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Occupational Exposures

The impact of alternative historical extrapolations of diesel exhaust exposure and radon in the Diesel Exhaust in Miners Study (DEMS)

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Abstract

Background: Previous results from the Diesel Exhaust in Miners Study (DEMS) demonstrated a positive exposure–response relation between lung cancer and respirable elemental carbon (REC), a key surrogate for diesel exhaust exposure. Two issues have been raised regarding DEMS: (i) the use of historical carbon monoxide (CO) measurements to calibrate models used for estimating historical exposures to REC in the DEMS exposure assessment; and (ii) potential confounding by radon.

Methods: We developed alternative REC estimates using models that did not rely on CO for calibration, but instead relied on estimated use of diesel equipment, mine ventilation rates and changes in diesel engine emission rates over time. These new REC estimates were used to quantify cumulative REC exposure for each subject in the nested case-control study. We conducted conditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals for lung cancer. To evaluate the impact of including radon as a potential confounder, we estimated ORs for average REC intensity adjusted for cumulative radon exposure in underground miners.

Results: Validation of the new REC exposure estimates indicated that they overestimated historical REC by 200–400%, compared with only 10% for the original estimates. Effect estimates for lung cancer using these alternative REC exposures or adjusting for radon typically changed by $<$10% when compared with the original estimates.

Conclusions: These results emphasize the robustness of the DEMS findings, support the use of CO for model calibration and confirm that radon did not confound the DEMS estimates of the effect of diesel exposure on lung cancer mortality.

Key words: Diesel, radon, lung cancer, exposure assessment

Key Messages

- Previous cohort and nested case-control analyses of data from the Diesel Exhaust in Miners Study (DEMS) demonstrated a positive exposure–response relation for lung cancer using respirable elemental carbon as a surrogate for diesel exhaust exposure.
- Issues have been raised regarding: (i) the retrospective exposure assessment approach in DEMS, which used empirical models calibrated by historical carbon monoxide measurements; and (ii) the role of radon as a potential confounder.
- We developed four alternative empirical models that did not rely on carbon monoxide for the historical estimation of diesel exhaust exposure and ran an additional risk model to adjust for radon.
- Results from these analyses indicate that radon is not a confounder and that the alternative historical exposure extrapolation models overestimated exposure, whereas estimates of relative risk and unit risk were similar to or slightly less than those from the original DEMS analyses.

Introduction

Diesel engine exhaust (DE) has been associated with several adverse health outcomes including lung cancer. In 2012, the International Agency for Research on Cancer (IARC) reclassified diesel exhaust from a probable (Group 2A) to a known (Group 1) carcinogen.[1] This re-classification was based on sufficient evidence in humans for the carcinogenicity of DE based on more than 10 lung cancer case-control studies and several large cohort studies. Two key studies in the IARC evaluation were the Diesel Exhaust in Miners Study (DEMS) and the Trucking Industry Particle Study (TRiPS), both yielding positive exposure carcinogen response relations for lung cancer using elemental carbon (EC) as a surrogate for DE.

After publication of the DEMS results[2,3] and exposure assessment, several papers questioned the exposure assessment and risk modelling in DEMS.[4–8] These questions focused on the use of carbon monoxide (CO) to calibrate mine-specific empirical models incorporating diesel engine horsepower and ventilation rates for back-extrapolation of measured respirable EC (REC), and on the potential confounding effect of radon on the observed associations between risk of lung cancer and average intensity and cumulative REC.

Here, we present additional sensitivity analyses in DEMS that aim to address these issues by considering alternative exposure estimates and the potential confounding effect of radon. These alternative estimates did not use CO but were based exclusively on historical extrapolation of measured REC using estimated horsepower (HP), ventilation rates, and temporal trends in particulate matter (PM) engine emissions per brake horsepower-hour. We compare these estimates to our original ('primary') exposure estimates and also compare risk estimates based on each exposure estimation scheme. We explore different scenarios for PM engine emission rates by changing the time interval ('delay') between engines meeting on-road standards and their introduction in the (underground) mining facilities. We also present analyses that adjust for radon, which we reported previously but did not present explicitly.

