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The Diesel Exhaust in Miners Study: A Cohort Mortality Study With Emphasis on Lung Cancer

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Background Current information points to an association between diesel exhaust exposure and lung cancer and other mortality outcomes, but uncertainties remain.

Methods We undertook a cohort mortality study of 12 315 workers exposed to diesel exhaust at eight US non-metal mining facilities. Historical measurements and surrogate exposure data, along with study industrial hygiene measurements, were used to derive retrospective quantitative estimates of respirable elemental carbon (REC) exposure for each worker. Standardized mortality ratios and internally adjusted Cox proportional hazard models were used to evaluate REC exposure–associated risk. Analyses were both unlagged and lagged to exclude recent exposure such as that occurring in the 15 years directly before the date of death.

Results Standardized mortality ratios for lung cancer (1.26, 95% confidence interval [CI] = 1.09 to 1.44), esophageal cancer (1.83, 95% CI = 1.16 to 2.75), and pneumoconiosis (12.20, 95% CI = 6.82 to 20.12) were elevated in the complete cohort compared with state-based mortality rates, but all-cause, bladder cancer, heart disease, and chronic obstructive pulmonary disease mortality were not. Differences in risk by worker location (ever-underground vs surface only) initially obscured a positive diesel exhaust exposure–response relationship with lung cancer in the complete cohort, although it became apparent after adjustment for worker location. The hazard ratios (HRs) for lung cancer mortality increased with increasing 15-year lagged cumulative REC exposure for ever-underground workers with 5 or more years of tenure to a maximum in the 640 to less than 1280 μg/m^3-y category compared with the reference category (0 to <20 μg/m^3-y; 30 deaths compared with eight deaths of the total of 93; HR = 5.01, 95% CI = 1.97 to 12.76) but declined at higher exposures. Average REC intensity hazard ratios rose to a plateau around 32 μg/m^3. Elevated hazard ratios and evidence of exposure–response were also seen for surface workers. The association between diesel exhaust exposure and lung cancer risk remained after inclusion of other work-related potentially confounding exposures in the models and were robust to alternative approaches to exposure derivation.

Conclusions The study findings provide further evidence that exposure to diesel exhaust increases risk of mortality from lung cancer and have important public health implications.

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The widespread use of diesel engines has long raised concerns regarding potential health effects from exposure to diesel exhaust (DE), especially with respect to lung cancer. More than 35 cohort and case–control studies of lung cancer incidence and mortality and DE have been published to date. A majority of studies have found an increased risk of lung cancer with surrogate measures of exposure (ie, job or tenure). However, few have measured workplace DE exposures, and fewer have used them directly or indirectly in their analysis [eg, the US railroad workers cohort (1–3), the US Teamster trucker study (4), German potash miner study (5), and a recent study of truckers (6)]. Criticisms of existing studies include small study size, lack of reliable historical quantitative exposure data, inadequate latency period, and potential confounding (7–10). Determinations by the International Agency for Research on Cancer (11) and the National Institute for Occupational Safety and Health (12), and reviews, meta-analyses, and one very large pooled analysis (13–16) have concluded that there is evidence that lung cancer is related to DE exposure, but other reviews have disagreed (9,17–20).

To provide additional information on lung cancer and other health outcomes possibly associated with DE exposure, and to address gaps and limitations in prior investigations, we conducted an epidemiological investigation of DE-exposed non-metal (ie, mineral) miners. The Diesel Exhaust in Miners Study (DEMS) consisted of a cohort mortality study (presented here), a nested case–control study of lung cancer mortality (21), and current and

CONTEXTS AND CAVEATS

Prior knowledge

Previous studies have suggested an association between diesel exhaust (DE) exposure and lung cancer, but few have used quantitative measurements of exposure directly or been conducted in mining operations.

Study design

In a cohort mortality study of 12 315 workers at eight US non-metal mining facilities, retrospective quantitative estimates of respirable elemental carbon exposure were used to estimate the association between DE exposure and lung cancer mortality.

Contribution

The risk of lung cancer mortality increased statistically significantly with level of DE exposure for ever-underground workers, especially for those with tenures greater than 5 years. There was also an increasing trend in risk of lung cancer mortality with increasing DE exposure for surface workers with longer tenures.

Implication

DE may be hazardous in both confined and open spaces and may represent a public health as well as an industrial hazard.

Limitations

Sampling was limited for some jobs in the mining facilities, and surrogate data were used for extrapolation to past exposures. Information was incomplete on potentially hazardous exposures in prior or later jobs held outside the study facilities, and information on lifestyle factors, including smoking, was not available.

From the Editors

retrospective exposure assessments (22–26). The objectives of the cohort study were to evaluate total and cause-specific mortality and to assess lung cancer mortality in relation to quantitative estimates of DE exposure. The study was specifically designed to have adequate statistical power, to use extensive current and historical quantitative DE exposure data, and to investigate an environment having low levels of potentially confounding workplace lung carcinogens (27). For these reasons, and because of the wide range in DE levels seen in the study mines, this study largely addressed the limitations of previous investigations.

Methods

Population

Ten mining facilities were originally selected for study after an extensive feasibility study of US non-metal mining facilities. These 10 facilities were estimated to have employed sufficient workers to enable the study to have a 90% probability (statistical power) of detecting a doubling in lung cancer risk associated with DE exposure. We excluded facilities with fewer than 50 employees for practical reasons. Two facilities were later rejected because of incomplete personnel records. However, because the remaining eight facilities had more employees than originally estimated, the study power was not reduced. The eight facilities included one low silica limestone, three potash, one salt (halite), and three trona ($Na_3H(CO_3)_2{\cdot}2H_2O$—a primary source of sodium carbonate) operations (Table 1). The facilities, which were located in Missouri (one limestone), New Mexico (three potash), Ohio (one salt), and Wyoming (three trona), were selected because available information indicated low exposure to potentially confounding workplace exposures (particularly silica, radon, and asbestos), extensive diesel engine usage, large numbers of workers, sufficient time since introduction of diesel equipment to provide an adequate latent period for lung cancer development, and extensive DE surrogate information to assist in development of quantitative estimates of past DE exposure (22–25). DE exposure among underground workers resulted from ore extraction, haulage, maintenance, and personnel transport vehicles. DE exposure on the surface resulted predominantly from forklift trucks, locomotives, and heavy equipment (22,23).

Personnel Record Selection and Processing

All workers who were ever employed in a blue-collar job for at least 1 year after dieselization at the study facilities were eligible for study. Individuals who held only administrative or management positions during their employment were excluded. We abstracted demographic and work history information from facility personnel records, including date of birth, sex, race/ethnicity, job titles and dates, prior employment, vital status, and next of kin. Information on race/ethnicity was unavailable for 64% of the workers. Race and ethnicity were coded to white/Hispanic or black. Unknowns were classified as white/Hispanic, because, where race/ethnicity was known, 98% were white or Hispanic. No smoking information was available to the cohort study.

