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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

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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

year, for each subject based on an extensive retrospective exposure assessment at each mining facility” (1). This letter identifies major uncertainties in the REC exposure assessments and, in turn, the validity and implications of the reported positive association with lung cancer. Estimated REC concentrations are based on extrapolations from CO and engine horse power (HP) and mine ventilation rates that are unreliable, inaccurate, and potentially biased (based on incorrect assumptions of linearity).

The authors’ bold characterization of the rigor of the REC exposure estimates is not supported by the underlying retrospective exposure assessment (3–7). Table 2 of Stewart et al. (3), which includes measurements of 14 agents that are the basis for the exposure assessment, shows that only 85 measurements of REC were made before the end of mortality follow-up (December 31, 1997). Essentially all the REC exposure values, which must have numbered in thousands, were extrapolated values. REC concentrations were extrapolated from CO concentrations, assuming a linear relationship between CO and REC that, in fact, did not exist (8–10). About half of the CO measurements were below detection limits. Because no samples of CO were taken before 1976, the REC concentrations for 1975 and earlier years were based on extrapolations from estimates of diesel engine HP and mine ventilation to CO and then from CO to REC. Importantly, there are no reliable relationships between REC and HP for estimating REC. The relationships among CO and REC concentration and HP are influenced by multiple factors and vary from engine to engine and over time with changes in technology (8–10). Moreover, concentrations of emission constituents in mines are influenced by the specific diesel equipment in use, mine volumes, and mine ventilation rates.

Attfield et al. (1) reported that “Initial (ie, a priori defined) analyses from the complete cohort did not reveal a clear relationship of lung cancer mortality with DE exposure.” Thus, all of the reported statistically significant positive associations (1,2) between estimated REC exposure and increased lung cancer are based on posterior analyses (such as deleting highest exposures) in the cohort analyses and model-shopping (eg, no statistically significant associations without lagging) in the case–control study. The

findings in both studies (1,2) are entirely dependent on highly uncertain extrapolated estimates of REC exposure. The DEMS results, if independently validated, have important implications for conducting cancer hazard classification and regulating diesel technology. Accordingly, it is important that the exposure assessments be evaluated by other investigators with access to the full data base. Then the reported epidemiological analyses (1,2) should be redone and extended to incorporate the actual uncertainties in the exposure analyses.

In an editorial on the DEMS results (1,2), Rushton (11) comments on the cancer risks of exposures to diesel engine exhaust. She notes that diesel engine exhaust is “characterized by polycyclic aromatic hydrocarbons (PAH) surrounding an elemental carbon core,” usually referred to as diesel exhaust particulates (DEP): “it is the particulate phase of the diesel exhaust that appears to be implicated as a lung carcinogen.” Rushton (11) did not critique the purported association between REC and lung cancer. She simply accepted the DEMS results as valid despite the many important issues pertaining to how the REC exposure-metric was estimated, as discussed above, and despite the fact that cancer risk coefficients were much higher than those observed in previous studies.

Rushton (11) noted that “median elemental carbon values in an Oxford Street Study were 7.5  $\mu\text{g}/\text{m}^3$  (range 3.9–16) compared with 1.3  $\mu\text{g}/\text{m}^3$  (range 0.4–6.7) in Hyde Park. The Oxford Street values are comparable to the lower exposure levels found in the mining study. Background rates of between 1 and 2  $\mu\text{g}/\text{m}^3$ , similar to those in Hyde Park, have been found in other studies of urban environments.” Rushton (11) also noted the increasingly stringent emission standards for diesel engines, referencing the standards published on the DieselNet website as an example (<http://www.dieselnet.com/standards/eu/ld.php#stds> for the European Union).

This letter complements and supplements Rushton’s European perspective with US-based information. Specifically, the US Environmental Protection Agency’s National Air Toxics Assessment (12) (Figure 1) shows dramatic reductions in annual county-average diesel particulate matter concentrations from 1996 to 2005. The 1996

concentrations at the high end were similar to those of Rushton (11) for Hyde Park. However, the 2005 concentrations in the United States were reduced by about a factor of 10.