Methods

Diesel Exhaust in Miners Study

DEMS was conducted jointly by the National Cancer Institute (NCI) and the National Institute for Occupational Safety and Health (NIOSH) and has been described previously in detail.[2,3] Briefly, eight non-metal mining facilities (three potash, three trona, one limestone and one salt) were selected because of their low co-exposures to known occupational lung carcinogens, such as radon, asbestos and silica, and their extensive use of diesel-powered equipment underground. The DEMS cohort consisted of 12 315 workers who worked in a blue-collar job for at least 1 year in one of the selected facilities. Follow-up of the cohort started after the first introduction of diesel equipment ('dieselization'), between 1947 and 1967 for the different mining facilities, and continued until 31 December 1997. The nested case-control study of lung cancer included 198 lung cancer deaths (International Classification of Disease – O code 162) and 562 control subjects. We used incidence density sampling to select controls, matching controls to cases on mining facility, sex, race/ethnicity (i.e. White, African American, American Indian, Hispanic) and birth year (within 5 years) from among all members of the cohort who were alive the day before the case died.

Original DE exposure assessment

A detailed description of the exposure assessment for DEMS was provided in a comprehensive series of papers.[9–13] Briefly, we estimated facility- and job-specific REC exposure values by year, back to the year of dieselization for each mining facility. We specified job- and facility-specific reference values (REC_R) from arithmetic means of REC measurements obtained during an industrial hygiene survey at each working mining facility from 1998 to 2001. For underground jobs, we modelled temporal changes using total diesel engine HP (weighted by the percentage of hours used) and ventilation rates in cubic feet per minute (CFM), which were deemed to be the most important determinants of DE-related concentrations. Because there were few historical REC measurements, we calibrated the temporal variations in diesel exposure using historical face-area air concentrations of CO. Adjusted model predictions based on ratios of CO concentrations in past years relative to those in 1998–2001 were then applied to modify the 1998–2001 REC_R values to estimate average historic annual REC concentrations for each job and year at each mining facility. The formula used for historical adjustment was $REC_x = REC_R (CO_x/CO_R)$, where R and x refer to the estimates for the reference and for other years, respectively.

For surface jobs, we assigned exposures based on the use of, or proximity to, diesel-powered equipment. For the purpose of the present analyses, we did not re-evaluate these surface estimates. The exposure assessment process was blinded to mortality outcomes.

Alternative DE estimates

For this paper, we developed a set of alternative REC exposure estimates, using only information on HP and ventilation in CFM and engine emission trends for the historical extrapolation of REC_R. This approach is similar to one suggested as a possible complementary approach by an independent expert panel of the Health Effects Institute (HEI), which was formed to evaluate the suitability of data from DEMS and TRiPS for quantitative risk assessment.[14] These alternative REC estimates omit any CO-related calibration of temporal effects of HP and CFM. No PM emission standards were introduced for off-road engines until the year 2000 in the USA.[15] We therefore accounted for changes in PM emission rates of grams per brake horsepower-hour (g/bhp-hr) in diesel engines using information provided by the US EPA from experimental laboratory studies on PM emissions of on-road engines by year of engine production. Figure 1 shows results from transient