For analysis, individuals who had worked at more than one study facility were assigned to the facility where they had worked the longest. However, their DE exposure estimates were derived from each facility at which they had worked. The final size of the cohort was 12 315 (12 382 based on the inclusion criteria and work history edit checks, less 67 with missing or invalid model covariate demographic information). This cohort study was approved by Human Subjects Review boards at the National Cancer Institute and the National Institute for Occupational Safety and Health, and by those states that requested it.

Ascertainment of Vital Status

End of mortality follow-up was December 31, 1997. The cohort was matched with the National Death Index (NDI-Plus) and the Social Security Administration (SSA) death files. Underlying and contributing cause of death information back to 1979 came from the NDI-Plus (28), whereas pre-1979 information came from death certificates coded by a certified nosologist. Causes of death were coded according to the *International Statistical Classification of Diseases* (ICD) revision in force at the time of death (See Supplementary Table 1, available online). There were 29 indications of death from SSA or other non-NDI-Plus sources for which the death certificate could not be located. These individuals were classified as deceased and included in the all-cause standardized mortality ratio (SMR) tabulations, but not in other standardized mortality ratio computations or internal analyses for specific causes of death. The 111 individuals who could not be matched with NDI-Plus or SSA were treated as alive until last observed date and then censored.

Table 1. Cohort and facility information overall, and by facility and worker location*

Variable	Facility									
	Limestone		Potash			Salt (halite)	Trona			All
	A	B	D	J	E	G	H	I		
Year of dieselization	1947	1964	1950	1952	1959	1962	1967	1956		1947–1967
Individuals submitted, No.†	2615	1561	3583	3212	1474	2377	4593	6386		25801
Study cohort, No. (person-y)‡										
Complete cohort	1676 (41381)	899 (17245)	2105 (53928)	1567 (38617)	547 (11460)	1135 (23024)	1935 (38448)	2451 (53938)		12315 (278041)
Ever-underground workers§	946 (22199)	753 (14041)	1297 (33289)	1228 (29846)	497 (10139)	584 (11531)	1429 (27302)	1573 (33505)		8307 (181852)
Surface-only workers‖	1319 (19182)	265 (3204)	1029 (20639)	554 (8771)	221 (1321)	750 (11493)	721 (11146)	989 (20433)		5848 (96189)
Mean year of first exposure to DE (95% CI)¶	1967 (1966 to 1968)	1976 (1976 to 1977)	1967 (1967 to 1968)	1969 (1968 to 1969)	1974 (1973 to 1975)	1975 (1975 to 1976)	1975 (1975 to 1976)	1973 (1972 to 1973)		1971 (1971 to 1972)
Mean underground tenure, y (95% CI)#	9.0 (8.4 to 9.6)	7.4 (6.9 to 7.9)	8.8 (8.4 to 9.2)	7.4 (7.0 to 7.9)	7.5 (6.8 to 8.2)	9.1 (8.4 to 9.7)	6.6 (6.2 to 6.9)	8.7 (8.3 to 9.1)		8.0 (8.4 to 9.2)

* CI = confidence interval; DE = diesel exhaust . Facilities coded according to industrial hygiene reports (22–25).

† Records for individuals submitted by facilities.

‡ After data cleaning and combining subjects who worked at multiple facilities.

§ Workers categorized as ever-underground after first going underground (even if at surface later).

‖ Workers categorized as surface only until first going underground (if ever).

¶ Year at which the individuals in the study were first exposed to DE (could be at, or after, first employment).

Jobs involving work in both surface and underground locations were prorated by fraction of time spent underground in years.

Work Histories

We standardized all occupation and department titles in the abstracted work histories within facilities (23). Systematic methods were made to fill gaps in the work histories. In situations where interviews with other workers and management did not resolve the issue, job information was imputed by study of similar jobs and patterns of employment. This and all exposure assessment procedures were subject to a range of quality assurance checks, such as double entry of the raw data and review by the facilities (26).

Exposure Assessment

The exposure assessment was performed blind to any findings from the mortality analyses. Its objective was to develop quantitative estimates of DE exposure based on respirable elemental carbon (REC) measurements (Table 2). The estimates were derived for all surface and underground jobs, by year and facility, from year of introduction of diesel-powered equipment in the facility (1947–1967, depending on the facility) to December 31, 1997. Jobs held before introduction of diesel equipment were assumed to be unexposed to DE. The REC measurements were personal samples (ie, where the sampler was worn by an individual) collected during 1998–2001 DEMS surveys at seven of the eight study facilities (the eighth facility had closed in 1993) (22,23). Arithmetic means of the DEMS REC measurements were designated 1998–2001 reference values (REC_R). For underground jobs, temporal trends in carbon monoxide (CO) face area air concentrations (based primarily on US Mine Safety and Health Administration [MSHA] Mine Information Data System [MIDAS] historical area CO compliance data) were modeled using DE-related determinants (eg, diesel engine horsepower and ventilation rates) (25). The modeled trends in CO concentrations for past years, relative to CO levels in 1998–2001, were then used to adjust the 1998–2001 REC_R to obtain historic annual REC concentration estimates for each job and prior year. These estimates are termed the primary exposure estimates.

Because of the low exposure levels of workers on the surface compared with levels underground (23), and because of the less specific information available on surface diesel equipment, surface REC personal exposure estimates were not adjusted for temporal changes in exposure levels apart from those arising from major events impacting the working environment (eg, when diesel-powered equipment replaced gasoline-powered equipment) (22). Finally, the REC intensity estimates were combined with the work history information from personnel records to derive personal REC cumulative and average intensity estimates over time (average intensity = cumulative exposure/years exposed).

The exposure estimates were compared with various sets of independent data. One such dataset comprised environmental sampling data collected in 1976–1977 as part of an earlier epidemiological study in most of the facilities (26). In addition, to evaluate the robustness of the assumptions adopted in the exposure assessment, three alternative REC exposure metrics were also developed and used in the mortality modeling (22). All three metrics used the historical CO MIDAS compliance measurements, but the first alternative metric used 5-year means of the CO data to predict REC time trends back to 1976 (start of compliance data) and the DE-related determinants before that. In the second metric

Table 2. Mean and 95% confidence interval (CI) of exposures to respirable elemental carbon (REC), silica, asbestos, non-diesel poly-aromatic hydrocarbons (non-DE PAHs), radon, and respirable dust by facility, by worker location within facility and over all facilities*

