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Letter to the Editor

SIX AUTHORS REPLY

We thank the *Journal* for the opportunity to respond to Young (1) regarding our study of acrylonitrile exposure and all-cause and cause-specific mortality (2). In his letter, Young introduces the extraneous issue of multiple testing when, in fact, multiple testing is not an issue. Instead, our a priori hypothesis was that acrylonitrile was associated with increased lung cancer mortality. This hypothesis was based on results from previous studies, including the first follow-up of the National Cancer Institute cohort, which suggested a positive association between acrylonitrile exposure and lung cancer (3–7). Thus, the curious counting of all tests by Young is not relevant to the specific result of an association between acrylonitrile and the targeted outcome of lung cancer. Because there was a single primary hypothesis, the issue of multiple testing is moot.

Young also fails to recognize that a *P* value, corrected or not, without context provides limited information. Here, we summarize the contextual considerations that can, and should, be used for a comprehensive interpretation of our results on lung cancer mortality in the cohort (2): 1) Our study is the largest study of acrylonitrile-exposed workers in the world; 2) the study design included a high-quality, quantitative, retrospective exposure-assessment component that was developed using historical exposure estimates for each job, department, plant combination by time period based on work histories, over 18,000 historical measurements from plant production records, and 400 measurements from personal monitoring; 3) we observed a significant exposure-response for cumulative acrylonitrile exposure and lung cancer mortality (Figure 1 and Web Table 6 in Koutros et al. (2), P for trend $= 0.02$), and significant exposure-response relationships are unlikely to be due to chance; 4) analyses for lung cancer were robust and appeared not to be confounded by cigarette smoking or coexposures; and 5) cessation of acrylonitrile exposure eventually resulted in diminished lung cancer mortality (Web Table 10 (2)). This observation is consistent with a key criterion used to assess causality (8).

Further, Young's suggested strategy to use a gatekeeper multiple-testing procedure runs counter to basic bias in occupational cohort studies. The healthy-worker effect has been well-described as the tendency for the actively employed to have a more favorable mortality experience than the population at large. In occupational cohorts, this can manifest as a deficit in risk and erroneously suggests that the chemical under study is associated with reducing mortality (9). As in numerous other occupational cohort studies, we observed a deficit in all-cause mortality in our study. According to Young, "In this case, the gatekeeper fails for an increase in 'all causes of death,' so testing could/should stop." Such an approach ignores the enormous evidence of the healthy-worker effect in occupational cohort studies and would preclude a scientifically rigorous exploration of the impact of acrylonitrile exposure on workers' health. Such an approach would have led to the erroneous conclusion that acrylonitrile was not associated with increased lung cancer mortality.

Ultimately, our approach to analysis was not agnostic but focused on an a priori hypothesis of an association between acrylonitrile and lung cancer. Thus, an excessive correction for all tests performed, as Young suggests, is not warranted and indeed methodologically unsupportable. The strategy to condition our analyses of acrylonitrile and lung cancer ($<10\%$ of all deaths in the cohort) on results of the association of acrylonitrile and all-cause mortality or all cancer mortality is flawed and unreasonable. Our results for lung cancer mortality and acrylonitrile are internally consistent. As we state in our manuscript, our results for other outcomes do warrant additional evaluation.

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Conflicts of interest: none declared.

References

1. Young SS. "RE: extended mortality follow-up of a cohort of 25,460 workers exposed to acrylonitrile" [letter]. *Am J Epidemiol*. 2020;184(4):360–361.
2. Koutros S, Lubin JH, Graubard BI, et al. Extended mortality follow-up of a cohort of 25,460 workers exposed to acrylonitrile. *Am J Epidemiol*. 2019;188(8):1484–1492.
3. Benn T, Osborne K. Mortality of United Kingdom acrylonitrile workers: an extended and updated study. *Scand J Work Environ Health*. 1998;24(suppl 2):17–24.
4. Blair A, Stewart PA, Zaebst DD, et al. Mortality of industrial workers exposed to acrylonitrile. *Scand J Work Environ Health*. 1998;24(suppl 2):25–41.
5. O'Berg MT, Chen JL, Burke CA, et al. Epidemiologic study of workers exposed to acrylonitrile: an update. *J Occup Med*. 1985;27(11):835–840.
6. Scélo G, Constantinescu V, Csiki I, et al. Occupational exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk (Europe). *Cancer Causes Control*. 2004;15(5):445–452.
7. Thiess AM, Frentzel-Beyme R, Link R, et al. Mortality study in chemical personnel of various industries exposed to acrylonitrile. *Zentralbl Arbeitsmed Arbeitsschutz Prophyl Ergonomie*. 1980;30(7):259–267.
8. Hill AB. The environment and disease: association or causation? *Proc R Soc Med*. 1965;58(5):295–300.

9. Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. *Epidemiology*. 1994;5(2): 189–196.

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