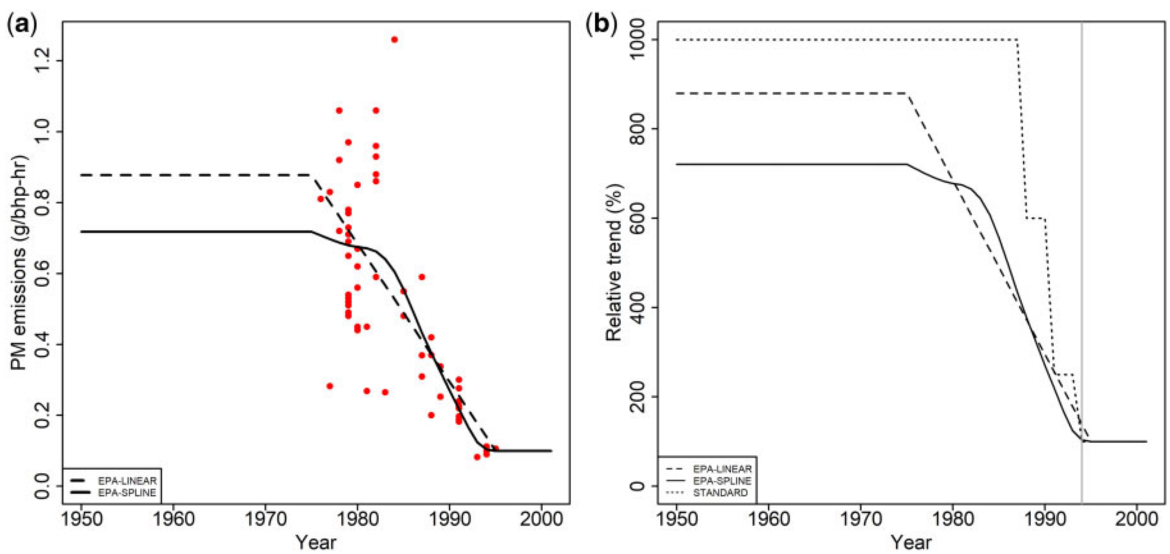

Figure 1. Left panel (a) showing diesel engine certification for engine PM emissions in grams per brake horsepower-hour (g/bhp-h) as a function of model year. Red dots are individual data points reproduced from[14] (Figure F-9). A linear trend as described by Crump *et al.*[6] (EPA-LINEAR) is presented as a dashed line. The solid line indicates the fit of the natural spline function (EPA-SPLINE). The right panel (b) shows relative emission factors based on trends described in the left panel plus a relative trend (dotted line) based on Figure F9 in the HEI report[14] (STANDARD). The reference year used in this panel is 1998.

emission tests that we extracted from figure F-9 in the HEI report.[14] We fitted two regression models to the experimental emission testing data: a linear model that was also used by Crump *et al.*[6] (EPA-LINEAR) and a spline-based model that allowed for a potential non-linear trend and also accounted for heteroskedastic (residual) variance in PM emission rates over time (EPA-SPLINE).

We converted these trends in absolute emission rates into proportional trends (proportional emission factors) using the ratio of yearly estimated PM emission rates to the estimated emission rate in 1998 (our reference year). Because there were no data to estimate emission rates before 1975 or after 1995, we assumed that the emission factors remained constant before 1975 and after 1995. We also estimated two additional proportional emission trends, one using data from regulatory emission standards for on-road diesel engines provided by Cummins in the HEI report (figure F-9[14]) (STANDARD) and another that assumed emission factors did not change across the entire study period (CONSTANT).

Using each proportional trend in emission rates, we back-extrapolated job- and facility-specific reference values (REC_R) to the year of dieselization for each facility in two steps. First, yearly estimates of the total diesel engine horse power used (HP) were multiplied by the year-specific proportional emission factor (PEF) for each trend and then divided by the yearly estimates of the ventilation rate (CFM) to obtain yearly ventilation- and emission rate-adjusted estimates of the facility-specific emission rate (ER). These rates were then divided by the facility-specific emission rate in 1998–2001 (the years when the REC reference measurements were obtained). These ratios were then multiplied by the job- and facility-specific REC reference values for that year to obtain historical job- and facility-specific REC exposure estimates. The formula used for historical adjustment was $REC_x = REC_R \text{ x } \%ER_x$, where R and X refer to the estimates for the reference and for other years and $\%ER_x$ the emission rate in year X, respectively. $\%ER = [(HP_x \text{ x } PEF_x)/CFM_x]/[(HP_R \text{ x } PEF_R)/CFM_R]$.

