

## Re: The Diesel Exhaust in Miners Study: A Nested Case-Control Study of Lung Cancer and Diesel Exhaust and a Cohort Mortality Study With Emphasis on Lung Cancer

Two reports published in the Journal present the main results of the Diesel Exhaust in Miners Study (DEMS) (1,2). Although some of the results support the hypothesis that diesel exhaust (DE) exposure increases the risk of lung cancer, some aspects of the results and potential limitations in the DEMS should be taken into consideration in the interpretation of the evidence.

In the analysis of continuous exposure variables (1), the hazard ratio for one unit of cumulative DE exposure (one  $\mu\text{g}/\text{m}^3\text{-y}$  respirable elemental carbon [REC]) was 1.001 among underground miners and 1.02 (ie, 20-fold higher) among surface miners. Corresponding HRs for one log-transformed unit of average REC intensity were 1.26 and 2.60, respectively. The authors interpret these results as indicating a stronger carcinogenic potential of “aged” DE. In the corresponding analysis of the nested case-control study, however, the risk of lung cancer among surface miners was not consistently increased [Table 4 in (2): a nonstatistically significant dose-dependent decrease in risk was shown for two of the variables]. The DEMS authors interpret these results in the light of the small number of lung cancer cases and the low levels of DE exposure in this group. The reader, however, remains uncertain as to whether surface miners, compared with underground miners, have between twofold and 20-fold higher DE-related risk or no increased risk at all. These results cast doubts on the validity of exposure assessment in the DEMS (3).

The anomalous result of a higher overall standardized mortality ratio (SMR) among surface miners than among underground miners in the cohort analysis is attributed to confounding by smoking. No clear evidence, however, is provided to support this interpretation. In the nested case-control study, the distribution of controls by smoking habit [Table 2 in (2)] suggests a lower amount of smoking in surface vs underground miners. Although controls are not representative samples of the two groups of miners, this finding contradicts the hypothesis of tobacco

smoking being a stronger confounder for surface miners than for underground miners. More importantly, the odds ratios for tobacco smoking were different in the two groups of miners; whereas the odds ratios in surface workers were consistent with previous studies (4), those in underground miners were much lower. The latter result is hardly credible and puts in question the way information on tobacco smoking was collected and analyzed in the DEMS.

The DEMS authors quote a number of previous studies of DE-exposed workers as supporting evidence of their results (5–11). However, the results of some of these studies only weakly support the hypothesis of a causal association [eg, (7)], and several well-designed studies that did not support the authors’ conclusions were not quoted [see (12) for a detailed review]. More importantly, these previous studies included drivers, machine operators, and railroad workers whose circumstances of DE exposure were closer to those of surface miners than to those of underground miners in the DEMS, for whom there was no clear evidence of an effect of DE exposure.

The results reported in the two articles do not match the plan of the statistical analysis outlined in the DEMS protocol (13). One particularly striking example concerns the use of lag in exposure-response analyses. In the study protocol, only a brief mention of lagged analyses is made: “In addition, lagged estimates of exposure will be explored to account for the latent period relating to lung cancer development” [(13), page 21], whereas strong emphasis is given to results of lagged analyses in both articles. The exclusion of miners with less than 5 years of employment and the exclusion of the category at highest exposure in dose-response analyses were not mentioned in the protocol, but the key results of the study are based on these exclusions. This is not to say that data-driven analyses should not be conducted and reported. When a study protocol is prepared, typically on the basis of limited data from a pilot study, it is impossible to figure out all the nuances and complexities of the final data, but to ignore systematically the plans outlined in the protocol is not good practice and may open the door to an arbitrary selection of results. At a minimum, the reports should have distinguished between a priori and a posteriori analyses.