	Facility exposures, mean (95% CI)								
	Limestone	Potash			Salt (halite)	Trona			
Variable	A	B	D	J	E	G	H	I	All
REC, μg/m³									
Complete cohort	45.3 (41.4 to 49.2)	181.3 (172.1 to 190.5)	92.9 (87.9 to 97.9)	96.3 (92.0 to 100.7)	155.2 (145.8 to 164.5)	79.3 (73.5 to 85.1)	78.4 (75.4 to 81.4)	65.0 (62.2 to 67.8)	87.0 (85.2 to 88.8)
Ever-underground workers†	78.1 (72.0 to 84.2)	216.1 (207.0 to 225.2)	150.2 (143.8 to 156.6)	122.7 (118.1 to 127.2)	170.5 (161.2 to 179.8)	152.1 (144.7 to 159.4)	105.6 (102.6 to 108.6)	100.7 (97.5 to 104.0)	128.2 (126.1 to 130.3)
Surface-only workers‡	2.5 (2.4 to 2.5)	2.0 (1.9 to 2.1)	0.9 (0.8 to 0.9)	1.0 (0.9 to 1.0)	3.2 (3.1 to 3.3)	2.1 (2.1 to 2.1)	1.6 (1.5 to 1.6)	1.1 (1.1 to 1.2)	1.7 (1.6 to 1.7)
Silica§									
Complete cohort	0.01 (0.00 to 0.01)	0.96 (0.94 to 0.97)	0.88 (0.86 to 0.89)	0.88 (0.87 to 0.90)	0.003 (0.00 to 0.01)	1.72 (1.69 to 1.76)	1.76 (1.74 to 1.78)	1.73 (1.71 to 1.76)	1.11 (1.10 to 1.13)
Ever-underground workers	0.004 (0.001 to 0.006)	0.98 (0.97 to 0.99)	0.94 (0.93 to 0.95)	0.95 (0.95 to 0.96)	0.003 (0.00 to 0.008)	1.91 (1.88 to 1.93)	1.84 (1.82 to 1.86)	1.87 (1.85 to 1.89)	1.18 (1.17 to 1.20)
Surface-only workers	0.005 (0.003 to 0.008)	0.85 (0.82 to 0.89)	0.73 (0.70 to 0.75)	0.68 (0.65 to 0.71)	0	1.58 (1.53 to 1.63)	1.55 (1.50 to 1.59)	1.48 (1.43 to 1.52)	0.88 (0.85 to 0.90)
Asbestos§									
Complete cohort	0.19 (0.17 to 0.21)	0.31 (0.29 to 0.34)	0.23 (0.21 to 0.25)	0.14 (0.13 to 0.16)	0.16 (0.13 to 0.19)	0.30 (0.28 to 0.33)	0.27 (0.25 to 0.28)	0.29 (0.27 to 0.30)	0.24 (0.23 to 0.25)
Ever-underground workers	0.16 (0.14 to 0.18)	0.34 (0.31 to 0.37)	0.19 (0.17 to 0.21)	0.14 (0.13 to 0.16)	0.17 (0.14 to 0.21)	0.25 (0.21 to 0.28)	0.23 (0.21 to 0.25)	0.27 (0.25 to 0.29)	0.22 (0.21 to 0.23)
Surface-only workers	0.16 (0.13 to 0.18)	0.13 (0.09 to 0.16)	0.25 (0.23 to 0.28)	0.10 (0.08 to 0.12)	0.06 (0.03 to 0.09)	0.27 (0.24 to 0.31)	0.31 (0.28 to 0.35)	0.29 (0.26 to 0.32)	0.22 (0.21 to 0.23)
Non-DE PAHs‖									
Complete cohort	0.15 (0.14 to 0.16)	0.31 (0.29 to 0.34)	0.23 (0.22 to 0.25)	0.17 (0.16 to 0.19)	0.16 (0.13 to 0.19)	0.26 (0.24 to 0.28)	0.24 (0.23 to 0.26)	0.27 (0.25 to 0.28)	0.23 (0.22 to 0.23)
Ever-underground workers	0.14 (0.12 to 0.16)	0.34 (0.31 to 0.37)	0.19 (0.17 to 0.21)	0.17 (0.15 to 0.18)	0.17 (0.14 to 0.21)	0.23 (0.20 to 0.27)	0.22 (0.20 to 0.23)	0.26 (0.24 to 0.28)	0.21 (0.21 to 0.22)
Surface-only workers	0.10 (0.09 to 0.12)	0.13 (0.09 to 0.16)	0.25 (0.23 to 0.28)	0.13 (0.11 to 0.16)	0.06 (0.03 to 0.09)	0.21 (0.19 to 0.24)	0.27 (0.24 to 0.30)	0.26 (0.23 to 0.28)	0.19 (0.18 to 0.20)
Radon, WL¶									
Complete cohort	0.005 (0.005 to 0.006)	0.014 (0.014 to 0.015)	0.010 (0.010 to 0.010)	0.007 (0.007 to 0.007)	0.014 (0.014 to 0.015)	0.009 (0.008 to 0.009)	0.006 (0.005 to 0.006)	0.005 (0.005 to 0.005)	0.008 (0.008 to 0.008)
Ever-underground workers	0.009 (0.009 to 0.010)	0.017 (0.016 to 0.017)	0.016 (0.016 to 0.017)	0.009 (0.009 to 0.009)	0.016 (0.015 to 0.016)	0.017 (0.016 to 0.017)	0.008 (0.008 to 0.008)	0.008 (0.008 to 0.008)	0.011 (0.011 to 0.012)
Surface-only workers	0	0	0	0	0	0	0	0	0
Respirable dust, mg/m³									
Complete cohort	0.89 (0.87 to 0.91)	2.66 (2.58 to 2.74)	1.29 (1.26 to 1.31)	2.63 (2.56 to 2.70)	1.06 (1.03 to 1.09)	1.55 (1.49 to 1.61)	1.53 (1.50 to 1.56)	1.07 (1.04 to 1.09)	1.51 (1.50 to 1.53)
Ever-underground workers	1.02 (0.99 to 1.05)	3.06 (2.99 to 3.12)	1.65 (1.62 to 1.67)	3.16 (3.09 to 3.22)	1.10 (1.08 to 1.12)	2.34 (2.27 to 2.40)	1.84 (1.81 to 1.87)	1.42 (1.40 to 1.44)	1.93 (1.91 to 1.95)
Surface-only workers	0.71 (0.70 to 0.73)	0.65 (0.64 to 0.67)	0.76 (0.74 to 0.78)	0.75 (0.73 to 0.77)	0.53 (0.48 to 0.58)	0.77 (0.75 to 0.79)	0.68 (0.67 to 0.70)	0.45 (0.44 to 0.46)	0.67 (0.67 to 0.68)

* WL = working level. Facilities coded according to industrial hygiene reports (22–25). Jobs involving work in both surface and underground locations were prorated by fraction of time spent underground in years.

† Workers categorized as ever-underground after first going underground (even if surface later).

‡ Workers categorized as surface only until first going underground (if ever).

§ Semiquantitative exposure categories coded on a relative scale (0, 1, and 2).

‖ Non-DE PAHs categorized as present or absent (0 and 1).

¶ The concentration of radon daughters is measured in units of working level (WL), which is a measure of the potential alpha particle energy per liter of air. One WL of radon daughters corresponds to approximately 200 pCi/L of radon in a typical indoor environment.

[termed the power model in the exposure assessment (24)], the formula used for historical adjustment was $REC_X = REC_R (CO_X/CO_R)^b$, where R and X refer to the estimates for the reference and for other years, respectively, and the constant, b = 0.58, was estimated from the DEMS measurements. The third set of estimates used medians of the DEMS REC measurements instead of arithmetic means to derive the 1998–2001 reference values.