Because these emission rate-based trends were derived from either on-road emission testing data (EPA-LINEAR and EPA-SPLINE) or on-road regulation data (STANDARD), these trends may not directly apply to off-road situations, such as diesel equipment in mining facilities. We therefore repeated the exposure assessment under various assumptions for the timing at which newer (on-road) engines were introduced in new or retrofitted diesel equipment in the mining facilities, using a delay of 1, 2 or 5 years.

Previously, we validated our primary exposure estimates against independent historical CO and REC measurements.[12] As we did not use CO in the derivation of the new alternative estimates, we here evaluated the validity of these alternative REC exposure estimates by comparing them with the available historical personal REC measurements by calculating absolute and relative differences.

To contrast facility- and job-specific REC estimates derived under these different modelling assumptions, we summarized the information on exposure levels across the entire study period by calculating the highest REC exposure estimate for each facility-job.

Exposure assessment for radon

We previously developed estimates of levels of radon gas for each job and year.[13] In brief, underground facility-specific radon levels were assigned based on past measurement data and ranged from 0.01 to 0.02 working levels (WL) (WL is a measure of the potential alpha particle energy from the short-lived decay products of radon per litre of air). These WL roughly correspond to 75–150 becquerels/m^3 (or 2–4 pico-Curies/L) in a typical indoor home environment. WL was then multiplied by the number of hours worked underground in units of 170 h to estimate WL months.

Risk analyses

We estimated odds ratios (ORs) and 95% confidence intervals (95%CI) for the effect of DE on lung cancer mortality with conditional logistic regression, categorizing exposure by using quartiles of the cumulative exposure in the cases, as was done in Silverman *et al.*[3] Adjusted models included a term that combined cigarette smoking status and smoking intensity with location worked (i.e. ever underground, surface only). Other terms included were employment in a high-risk occupation for lung cancer for at least 10 years and history of nonmalignant respiratory disease diagnosed at least 5 years before death/reference date. To test for a null linear trend, we conducted a Wald test after assigning the median exposure among control subjects in each quartile of exposure to all subjects in that exposure category.

For the evaluation of radon, we limited analyses to ever underground workers because the surface workers were exposed to little or no radon and most of the diesel exposure in the study facilities occurred underground. We estimated the risk associated with average REC intensity, rather than cumulative REC, lagged 15 years, to avoid inclusion of duration underground in both exposure metrics [WL months of radon exposure includes hours exposed (underground) in units of 170 h; cumulative REC includes number of years exposed to REC, which mainly occurs underground]. The Pearson correlation coefficient for cumulative REC and cumulative radon exposure was 0.73, and thus estimates of risk for cumulative REC adjusted for cumulative exposure to radon (in WL months) would be unstable.

Results

Figure 1(a) provides an overview of the linear (EPA-LINEAR) and spline-based (EPA-SPLINE) models that we used to estimate emission factors from the available data on absolute emission rates for diesel engines. Predictions from the spline-based regression model suggest that average emissions at the start of the testing data collection period were lower than predicted by the linear model. Proportional trends were much steeper for the STANDARD trend than for the EPA-LINEAR and EPA-SPLINE trends and suggest a 10-fold decrease in emission levels over the relatively short time period from 1980 to 1995 (Figure 1b). The slopes of the EPA-LINEAR and EPA-SPLINE trends are roughly similar.

Figure 2 compares, for each facility-job, the maximum estimated REC concentration over the study period for the primary exposure estimates with those obtained using the four alternative approaches. The year at which this maximum estimate occurred varied between jobs and between different trend estimates. (Maximum) REC exposure levels tended to be much higher for the EPA-LINEAR, EPA-SPLINE and STANDARD models than those based on the original CO-calibrated models for all jobs, which led to maximum estimated REC levels exceeding 1000 μg/m^3 for several jobs. When no emission trend was assumed (CONSTANT; Figure 2, blue triangles), maximum exposures were on average slightly lower than the primary estimates, although some estimates were still higher for some facility-jobs. Pearson correlations between job-estimates across all mines based on the different extrapolation models ranged between 0.65 and 0.99 (median 0.86).

