 (0.69 to 1.55)
13.20+	4	1.63 (0.38 to 6.95)	53	0.89 (0.58 to 1.35)

*From table 4.4 of Boffetta *et al*.³

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