Estimates of exposure to potential occupational confounders (ie, silica, radon, asbestos, non-diesel polycyclic aromatic hydrocarbons [non-DE PAHs], and respirable dust) were also developed for each job and year (22) and used in the risk analysis, in which semiquantitative values derived from measurement data were assigned for silica (0–3) and asbestos (0–3). Silica and asbestos categories 2 and 3 were merged in the analysis (only three of the 1217 job-year estimates were category 3 for each exposure type). Note that the measured silica levels were in the range 0.01–0.02 mg/m^3 or nondetectable; the measured asbestos levels were all less than 0.1 fibers/cc or nondetectable (22). Non-DE PAH exposure estimates, classified as present or absent (0 or 1), were based on job title. Underground mine–specific radon levels were assigned on the basis of past measurement data and ranged from 0.01 to 0.02 working levels (WL; the concentration of radon daughters is measured in units of working level, which is a measure of the potential alpha particle energy per liter of air. One WL of radon daughters corresponds to approximately 200 pCi/L of radon in a typical indoor environment.) Because of very low levels and few observations, exposures to arsenic, nickel, and cadmium were not evaluated. Further information on the exposure assessment is available elsewhere (22–26).

Statistical Analysis

Stratification by Worker Location. Analyses were undertaken separately by worker location, termed ever-underground workers and surface-only workers, as well as for the complete cohort. Worker location was time dependent because some workers moved between surface and underground operations while employed at the study facilities. For example, individuals who started work on the surface were termed surface-only workers until such time as they took an underground job (if ever), at which point they became ever-underground workers.

Standardized Mortality Ratio Analysis. In our external analysis, we computed standardized mortality ratios for underlying causes of death using the NIOSH Life Table Analysis System (LTAS) version 2.0 (29), taking into account race/ethnicity (white/Hispanic, black) and sex. Because lung cancer rates in the states where the facilities were located differed markedly from national rates, we stratified the analysis by state. Individuals who worked at multiple facilities were assigned to the state for the facility where they worked the longest. Because the state-based death rates only existed from 1960, the cohort was slightly smaller for the standardized mortality ratio analysis (12 270 individuals, 264 661 person-years, and 2185 total deaths) than for the internal analysis.

Cox Proportional Hazard Models. Cox proportional hazard models, using PROC PHREG from the SAS/STAT software (version 9.2, SAS Institute, Inc., Cary, NC) (30), were used in internal analyses to assess the relationship of REC exposure with lung cancer mortality. Analyses were focused on lung cancer defined on the basis of malignant neoplasm of the bronchus and lung (ie, excluding tracheal cancer) as underlying cause of death. In the proportional hazard models, three of the 203 deaths in the standardized mortality ratio tabulations were excluded from the internal analysis [two tracheal cancers and one rejected on the basis of pathological information from the companion case–control study review (21)]. Selected analyses were repeated including lung cancer as a contributing cause (N = 212).

REC cumulative exposure and average intensity were modeled as time-dependent variables, using the model $h(t) = \exp(\sum_1^k \beta_i x_i + \beta_{DE} x_{DE}) h_0(t)$ where t was attained age (ie, age at time of event), $h(t)$ and $h_0(t)$ were the estimated and baseline hazards, the x_i were time-independent race/ethnicity, sex, and birth year, and the x_{DE} were the exposure metrics. The analyses were stratified by state (study facility location) with the assignment of individuals to state being the same as in the standardized mortality ratio analysis. For the complete cohort, we undertook analysis with and without a time-dependent dichotomous variable representing worker location.

We evaluated unlagged and lagged REC cumulative and average intensity exposures. We performed analyses using 0 and 15-year lag periods (ie, REC exposure that occurred in the 15 years before the date of each death of interest was excluded for all individuals contributing to the risk set for that death). The choice of lag period was confirmed by examination of model deviance (a measure of goodness of fit), which supported the use of a 15-year lag in seven of the 12 reported categorical and continuous models (expanded categories and untransformed and log continuous exposures for each exposure metric [six models], for ever-underground and surface-only workers). For the remainder, the deviances were almost the same in four models, whereas the results for one favored the 0 lagged analysis (data not shown).

Analyses were undertaken based on quartiles of exposure, using the lung cancer death data to set the cut points. In addition, we also undertook a categorical analysis using expanded cut points (termed the expanded categories) at 2, 4, 8, 16, 32, 64, and 128, and ≥128 μg/m^3 for 15-year lagged average REC intensity (where the REC level of the least exposed surface workers formed the basis for the reference category, with a doubling in exposure level thereafter). For cumulative REC exposure, we used those same cut points multiplied by 10 years. Because the cut points are the same for ever-underground and surface-only workers, this categorical analysis permits direct comparison across locations as well as facilitating a better understanding of trends.

Exposure–response trends were assessed by fitting continuous exposure variables to the data. Consistent with our a priori strategy, we fitted continuous exposure models using untransformed (log-linear) REC cumulative exposure and average REC intensity for the full exposure range, but based on the patterns of data observed, we also undertook additional secondary analyses. These included cumulative REC exposure restricted to less than 1280 μg/m^3-y, undertaken to improve the characterization of the exposure–response trend in the lower part of the cumulative REC exposure range. We also used log-transformed exposure (a power model) to accommodate the leveling-off in the exposure–response trend we observed at the highest exposures. Cumulative exposures

to potential occupational confounders (silica, asbestos, non-DE PAHs, radon, and respirable dust) were added to the continuous models to examine the robustness of the findings.

In addition to results from the complete cohort, to account for an observed differential mortality pattern in short-term workers, we present results excluding those with less than 5 years tenure (ie, delaying follow-up by 5 years). Although potential selection effects up to 10 years were observed, 5 years was chosen for analysis so as not to affect study power too adversely (with a 10-year restriction, we would have lost half of the lung cancer deaths). We also evaluated age of entry into the study in connection with the short-term worker effect because workers starting employment at the study facility at older ages had more potential for prior high levels of confounding exposures. Several other ancillary analyses were undertaken to explore certain aspects of the data, to evaluate different approaches, and to check the findings (see Supplementary Tables 3–17, available online).

Statistical tests were two-sided and based on a χ^2 Wald test. There was no evidence that the proportional hazard assumption had been violated in the Cox modeling. The assumption was checked by replacing the DE exposure variables by four separate exposure terms specific to age at event (<60, 60 to <70, 70 to <80, ≥80), and formally comparing the −2× log-likelihood values using χ^2 tests.

Results

The cohort was predominantly male (96%), and white. Of the 5670 individuals with information on race/ethnicity, 88% were white, 2% black, and 10% Hispanic. The number of workers at each facility varied from 547 to 2451. Mean age at start of exposure was 29 years and was virtually identical across ore types (limestone, 29; potash, 30; salt, 31; and trona, 29 years).

About 35% (12%–50% across facilities) of the person-years were accrued on the surface, either exclusively or before moving underground (Table 1). The average year of first exposure to DE in the study cohort varied from 1967 to 1976 across facilities with an overall mean of 1971 (the range for individuals was from 1947 to 1996). Mean tenure underground overall was 8.0 years, with a range across facilities from 6.6 to 9.1 years (Table 1). The range across individuals was from close to 0 to 44 years. A total of 2220 (18%) individuals were deceased at the study mortality cutoff date.