Table 1 shows the difference between measured and predicted REC levels for the continuous miner and foreman in facility B in 1994, which were the only jobs for which historical REC measurements were available for comparable DEMS jobs. The differences were all negative, indicating that the predicted average REC levels exceeded observed average REC levels. The difference was smallest when no trend was assumed (CONSTANT) and small (<10%) when using our primary exposure model, but it was clearly higher for all alternative models, with absolute differences >170–400 μg/m^3 REC and relative differences >100%.

Risk estimates for the association between different estimated REC exposure levels and lung cancer are provided in Table 2. All risk estimates were generally very close to those based on the primary estimated exposures. Estimated ORs for subjects in the 2nd and 3rd quartiles (i.e. Q2 and Q3) of exposure were similar across all models and differed by at most 12% from the primary estimates (Table 2). In the 4th quartile (i.e. Q4), the ORs were highest for the primary exposure estimates and the EPA-SPLINE model. The ORs were lowest when using the linear (CONSTANT) model. Most of the ORs for the highest quartile were statistically significant as were the linear trends.

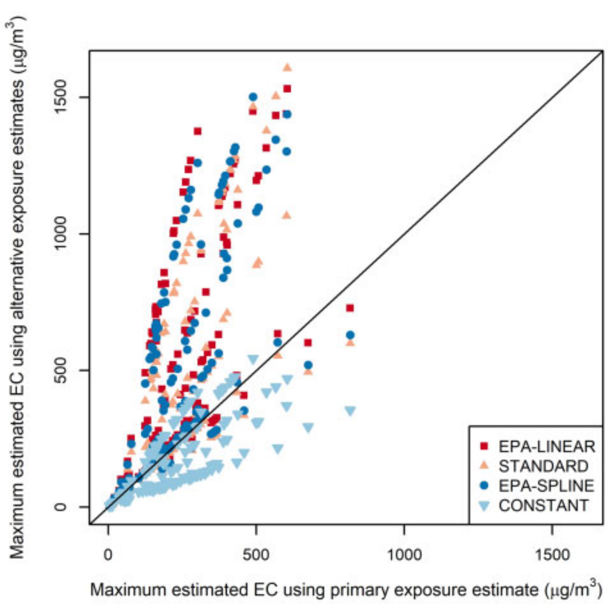

Figure 2. Maximum estimated respirable elemental carbon (REC) exposure levels by job title and facility per estimate type. Estimates derived using alternative approaches to derive the historical trend are compared with those derived after calibration with CO (primary estimates). The solid line is the line of identity.

Table 1. Assessment of absolute differences between the primary and alternative facility-specific predicted personal respirable elemental carbon (REC) estimates in Facility B in 1994 and the arithmetic means of the REC personal measurements collected in 1994 (Stanevich *et al.*[16])

Trend	Absolute differences (μg/m^3)[a] between predicted and measured personal REC levels in 1994, Facility B	
	Continuous miner	Foreman
Primary estimates[b]	−24.3	−9.6
EPA-LINEAR	−300.6	−187.9
STANDARD	−398.2	−250.8
EPA-SPLINE	−275.4	−171.6
CONSTANT	−1.8	−4.9

[a]Difference between the AM of the REC measurements in facility B in 1994 for the continuous miner (248.4 μg/m^3) and the foreman (166.3 μg/m^3) and the estimated REC exposure level for the same two jobs.

[b]Primary estimates refers to the original exposure estimates in DEMS.[3] EPA-LINEAR and SPLINE are relative trends based on EPA particulate matter emission factors,[14] whereas STANDARD is based on changes in regulatory emission standards over time,[14] and CONSTANT is based on no change in emission factors over time.

Figure 3 shows ORs and 95% CIs for estimated exposures derived under different assumptions about how quickly technical advances in on-road engine design translated into lower emission rates for engines used in underground mining facilities. Risk estimates for exposures derived by delaying the adaptation of new technology by 1, 2 or 5 years showed similar patterns for the EPA-LINEAR, EPA-SPLINE and STANDARD models. Delaying trends for more than 2 years resulted in slightly higher risk estimates for the 3rd quartile and slightly lower risk estimates for the 4th quartile, when compared with using smaller delays or not delaying at all.

