CORRESPONDENCE

Author response: Extended follow-up of lung cancer and non-malignant respiratory disease mortality among California diatomaceous earth workers

We will address the comments offered by Mundt and Boffetta[1] on our manuscript describing findings from an update of mortality among California diatomaceous earth (DE) workers.[2] We regard the sustained dose–response trends for lung cancer and non-malignant respiratory disease (NMRD) (tables 3 and 4, respectively) as the most important findings regarding risks associated with crystalline silica. The reduction of overall mortality for these outcomes, indicated by reduced standardised mortality ratios (SMR), is more likely to be a 'depletion of susceptibles' phenomenon than a 'balancing out' effect. We agree that a healthy worker effect is an unlikely explanation for the reduced lung cancer SMR. However, support for the assertion that the healthy worker effect generally declines with employment duration could only be obtained in occupational cohorts where exposure effects and survival effects are sufficiently taken into account, a condition rarely achieved in published studies.

Our application of the Axelson and Steenland[3] method of indirect adjustment to address potential confounding by smoking is a relatively crude approach, but has been commonly applied in many occupational studies with limited data on smoking history. When we adjusted the results for each follow-up period, we found a similar attenuation of the estimates in the first follow-up period as in the second follow-up period, and overall. Adjusted results were similar whether we assumed a 10-fold vs a 20-fold increased risk for smoking. For example, the lung cancer relative risk estimate for the highest (unlagged) exposure category for the entire follow-up period changed from 2.03 to 1.60 after adjustment for smoking, assuming a 10-fold increased risk for smoking; the smoking-adjusted relative risk assuming a 20-fold risk for smoking was 1.57. Thus, the adjusted results demonstrate that smoking is an unlikely explanation for the observed dose–response trends for lung cancer and NMRD.

Whether our findings indicate a threshold effect for crystalline silica and these outcomes is a matter of speculation. It is seldom possible to determine exposure thresholds in a single study, especially a study with a relatively modest sample size, such as ours. There is insufficient statistical power to draw any conclusions on threshold in this study. We therefore strongly encourage efforts to pool data from multiple studies of silica-exposed occupational cohorts to estimate the true shape of dose–response curves, including possible exposure threshold values, with statistical precision for outcomes of interest, and to control for potential confounding from smoking and other non-occupational risk factors, to the extent that data are available. Sensitivity analyses incorporating plausible ranges of relative risks for potential confounders could be incorporated into indirect adjustment when person-level are not available, which is often the case. Data pooling also permits inspection of variable findings among studies, which may be explained by differences in demographic or exposure-related factors, such as the use of protective equipment or coexposures to other respiratory toxicants. The pooled analysis conducted by Steenland *et al*[4] provides a valuable template. Future pooling efforts should include updated cohorts, such as this DE cohort, and data from newly reported cohorts.

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Response to Mundt and Boffetta

Contributors LG completed additional analyses to respond to letter. LG, RMP and HC contributed comments to written response.

Competing interests None declared.

Patient consent Obtained.

Ethics approval University of Washington Institutional Review Board.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Gallagher L, Park RM, Checkoway H. *Occup Environ Med* 2016;**73**:72.

Received 3 October 2015
Accepted 20 October 2015
Published Online First 11 November 2015

▶ http://dx.doi.org/10.1136/oemed-2015-103235

Occup Environ Med 2016;**73**:72.
doi:10.1136/oemed-2015-103362

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Occup Environ Med 2016 73: 72 originally published online November 11, 2015
doi: 10.1136/oemed-2015-103362

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