Average intensity of REC exposure, based on each individual's full work history at the study facilities, was 87.0 μg/m^3 for all workers, 128.2 μg/m^3 for ever-underground workers, and 1.7 μg/m^3 for surface-only workers (Table 2). These and the other exposure data in Table 2 pertain to an individual's complete work history; surface work exposures were truncated at the time the individual first went underground, whereas ever-underground exposures were computed from first time underground. There were substantial differences across facilities in levels of REC exposure underground (average REC intensity range: 78–216 μg/m^3). In general, estimated REC levels rose from dieselization, typically peaking in the late 1970s or early 1980s and then falling to about half the peak levels by end of study (25). The exception was facility A, at which estimated underground REC levels rose continuously from the mid-1960s. Mean levels of all potential confounders, including silica, asbestos, non-DE PAHs, radon, and respirable dust, were low and, in contrast to REC, typically differed little between surface and underground work (Table 2).

Standardized Mortality Ratio Analysis

Underlying all-cause mortality (SMR) in the complete cohort was less than expected (SMR = 0.93, 95% CI = 0.89 to 0.97, Table 3). Among the a priori causes of death of specific interest, statistically significantly higher mortality was seen for lung cancer (SMR = 1.26, 95% CI = 1.09 to 1.44). The standardized mortality ratios for the following a priori causes, bladder cancer, kidney cancer, intestinal (including colon) cancer, pancreatic cancer, prostate cancer, leukemia, pneumonia, chronic obstructive pulmonary disease, ischemic heart disease, cerebrovascular disease, and cirrhosis of the liver were generally close to and not statistically significantly different from 1.00 (Table 3). Other a priori causes (rectal cancer, multiple myeloma, Hodgkin lymphoma, and influenza) had fewer than 10 deaths; their standardized mortality ratios were all less than 1.10 (not shown). Mortality from all cancers was statistically significantly increased (SMR = 1.10, 95% CI = 1.01 to 1.20), due largely to the increase in lung cancer deaths (SMR = 1.03, 95% CI = 0.93 to 1.15 for all cancers without lung cancer).

Among causes of death not selected a priori, statistically significant increases occurred for esophageal cancer (SMR = 1.83, 95% CI = 1.16 to 2.75), other pneumoconiosis (coal workers', inorganic, and unspecified pneumoconiosis) (SMR = 12.20, 95% CI = 6.82 to 20.12), explosion (SMR = 4.22, 95% CI = 1.82 to 8.31), drowning (SMR = 2.80, 95% CI = 1.66 to 4.43), and electrocution (SMR = 2.88, 95% CI = 1.38 to 5.30). Further information on non-a priori causes of death, including results for causes with 10 or more deaths are given in Supplementary Table 2 (available online).

Apart from accidents, the standardized mortality ratios in the ever-underground and surface-only worker groups were similar to those reported above for the complete cohort (Table 3). Deaths from lung cancer were statistically significantly higher in both groups (ever-underground: SMR = 1.21, 95% CI = 1.01 to 1.45; surface only: SMR = 1.33, 95% CI = 1.06 to 1.66; Table 3). Other pneumoconiosis mortality was also higher in both groups (ever-underground: SMR = 16.21, 95% CI = 8.37 to 28.32; surface only: SMR = 6.13, 95% CI = 1.26 to 17.91; Supplementary Table 2, available online). The standardized mortality ratio for esophageal cancer was higher in both groups but statistically significant only for the ever-underground workers (SMR = 2.01, 95% CI = 1.15 to 3.26). All-cause mortality was less than expected in both groups (SMR = 0.95, 95% CI = 0.90 to 1.01 and SMR = 0.90, 95% CI = 0.84 to 0.96, respectively). The excess mortality noted overall for explosions, drowning, and electrocution was confined solely to ever-underground workers. In addition, ever-underground workers had a statistically significant excess of deaths from machine injuries (SMR = 2.56, 95% CI = 1.27 to 4.58). Deaths from alcoholism were statistically significantly less than expected for ever-underground workers (SMR = 0.33, 95% CI = 0.12 to 0.71) as were deaths from cirrhosis of the liver (SMR = 0.53, 95% CI = 0.26 to 0.94) in surface-only workers (Table 3).

Cox Proportional Hazard Modeling of Lung Cancer and DE

Initial (ie, a priori defined) analyses from the complete cohort did not reveal a clear relationship of lung cancer mortality with DE

Table 3. Observed numbers of deaths, person-years, and standardized mortality ratios (SMRs) for selected causes of death, overall and by worker location*

Cause of death	Worker location					
	Complete cohort, person-years†, SMR (95% CI)	*P*	Ever-underground workers‡, person-years, SMR (95% CI)	*P*	Surface-only workers§, person-years, SMR (95% CI)	*P*
All-cause	2185, 0.93 (0.89 to 0.97)	.001	1388, 0.95 (0.90 to 1.01)	.080	797, 0.90 (0.84 to 0.96)	.002
All-cancer	556, 1.10 (1.01 to 1.20)	.027	347, 1.10 (0.99 to 1.23)	.074	209, 1.10 (0.95 to 1.25)	.202
Lung cancer	203, 1.26 (1.09 to 1.44)	.002	122, 1.21 (1.01 to 1.45)	.040	81, 1.33 (1.06 to 1.66)	.015
Bladder cancer	13, 1.09 (0.58 to 1.86)	.840	5, 0.69 (0.23 to 1.62)	.553	8, 1.68 (0.72 to 3.30)	.221
Kidney cancer	14, 0.98 (0.54 to 1.64)	.919	10, 1.11 (0.53 to 2.04)	.835	4, 0.76 (0.21 to 1.95)	.796
Intestinal (includes colon) cancer	44, 1.04 (0.76 to 1.40)	.825	31, 1.19 (0.81 to 1.69)	.381	13, 0.81 (0.43 to 1.38)	.526
Pancreatic cancer	30, 1.12 (0.76 to 1.60)	.575	19, 1.14 (0.68 to 1.78)	.638	11, 1.10 (0.55 to 1.97)	.834
Prostate cancer	38, 0.85 (0.60 to 1.16)	.343	27, 1.00 (0.66 to 1.46)	.964	11, 0.61 (0.31 to 1.10)	.111
Leukemia	25, 1.18 (0.76 to 1.74)	.459	13, 0.98 (0.52 to 1.68)	.903	12, 1.51 (0.78 to 2.64)	.216
Pneumonia	50, 0.98 (0.73 to 1.29)	.961	32, 1.07 (0.73 to 1.51)	.762	18, 0.86 (0.51 to 1.35)	.599
Chronic obstructive pulmonary disease	90, 0.86 (0.69 to 1.05)	.154	51, 0.80 (0.59 to 1.05)	.115	39, 0.95 (0.68 to 1.30)	.824
Ischemic heart disease	582, 0.99 (0.91 to 1.07)	.738	347, 0.97 (0.87 to 1.08)	.605	235, 1.01 (0.88 to 1.14)	.933
Cerebrovascular disease	96, 0.89 (0.72 to 1.09)	.292	64, 1.03 (0.79 to 1.31)	.875	32, 0.71 (0.49 to 1.00)	.053
Cirrhosis and other chronic liver disease	47, 0.75 (0.55 to 1.00)	.048	36, 0.86 (0.60 to 1.19)	.418	11, 0.53 (0.26 to 0.94)	.028

* CI = confidence interval; *P* = probability based on two-sided normal approximation to a Poisson distribution when number of deaths greater than 10 or exact method otherwise.