Table 2. Comparison of results as presented by Silverman *et al.*[3] with results based on exposure reconstructions using alternatives for historical back-extrapolation of respirable elemental carbon (REC) relying on trends in emission factors; odds ratios (ORs) and 95% confidence intervals (CIs) for quartiles (Q) of cumulative REC lagged 15 years[a]

	Q2			Q3			Q4			
Trend	OR	95%CI		OR	95%CI		OR	95%CI		*P*-trend
Primary estimates[b]	0.7	0.40	1.38	1.5	0.7	3.20	2.8	1.3	6.3	0.0008
EPA-LINEAR	0.8	0.41	1.38	1.5	0.7	3.21	2.4	1.1	5.4	0.0116
STANDARD	0.8	0.40	1.37	1.5	0.7	3.12	2.5	1.1	5.8	0.0064
EPA-SPLINE	0.7	0.40	1.36	1.5	0.7	3.20	2.7	1.2	6.1	0.0046
CONSTANT	0.8	0.42	1.40	1.6	0.8	3.33	2.2	1.0	4.9	0.0284

[a]Adjusted for smoking status/smoking intensity/mine location combination, history of high-risk jobs for lung cancer for ≥10 years, and history of respiratory disease ≥5 years before date of death/reference date.

[b]Primary estimates refers to the original exposure estimates in DEMS.[3] EPA-LINEAR and SPLINE are relative trends based on EPA particulate matter emission factors,[14] whereas STANDARD is based on changes in regulatory emission standards over time,[14] and CONSTANT is based on no change in emission factors over time.

To evaluate the impact of radon adjustment, we compared previously published ORs without radon in the model for average REC intensity lagged 15 years among underground workers with ORs estimated from the same model but including radon. ORs from Table 4 in Silverman *et al.*[3] were: 1.0, 1.04 (95%CI = 0.45–2.43), 2.19 (95%CI = 0.87–5.53), 5.43 (95%CI = 1.92–15.31), *P*-trend = 0.001. ORs including radon in the model using the primary REC estimates were: 1.0, 1.01 (95%CI = 0.42–2.42), 2.12 (95%CI = 0.82–5.48), 5.09 (95%CI = 1.70–15.19), *P*-trend = 0.002.

Discussion

Previously, we showed that estimated cumulative exposure to REC as a surrogate for DE was positively associated with lung cancer risk and that risk estimates from our models were comparable to earlier studies that used cumulative REC.[2,3,17] Since publication of the DEMS results, several investigators have reanalyzed the DEMS cohort and case-control data,[4–8] focusing mainly on two aspects of the study. The first aspect was the use of historical CO measurements to calibrate historical changes in diesel equipment and ventilation for back-extrapolating from 1998 to 2001 measured REC levels. The second was the adjustment of the lung cancer risk analyses for exposure to radon, which we previously reported but did not explicitly present.

We addressed both aspects in this paper by sensitivity analyses using alternative exposure assessments that did not include CO and by performing risk analyses using the average REC intensity exposure metric with adjustment for cumulative radon exposure. Both sets of analyses showed only minimal changes in estimated risks that were generally <10%.

The criticism of using CO in the historical back-extrapolation of REC in DEMS stems from the observation

