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Meta-Analysis of Lung Cancer Risk from Exposure to Diesel Exhaust: Study Limitations

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Vermeulen et al. (2014) published a meta-analysis of the risk of lung cancer from exposure to diesel exhaust using data from three case–control studies—two of workers in the trucking industry (Garshick et al. 2012; Steenland et al. 1998) and one of workers in the mining industry (Silverman et al. 2012). Each of the studies quantified diesel exhaust exposure using cumulative exposure to elemental carbon. However, exposures in the trucking studies were lagged 5 years and those in the mining study were lagged 15 years. Vermeulen et al. (2014) applied these data in a linear regression that regressed the log odds ratio (logOR) versus cumulative lagged elemental carbon. They used the regression parameter from this analysis to predict lifetime excess risks for several lifetime occupational and environmental exposure scenarios, and also to predict the fraction of annual lung cancer deaths attributable to diesel exhaust. These excess risk calculations assumed a lag of 5 years.

In their analysis, Vermeulen et al. (2014) inappropriately mixed data from exposures lagged 5 years and 15 years. The assumption of a 5-year lag used in the excess risk calculations is appropriate only if the exposures in all the underlying studies are also lagged 5 years. To obtain some idea of the quantitative effect of this error, I first reran the analysis of Vermeulen et al. (keeping the mixed lags), except that I did not model the dependence among the ORs from the same study. (I did not have access to data needed to model that dependence.) My analysis yielded a regression parameter [0.88; 95% confidence interval (CI): 0.65, 1.11] similar to that obtained by Vermeulen et al. (0.98; 95% CI: 0.55, 1.41). Next, I conducted the same analysis using this model, except I used all 5-year lags, obtaining (0.38; 95% CI: –0.03, 0.96). This analysis consequently yielded a considerably smaller slope, which was not statistically significantly different from 0. The predictions from my analysis were clearly consistent with the underlying ORs all plotted using a 5-year lag, whereas the predictions from the Vermeulen et al. model clearly were not [e.g., the OR at the highest 5-year lagged exposure was 1.25 (95% CI: 0.55, 2.84)]; the model of Vermeulen et al. (2014) predicted an OR of 5.5, and my model predicted an OR of 2.17). Similar results were obtained using a 0-year lag (5-year and 0-year were the only lag data to which we had access).

There are other limitations of the analysis by Vermeulen et al. (2014): Garshick et al. (2012) employed a second measure of diesel exposure (exposure duration), which Vermeulen et al. did not account for in the analysis; and Vermeulen et al. used very crude exposure summaries (e.g., midpoints of exposure intervals).

Estimates of excess risks should be based on the same lag that is common to the underlying studies. Consequently, it would be inappropriate to base public policy regarding exposures to diesel exhaust upon the meta-analysis of Vermeulen et al. (2014).

Some of the results reported here are based on unpublished data underlying the case–control study by Silverman et al. (2012), and I express appreciation to the authors for their efforts in making these data available.

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Kenny Crump

Private Consultant, Ruston, Louisiana, USA
E-mail: kennycrump@email.com

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Meta-Analysis of Lung Cancer Risk from Exposure to Diesel Exhaust: Vermeulen et al. Respond

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Crump asserts that we "inappropriately mixed data from exposures lagged 5 years and 15 years" in our study published in *Environmental Health Perspectives* (Vermeulen et al. 2014). Exposure metrics from different studies available for meta-analysis are rarely, if ever, completely comparable. Therefore, even exposures labeled exactly the same (e.g., "cumulative exposure lagged 15 years") differ between studies because of differences in exposure assessment (cumulative exposure is accrued in different ways in different populations) and because of differences in age composition and extent of follow-up. As a result, in epidemiological studies, optimal lag times to exclude exposures not affecting risk may be variable across studies. For our meta-regression, we included the exposure–response relationships that were presented as the main analyses in the respective papers. For the two trucking studies (Garshick et al. 2012; Steenland et al. 1998), the exposure metric was lagged 5 years, whereas for the Diesel Exhaust in Miners Study (DEMS; Silverman et al. 2012) it was 15 years. Results for an analysis using a 5-year lag in DEMS were not published, although the 5-year lag had been included in analyses to examine changes in model fit as a function of lag. From those analyses (Silverman et al. 2012, Supplementary Figure 1), it is apparent that a 5-year lag showed the worst model fit of all lags (0–25 years); thus, it does not make sense to use this particular analysis as the primary exposure–response relation simply because the label "5-year lag" coincides with that of the other two studies.