† Person-years based on 12 270 individuals, which is the number in the study from 1960 to 1997, the period for which state rates were available (1960–2004): overall, 264 661; ever-underground, 175 058; surface only, 89 603.

‡ Workers categorized as ever-underground after first going underground (even if surface later).

§ Workers categorized as surface only until first going underground (if ever).

exposure. The hazard ratios (HRs) for the upper three quartiles of cumulative REC exposure were all less than 1.0, although they did increase in magnitude with exposure level (mortality HR = 0.58, 0.71, and 0.93 for cumulative REC exposure 2.5 to <56 μg/m^3-y, 56 to <583 μg/m^3-y, and ≥583 μg/m^3-y, respectively). For average REC intensity, the hazard ratios were generally close to 1.0, with a small statistically nonsignificant elevation at quartile 3 (HR = 1.12, 1.32, and 1.04 for average REC intensity 0.86 to <5.2 μg/m^3, 5.2 to <60 μg/m^3, and ≥60 μg/m^3, respectively). Subsequently, after stratification by worker location, it was found that there was clear evidence of DE exposure–response with lung cancer mortality, but that different patterns of lung cancer mortality by location (ie, ever-underground vs surface only) had obscured exposure–response in the complete cohort. Accordingly, further presentation relates to results from analysis by, or adjusting for, worker location.

Ever-Underground Workers. In contrast to the complete cohort, hazard ratios that increased with level of exposure were seen for ever-underground workers using quartiles of REC exposure (Table 4). Using the expanded exposure categories, hazard ratios for 15-year lagged cumulative REC exposure rose with increasing exposure, the trend being more pronounced when workers with shorter tenures were excluded (Figures 1 and 2). The hazard ratios rose to a maximum for 15-year lagged cumulative REC exposures in the 640 to <1280 μg/m^3-y category (Table 4) excluding workers with less than 5 years tenure (HR = 5.01, 95% CI = 1.97 to 12.76, *P* = .001), whereas the 15-year lagged average REC intensity hazard ratios peaked in the 32 to less than 64 μg/m^3 exposure category (HR = 3.20, 95% CI = 1.36 to 7.51, *P* = .008, Table 4).

For both exposure variables, the hazard ratios were somewhat lower in the highest categories (cumulative exposure: HR = 2.39, 95% CI = 0.82 to 6.94, *P* = .109; average intensity: HR = 3.04, 95% CI = 1.20 to 7.71, *P* = .019). The same basic trends were seen for the quartiles and expanded exposure categories using unlagged exposure data (Supplementary Tables 3 and 4, available online), and without excluding short-tenured workers using 15-year lagged and unlagged exposures (Supplementary Tables 5 and 6, available online).

Because of a decline in risk in workers with the highest cumulative REC exposure group of the expanded categorical analysis (Table 4), continuous log-linear models applied across the full range of 15-year lagged cumulative REC exposure were not statistically significant (Table 4). However, statistically significant exposure–response relationships were seen when log cumulative REC exposure was used or the exposure range was limited to less than 1280 μg/m^3-y (Table 4). This general finding was true whether or not those with less than 5 years tenure were included or excluded, and regardless of lagging period (Supplementary Table 7, available online). The hazard ratio estimated from the model with cumulative REC exposure less than 1280 μg/m^3-y for an exposure level of 1000 μg/m^3-y (HR = 4.06, 95% CI = 2.11 to 7.83) was similar to the value shown for the expanded category findings in the 640 to less than 1280 μg/m^3-y range (HR = 5.01, 95% CI = 1.97 to 12.76; Table 4). A statistically significant exposure–response relationship for log average REC intensity was

Table 4. Proportional hazard ratios on underlying cause lung cancer mortality for 15-year lagged REC cumulative exposure and average intensity for ever-underground workers: quartiles, expanded categories, and continuous modeling results*

Analyses	Results for quartiles, expanded categories, and continuous models for ever-underground workers							
Quartiles (122 LC deaths)								
Cumulative REC exposure (μg/m³-y)								
Exposure range	0 to <108	108 to <445	445 to <946	≥946				
No. LC deaths	30	31	30	31				
REC HR (95% CI)	1.00 (referent)	1.50 (0.86 to 2.62)	2.17 (1.21 to 3.88)	2.21 (1.19 to 4.09)				
P		.152	.009	.012				
Average REC intensity (μg/m³)								
Exposure range	0 to <11	11 to <51	51 to <111	≥111				
No. LC deaths	30	31	30	31				
REC HR (95% CI)	1.00 (referent)	1.73 (0.99 to 3.05)	2.11 (1.14 to 3.90)	1.86 (0.98 to 3.52)				
P		.056	.018	.057				
Expanded categories (excluding <5 year tenure, 93 LC deaths)								
Cumulative REC exposure (μg/m³-y)								
Exposure range	0 to <20	20 to <40	40 to <80	80 to <160	160 to <320	320 to <640	640 to <1280	≥1280
No. LC deaths	8	3	2	10	12	14	30	14
REC HR (95% CI)	1.00 (referent)	1.39 (0.36 to 5.39)	0.82 (0.17 to 4.03)	2.69 (0.99 to 7.37)	2.67 (0.98 to 7.27)	2.21 (0.82 to 5.97)	5.01 (1.97 to 12.76)	2.39 (0.82 to 6.94)
P		.634	.807	.054	.055	.119	.001	.109
Average REC intensity (μg/m³)								
Exposure range	0 to <2	2 to <4	4 to <8	8 to <16	16 to <32	32 to <64	64 to <128	≥128
No. LC deaths	9	2	5	8	8	27	14	20
REC HR (95% CI)	1.00 (referent)	0.93 (0.19 to 4.49)	1.00 (0.31 to 3.18)	1.79 (0.65 to 4.92)	2.01 (0.74 to 5.50)	3.20 (1.36 to 7.51)	2.11 (0.81 to 5.48)	3.04 (1.20 to 7.71)
P		.930	.998	.261	.173	.008	.125	.019
Continuous models (excluding <5 y tenure)								
Cumulative REC exposure								
Exposure range	Full		Full		<1280 μg/m³-y			
Exposure units	1000 μg/m³-y		Log μg/m³-y		1000 μg/m³-y			
No. LC deaths	93		93		79			
REC HR (95% CI)	1.07 (0.85 to 1.35)		1.19 (1.04 to 1.37)		4.06 (2.11 to 7.83)			
P	.585		.015		<.001			
Average REC intensity								
Exposure range	Full		Full					
Exposure units	100 μg/m³		Log μg/m³					
No. LC deaths	93		93					
REC HR (95% CI)	1.25 (0.93 to 1.68)		1.26 (1.06 to 1.50)					
P	.138		.010					

* CI = confidence interval; HR = hazard ratio; LC = lung cancer; REC = respirable elemental carbon; *P* = HR probability from two-sided χ^2 Wald test. Workers categorized as ever-underground after first going underground (even if surface later). Models adjusted for race/ethnicity and birth year; stratified by state. Race/ethnicity was unstable in model with restricted cumulative REC exposure range and was omitted. Inclusion of the variable had little impact.