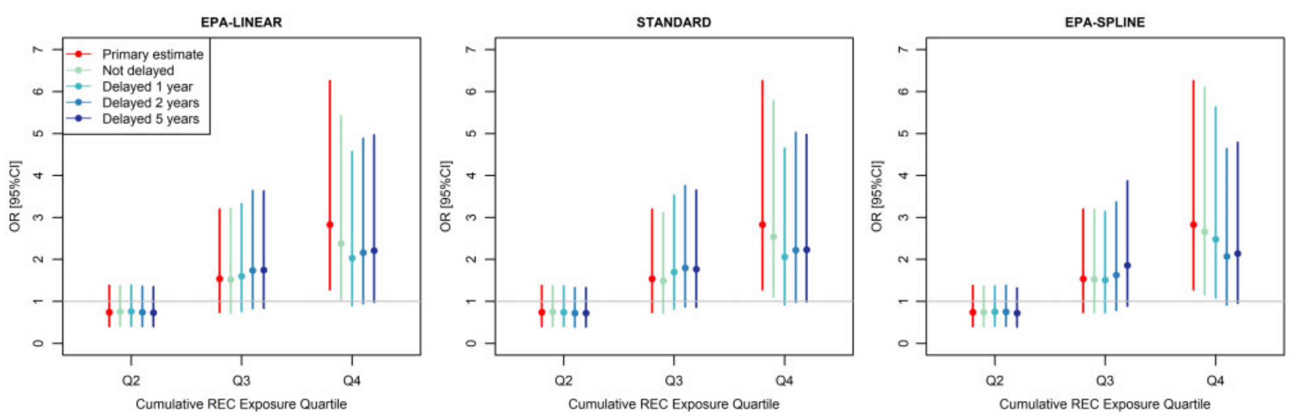

Figure 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for quartiles of cumulative respirable elemental carbon (REC) lagged 15 years based on three alternative historical trends used to derive personal REC estimates. Adaptation of new technology was assumed to vary between instantaneous (not delayed) and delays of 1, 2 and 5 years. For comparison, the original results of analyses presented by Silverman *et al.*[3] are given (primary estimate).

that there is no direct (positive) relation between CO and REC for a single engine.[14] However, this does not preclude REC and CO from being positively correlated when comparing situations where the number of diesel engines and ventilation rates widely vary. As an (extreme) example, a strong positive correlation between CO and REC is likely to be found when comparing a work site with 1 diesel engine to a work site where 50 diesel engines are used. We have shown previously that indeed REC and CO were positively correlated in the 1998–2001 surveys over a range of underground working situations where both the use of diesel engines (507–9181 HP) and ventilation (0–1670 kCFM) varied widely.[11] We considered the wide range in the amount of diesel equipment used and the ventilation rates applied underground over time to be the primary driving forces for changes in REC levels over time. In the absence of any universal physical model that could be applied, we sought to calibrate the effect of these changes on DE exposure levels by quantifying the effects on changes in historical CO levels. Validation of the CO calibration models indicated that we were able to estimate average CO area measurements in the face area of our study mines in 1976 within 30%. Historical average personal REC levels in 1994, which were available for two jobs within one of the study mines, were predicted with an error of <10%.[12]

For sensitivity analyses, we compared our primary exposure and risk estimates with those from four alternative exposure metrics that were estimated without making use of the CO calibration-models. In these alternative models, we relied on estimated trends in emission rates for on-road diesel engines as suggested as a possible alternative by the HEI panel in their evaluation of the DEMS and TRiPS studies.[14] The amount of HP and ventilation rates in the mines by calendar year used in these models were the same as those used in our primary exposure model. We relied on data from the EPA on diesel engine certification for engine PM emissions by model year, and on regulatory standards for emissions from on-road diesel engines to estimate alternative time trends in emission rates, because no historical data were available for off-road diesel engines. We additionally explored the effect of allowing for a delayed introduction (1–5 years) of any new engine technology in underground mining because we had no information on the speed at which newer engine technologies were introduced in the study mines, as regulation of off-road emissions occurred only after the end of follow-up for DEMS. Predicted historical REC levels from these models were much higher than historical measurements (absolute differences >170–400 μg/m^3 REC and relative differences >100%), whereas predicted estimates from our primary model using CO calibration were much closer (within 10%) to historical measurements. Furthermore, estimated exposure levels from these models were >1000 μg/m^3 for many jobs. REC exposure levels >1000 μg/m^3 have not been reported in the literature[18] and seem unrealistically high. Nevertheless, risk analyses using any of the alternative trend models resulted in relative risk estimates for lung cancer by quartiles of DE exposure that were similar to our primary estimates.