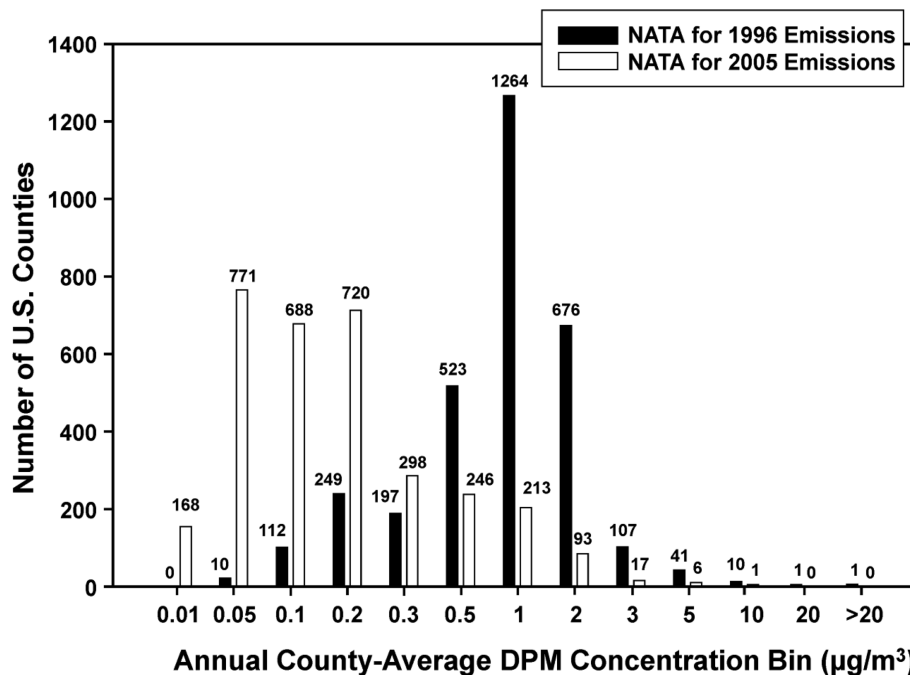
Hesterberg et al. (13) and McClellan et al. (14) reviewed the increasingly stringent US diesel emission standards for particulate matter (PM) and the industry’s response in producing engines with ultra-low PM emissions. The US 2007 PM emissions standard for heavy-duty on-highway (HDOH) engines is 0.01 grams per brake horsepower-hour, about 1% of typical emissions in the 1980s. The industry has responded with revolutionary technological advances, in particular, use of ultra-low sulfur (<15 ppm) fuel, wall-flow diesel exhaust particulate filters, and oxidation catalysts. The resulting emissions have been identified as new technology diesel exhaust (NTDE) in contrast to traditional diesel exhaust (TDE) from older technology (12,13). Key constituents such as elemental carbon and PAHs in NTDE are remarkably lower than in TDE, and the composition of the particulate mass is very different: NTDE is virtually free of the DEP that characterizes TDE. The introduction of new diesel technologies in all heavy-duty on-highway engines sold in the United States in 2007 and later will result in continued dramatic reductions in DEP in ambient air as old engines are replaced and more engines conform to current emission standards.

In conclusion, the DEMS results are premised on unreliable exposure estimates and so are uncertain and unverified. Moreover, given the revolutionary advances in diesel technology and fuels, the DEMS results are not applicable to contemporary emissions.

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**Figure 1.** Histogram of predicted annual county-average ambient diesel particulate matter concentrations for the U.S. Environmental Protection Agency National-Scale Air Toxics Assessment (NATA) modeling analyses of 1996 and 2005 air pollution emissions, including both on-road and non-road emissions. Number of counties (1996, 3191 counties; 2005; 3221 counties) in each bin shown above each bar (USEPA) (12).

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## Re: The Problem With Diesel

The title of the editorial by Rushton (1) is misleading because considerable improvements in diesel engine and emissions technologies over the last decades have resulted in remarkable differences in the quality and quantity of current exposures, especially

regarding polycyclic aromatic compounds (PAHs). The Kotin et al. article (2) cited by Rushton reported that solvent extracts of diesel emissions can cause tumors in mouse skin painting assays. This has been neither relevant for lung cancer nor for bladder cancer in human beings. Heinrich et al. and Mauderly et al. have shown in several rat studies that PAH-free particles can produce results similar to diesel particles containing PAHs (3,4). In addition, those health effects are caused by particle overload in the rat lung and not by organic compounds (5). A recent review by Hesterberg et al. revealed the relevant decrease of chemical substances in diesel exhaust from contemporary engines by concrete measurement data for PAHs (6).

Stringent emission standards and air quality regulations in the European Union (EU) do not only apply to new engines, as indicated in the editorial (1). Retrofitting of catalysts or diesel particulate traps is feasible and not only available for older diesel engines but for off-road equipment as well (<http://www.arb.ca.gov/msprog/decsinstall/decsinstall.htm>). (Ultra-)low sulphur fuel quality has been introduced by government directives and is widely available, leading to lower particulate emissions (7) ([www.epa.gov/oms/fuels/dieselfuels/index.htm](http://www.epa.gov/oms/fuels/dieselfuels/index.htm)). Financial and tax incentives are offered by certain EU governments to