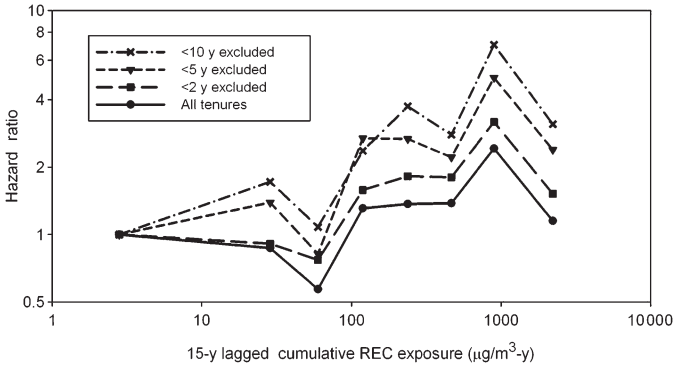

Figure 1. Lung cancer hazard ratios against 15-year lagged cumulative respirable elemental carbon (REC) exposure (μg/m³-y) for ever-underground workers, for all tenures, and after excluding workers with less than 2, less than 5, and less than 10 years tenure at time of event (see Table 4 for <5 year exclusion results). Analyses were performed with the Cox proportional hazards model and probabilities determined with a two-sided χ^2 Wald test.

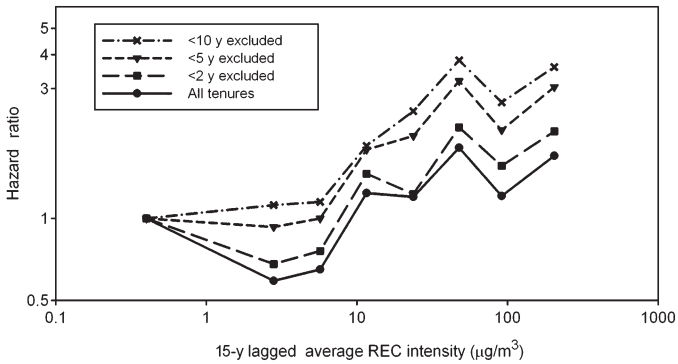

Figure 2. Lung cancer hazard ratios against 15-year lagged average respirable elemental carbon (REC) intensity (μg/m³) for ever-underground workers, for all tenures, and after excluding workers with less than 2, less than 5, and less than 10 years tenure at time of event (see Table 4 for <5 year exclusion results). Analyses were performed with the Cox proportional hazards model and probabilities determined with a two-sided χ^2 Wald test.

also observed (Table 4). In addition, the effect was seen for unlagged log intensity regardless of tenure exclusion, and for untransformed unlagged intensity with little or no tenure exclusion (Supplementary Table 7, available online).

Surface Workers. Among surface-only workers, no clear elevation or trend in mortality was apparent for cumulative REC exposure in the quartile analysis (Table 5). However, the hazard ratios for most of the quartiles for average REC intensity were statistically significantly higher, with evidence of an increasing trend in risk with increasing exposure (formal analysis of trends using continuous exposure models is described below). Using the expanded number of exposure categories and excluding those workers with less than 5 years tenure, lung cancer risk was higher for both 15-year lagged REC cumulative exposure and average intensity at the higher exposures (Table 5).

The continuous models for surface-only workers, using untransformed 15-year lagged exposures and excluding those with less than 5 years tenure, also showed evidence of a relationship between lung cancer mortality and exposure (Table 5). Untransformed average REC intensity (HR = 1.42, 95% CI = 1.10 to 1.82) showed the greatest statistical significance (P = .006). Results for untransformed cumulative REC exposure (HR = 1.02, 95% CI = 1.00 to 1.03, P = .026) and log-transformed average REC intensity (HR = 2.60, 95% CI = 1.07 to 6.29, P = .034) were also statistically significant. Similar findings to those for the 5-year tenure exclusion and 15-year lag were found for other tenure exclusions and lag periods (Supplementary Table 8, available online).

The estimated exposure–response coefficients for average REC intensity were greater for the surface-only workers compared with those for ever-underground workers. We undertook formal tests of the exposure–response slopes for the ever-underground and surface-only workers (cumulative REC exposure: 4.06 per 1000 μg/m³-y = 1.001 per μg/m³-y for the exposure range–restricted analysis vs 1.02 per μg/m³-y, respectively; average REC intensity: 1.26 vs 2.60 per log μg/m³, respectively). These tests indicated a statistically significant difference at the 5% level for average REC intensity but not for cumulative REC exposure.

Complete Cohort Adjusted for Location. Given the evidence of exposure–response for both worker location groups, we repeated the quartile analysis for the complete cohort but including a time-dependent location variable in the models. In essence, this variable is set initially to 0 for each individual and is set to 1 the first time the worker took an underground job (if ever). The mean hazard ratio for the time-dependent location variable (surface-only vs ever-underground work) was 1.9 (range: 1.64–2.28) for the estimates applicable to the six analyses (quartiles, expanded categories, and continuous models shown in Table 6 for cumulative REC exposure and average REC intensity [HRs not shown in table]). The quartile hazard ratios (Table 6) were greater compared with those without the location variable (reported in text at the start of the proportional hazard modeling section above and also in Supplementary Table 9, available online). Use of the expanded categories after exclusion of workers with less than 5 years of tenure resulted in HRs similar to those for ever-underground workers at the higher levels of REC exposure (Table 6). At lower cumulative REC exposures, the adjusted complete cohort HRs tended to fall between the ever-underground and surface-only hazard ratios.

The continuous modeling results for the complete cohort excluding those with less than 5 years tenure revealed statistically significant exposure–response slopes that were similar to those observed among the ever-underground workers (complete cohort vs ever-underground workers, cumulative REC exposure: HR = 3.62 vs 4.06 per 1000 μg/m³-y; average REC intensity: HR = 1.20 vs 1.26 per μg/m³) (Table 6 vs Table 4) (Supplementary Tables 9–11, available online, facilitate comparison across worker locations of the results given in Tables 4–6 of the main article.)