Crump *et al.*[6] previously also published risk analyses based on using a single non-CO model that was similar to our EPA-LINEAR model. Crump *et al.* included body mass and childhood environmental tobacco exposure as confounders in their non-radon risk models, but did not include smoking intensity and worker location (important confounders in DEMS[2,3]), which precludes making any direct comparisons with our published findings. Nonetheless, their reported ORs of 1.0, 1.05 (95%CI = 0.58–1.93), 1.60 (95%CI = 0.79–3.24), 2.37 (95%CI = 1.02–5.50) are still similar to the results obtained in this study for the EPA-LINEAR model (Table 2). However, due to the likely overestimation of historical REC levels by the EPA-LINEAR non-CO model, their published risk per unit of exposure was lower than that based on their primary estimates (0.00016 versus 0.00073 μg/m^3.year).[6] If we calculate the risk per unit of exposure for our alternative estimates, the slopes were also lower (log risk ratio per μg/m^3.year = 0.00038–0.00048) than our primary estimate (slope 0.001), whereas the CONSTANT alternative provided an estimate that was quite similar to our primary slope estimate (0.0008).

Each of the models used here has its limitations and advantages. The LINEAR, SPLINE and STANDARD models reflect possible changes in emissions that the CONSTANT model does not. However, they are not likely to represent the actual annual emissions in the mining facilities, because the equipment and engines in the mines were used for years before being replaced, and emission profiles, depending on maintenance, likely varied over the lifetime of each engine. The CONSTANT model does not require any assumptions of emission changes; however, this model likely reflects too little change. We believe our primary model represents the best of the models as the changes in CO over time likely reflect both the changes in emissions from new equipment and engines as they occurred in each of the mines, as well as other non-quantified conditions such as effectiveness of the ventilation and the maintenance of the diesel engines.

It has been suggested that radon was a confounder in the DEMS analyses,[6–8,19] even though radon levels at the DEMS mining facilities were very low (i.e. arithmetic means were ≤0.02 WL, which is one-fiftieth of the maximum permissible concentration of 1.0 WL in US mines) and were equal to or below the US residential limit of 148 becquerels/m^3 (or 4 pico-Curies/L).[9] An expert panel of the HEI, tasked with evaluating the recent epidemiological evidence for a quantitative risk assessment of diesel exhaust, also examined the possible confounding effect of radon. They estimated a relative risk of 1.06 for the top quartile of radon exposure in DEMS using Biological Effects of Ionizing Radiation VI models to estimate lung cancer risk due to radon exposure in these miners, and concluded that radon is unlikely to be a major confounder in DEMS.[14] We here performed analyses in which average REC intensity lagged 15 years was adjusted for WL months of radon (cumulative radon), which reduced the correlation between the radon and REC to 0.37 (compared with 0.73 for cumulative radon and cumulative REC). The addition of radon to the model had a minimal effect on the estimates of risk since all point estimates changed by <10% (in the highest quartile, ORs = 5.43 vs 5.09), indicating that the previously reported effect of DE on lung cancer risk in DEMS was not due to confounding by radon.

In summary, we show that the results of DEMS are robust to assumptions regarding historical exposure trends. Estimated exposures from alternative exposure models that do not use CO for historical back-extrapolation resulted in risk estimates for quartiles of exposure that were similar to those from our primary analyses based on CO-calibrated REC exposure models. However, estimated exposure levels of historical REC exposure from these alternative models likely overestimated historical REC exposures, suggesting less validity than the primary exposure estimates used in DEMS. In part this may be reflected in the fact that the primary DEMS risk estimates were slightly higher than those based on any of the alternative models, which suggests that our primary exposure estimates may have less exposure misclassification than the alternative exposure estimates. Overestimation of historical REC exposures by the alternative non-CO models, which we estimated could be up to a factor of 2–4, led to underestimation of the risk per unit of exposure in continuous risk models. As such, the original CO-calibrated models, which were constructed *a priori* and were shown to be within 10% of historical REC measurements, are the most appropriate models to estimate REC exposure for risk assessment. Finally, adjustment for radon exposure does not explain the association between REC and lung cancer.

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