We acknowledge that the interpretation of the risk function may be affected by differences in exposure between lag times. For this reason, we performed sensitivity analyses that included different lags from each study; overall results changed only slightly. We extended our earlier sensitivity analyses by including the unpublished 5-year lagged data from Silverman et al. (Silverman DT, personal communication).We note again, however, that these 5-year lagged data from the DEMS do not fit nearly as well as the 15-year lagged data. We stress our belief that they should not be the primary data for use in any risk assessment/meta-regression.

Crump argues that his alternative analyses using the 5-year lagged data were more consistent with the underlying DEMS data. Figure 1 includes the individual risk

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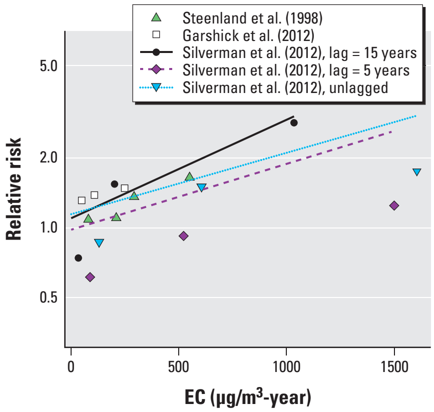

Figure 1. Predicted exposure–response curve of cumulative elemental carbon (EC) and lung cancer risk using different lag-times based on a log-linear regression model using relative risk estimates from the three cohort studies.

estimates for all three studies, with three alternative lag times for DEMS. It is clear from Figure 1 that the 5-year lagged risk estimates for DEMS selected by Crump for his meta-analysis are considerably lower than those of the two trucking studies and the alternative lag times for DEMS. We also included in the figure three different regression lines based on the two trucking studies and one of three different sets of results for DEMS, obtained using the exposure data lagged 0, 5, and 15 years. All models are fitted using the full estimated covariance matrix to appropriately account for the correlation between categorical point estimates from the same study, a correction ignored by Crump. The lowest meta-regression slope, using the 5-year lagged exposure results from DEMS, *a*) is higher than that reported by Crump using the variance estimates only; *b*) is statistically significant (0.00065; 95% CI: 0.00028, 0.0010); and *c*) falls within our previous sensitivity analyses (Vermeulen et al. 2014). It is also clear that the exposure–response function derived using the 15-year lagged exposure data from DEMS is a much better fit overall.

In summary, we strongly disagree with the assertions made by Crump in his letter that we inappropriately mixed lag times. On his other points, we note that adjustment for employment duration in the trucking industry cohort study was not a second exposure measure, but appropriately reduced bias attributable to a healthy worker survivor effect.

Additional analyses presented here confirm that the original findings from the meta-analyses are robust. Therefore, we firmly stand with the conclusions of our original paper.

The authors declare they have no actual or potential competing financial interests.

Roel Vermeulen,[1] Lutzen Portengen,[1] Debra T. Silverman,[2] Eric Garshick,[3] and Kyle Steenland[4]

[1]Utrecht University, Utrecht, the Netherlands; [2]National Cancer Institute, Rockville, Maryland, USA; [3]VA Boston Healthcare System, Boston, Massachusetts, USA; [4]Emory University, Atlanta, Georgia, USA

E-mail: r.c.h.vermeulen@uu.nl

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