The DEMS authors state (2) that exposure to REC in the range of 2–6  $\mu\text{g}/\text{m}^3$  over a lifetime would result in cumulative exposures comparable to those of underground miners with low exposures in their study and that these workers had at least a 50% increased lung cancer risk. It is unclear why the authors chose underground miners rather than surface miners for their extrapolation to non-occupational exposure because the latter group experienced circumstances of exposure more similar to that of the population at large than that of the underground miners. More importantly, the exposure reconstruction is subject to substantial uncertainties (3). If historical exposure estimates are systematically underestimated (a plausible scenario given that most available measurements were from recent years), the slope of a dose-response relation would be overestimated, even in case of nondifferential misclassification.

The many assumptions involved in the DEMS study design, notably in the exposure reconstruction, and the anomalies in the results of key analyses require a careful interpretation and an in-depth quantitative bias analysis (14), but little along these lines is present in the two articles (1,2). Conclusions of the DEMS authors with respect to DE-related lung cancer risk in underground miners, other exposed workers, and the population at large do not seem to be supported by available results.

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## Notes

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## Re: The Diesel Exhaust in Miners Study: A Nested Case–Control Study of Lung Cancer and Diesel Exhaust

In a recent article in the Journal on diesel exhaust exposure and lung cancer mortality among workers in US non–metal mining facilities, Silverman et al. (1) reported

a statistically significantly increasing trend in lung cancer mortality with increasing exposure to cumulative respirable elemental carbon (REC) and average REC intensity, lagged and unlagged 15 years. The major advantage of this nested case–control study over previous epidemiological studies is the ability to obtain lifetime diesel exhaust exposure (represented by REC) of individual workers by incorporating historical industrial hygiene measurements with specific job titles and the calendar year. The overall results regarding the exposure–response relationship between diesel exhaust and lung cancer are generally plausible; however, we have questions about the results and interpretation of the interaction between smoking status/intensity and diesel exhaust exposure.

The authors observed an attenuation of the effect of cigarette smoking among workers who were exposed to high levels of diesel exhaust, after adjustment for history of respiratory disease at least 5 years before date of death/reference date, history of a high-risk job for lung cancer for at least 10 years, and mine location (surface only vs ever underground work). The authors had proposed several mechanisms to explain the observed attenuated interactive effect, such as hypotheses about enzyme saturation and enzyme suppression (eg, reduced activity of cytochrome P450, subfamily IIB [CYP2B1]); however, it is possible that the attenuated smoking effect in the presence of high levels of diesel exhaust exposure is the result of a negative residual confounding effect of smoking.

We derived the smoking prevalence separately for the surface and underground workers from the data provided in the article and found that the underground workers were more likely to quit smoking compared with the surface-only workers (33.9% vs 42.3%). We suspected that underground workers may have smoked less and had also quit smoking earlier than surface workers because smoking is likely to be prohibited in underground working environments where a high level of diesel exhaust exposure is expected, as is the case in the study of Silverman et al. (eg,  $\geq 304 \mu\text{g}/\text{m}^3\text{-y}$ ). However, the authors did not take into consideration the potential negative confounding effect of smoking that is possibly related to the underground miners who were exposed to high levels of

diesel exhaust. There is a possibility that the observed interaction between smoking and diesel exhaust exposure would disappear if the residual negative confounding effect of smoking could be adequately addressed by the authors.

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## Notes

The authors declare no conflicts of interest.

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## Re: The Diesel Exhaust in Miners Study: A Nested Case–Control Study of Lung Cancer and Diesel Exhaust, a Cohort Mortality Study With Emphasis on Lung Cancer, and the Problem With Diesel

Diesel exhaust is a complex mixture of variable composition, including gases such as CO, CO<sub>2</sub> and NO<sub>2</sub>, and particulate material, predominantly elemental carbon nanoparticles with associated hydrocarbons, sometimes sampled as respirable elemental carbon (REC). Two recent articles (1,2) report an association between diesel exhaust exposure and lung cancer for 12 315 non-metal miners, the Diesel Exhaust in Miners Study (DEMS). The findings purport to be based on “quantitative data on historical diesel exposure coupled with adequate sample size to evaluate the exposure–response relationship between diesel exhaust and lung cancer” (1). They “estimated diesel exhaust exposure, represented by respirable elemental carbon (REC), by job and