Potential Workplace Confounder Exposures. Addition of cumulative exposures for silica, asbestos, non-DE PAHs, and respirable dust to the models had only minor effects on the findings and actually led to an increase in the continuous REC HRs shown in Tables 4–6 by about 5% overall. Among ever-underground workers, there was some evidence of a cumulative radon exposure effect (P = .037, results not shown). However, this effect was absent

Table 5. Proportional hazard ratios on underlying cause lung cancer mortality for 15-year lagged REC cumulative exposure and average intensity for surface-only workers: quartiles, expanded categories, and continuous modeling results*

Analyses	Results for quartiles, expanded categories, and continuous models for surface-only workers			
Quartiles (78 LC deaths)				
Cumulative REC exposure (μg/m³-y)				
Exposure range	0 to <0.70	0.70 to <4.6	4.6 to <14	≥14
No. LC deaths	19	20	19	20
REC HR (95% CI)	1.00 (referent)	1.28 (0.64 to 2.58)	0.73 (0.35 to 1.53)	1.00 (0.44 to 2.28)
P		.490	.407	.998
Average REC intensity (μg/m³)				
Exposure range	0 to <0.57	0.57 to <0.91	0.91 to <1.4	≥1.4
No. LC deaths	19	18	21	20
REC HR (95% CI)	1.00 (referent)	1.71 (0.82 to 3.58)	2.22 (1.01 to 4.90)	2.56 (1.09 to 6.03)
P		.154	.049	.031
Expanded categories (excluding <5 year tenure, 57 LC deaths)				
Cumulative REC exposure (μg/m³-y)				
Exposure range	0 to <20	20 to <40	40 to <80	≥80
No. LC deaths	44	7	4	2
REC HR (95% CI)	1.00 (referent)	1.16 (0.46 to 2.94)	2.29 (0.60 to 8.75)	8.68 (1.61 to 46.90)
P		.756	.224	.012
Average REC intensity (μg/m³)				
Exposure range	0 to <2	2 to <4	≥4	
No. LC deaths	44	11	2	
REC HR (95% CI)	1.00 (referent)	2.33 (1.11 to 4.90)	4.63 (0.99 to 21.55)	
P		.026	.051	
Continuous models (excluding <5 y tenure)				
Cumulative REC exposure				
Exposure range	Full		Full	
Exposure units	μg/m³-y		Log μg/m³-y	
No. LC deaths	57		57	
REC HR (95% CI)	1.02 (1.00 to 1.03)		1.03 (0.75 to 1.42)	
P	.026		.842	
Average REC intensity				
Exposure range	Full		Full	
Exposure units	μg/m³		Log μg/m³	
No. LC deaths	57		57	
REC HR (95% CI)	1.42 (1.10 to 1.82)		2.60 (1.07 to 6.29)	
P	.006		.034	

* CI = confidence interval; HR = hazard ratio; LC = lung cancer; REC = respirable elemental carbon; *P* = HR probability from two-sided χ^2 Wald test. Workers categorized as surface-only until first going underground (if ever). Models adjusted for race/ethnicity, birth year, and sex; stratified by state.

Table 6. Proportional hazard ratios on underlying cause lung cancer mortality for 15-year lagged REC cumulative exposure and average intensity for complete cohort adjusted for worker location: quartiles, expanded categories, and continuous modeling results*

Analyses	Results for quartiles, expanded categories, and continuous models for complete cohort							
Quartiles (200 LC deaths)								
Cumulative REC exposure (μg/m³-y)								
Exposure range	0 to <2.5	2.5 to <56	56 to <583	≥583				
No. LC deaths	50	50	50	50				
REC HR (95% CI)	1.00 (referent)	0.55 (0.35 to 0.85)	1.03 (0.60 to 1.77)	1.39 (0.78 to 2.48)				
P		.007	.925	.261				
Average REC intensity (μg/m³)								
Exposure range	0 to <0.86	0.86 to <5.2	5.2 to <60	≥60				
No. LC deaths	50	50	50	50				
REC HR (95% CI)	1.00 (referent)	1.13 (0.72 to 1.76)	1.98 (1.12 to 3.52)	1.57 (0.86 to 2.86)				
P		.600	.019	.144				
Expanded categories (excluding <5 y tenure, 150 LC deaths)								
Cumulative REC exposure (μg/m³-y)								
Exposure range	0 to <20	20 to <40	40 to <80	80 to <160	160 to <320	320 to <640	640 to <1280	≥1280
No. LC deaths	52	10	6	12	12	14	30	14
REC HR (95% CI)	1.00 (referent)	0.92 (0.45 to 1.91)	0.93 (0.36 to 2.37)	3.14 (1.39 to 7.14)	2.64 (1.13 to 6.20)	1.99 (0.87 to 4.53)	4.48 (2.13 to 9.40)	2.12 (0.89 to 5.06)
P		.826	.876	.006	.026	.103	<.001	.089
Average REC intensity (μg/m³)								
Exposure range	0 to <2	2 to <4	4 to <8	8 to <16	16 to <32	32 to <64	64 to <128	≥128
No. LC deaths	53	13	7	8	8	27	14	20
REC HR (95% CI)	1.00 (referent)	1.72 (0.91 to 3.26)	1.90 (0.75 to 4.80)	2.70 (1.07 to 6.79)	2.48 (0.98 to 6.30)	3.62 (1.72 to 7.60)	2.19 (0.95 to 5.06)	2.94 (1.31 to 6.60)
P		.095	.174	.035	.056	.001	.067	.009
Continuous models (excluding <5 y tenure)								
Cumulative REC exposure								
Exposure range	<1280 μg/m³-y							
Exposure units	1000 μg/m³-y							
No. LC deaths	136							
REC HR (95% CI)	3.62 (1.99 to 6.60)							
P	<.001							
Average REC intensity								
Exposure range	Full							
Exposure units	Log μg/m³							
No. LC deaths	150							
REC HR (95% CI)	1.20 (1.04 to 1.39)							
P	.015							

* CI = confidence interval; HR = hazard ratio; LC = lung cancer; REC = respirable elemental carbon; *P* = HR probability from two-sided χ^2 Wald test. Models adjusted for race/ethnicity, birth year, sex, and worker location (time-dependent variable based on status); stratified by state.

in seven of the mines, and in the eighth (mine A) was driven by workers aged 40 years or older employed before 1947. The cumulative radon exposure effect at the eighth facility was large in some models; for example, in the model with cumulative REC exposure less than 1280 μg/m³-y in Table 4, the categorical HR for radon was 6.2 (P = .020) for exposures of 6.15 to 6.98 WL-months for all underground workers accumulated over their complete tenure at the facility (mean = 31 years). Excluding the early, older workers removed the radon exposure effect both within that facility and overall.

Other Models and Findings. As noted above, the trends with exposure seen in the expanded categories and continuous models in Tables 4–6 were also evident either using unlagged REC exposures or employing no tenure exclusion (Supplementary Tables 5–8, available online). In addition, the short-term worker effect in ever-underground workers was greater for those who started work at the study facilities at age 40 or older (Supplementary Table 12, available online). The results based on the three alternative REC exposure estimates were very consistent with those from the primary exposure estimate (Supplementary Table 13, available online). Statistically significant exposure–response was detected among ever-underground workers for three of the four subgroups defined by state/ore type (the fourth had only six lung cancer deaths) (Supplementary Table 14, available online). The results were unchanged after including contributing cause lung cancer deaths (Supplementary Table 15, available online).

The finding of higher esophageal cancer mortality in the external analysis was investigated further by relating it to DE exposures using the same continuous models used in Tables 4–6. The HRs followed the same general pattern as for lung cancer and were higher for underground workers (HR range = 1.19–2.77) but were not statistically significant (Supplementary Table 16, available online).

Discussion

The results of this study indicate a higher lung cancer mortality risk associated with DE exposure among ever-underground workers (ie, those with the greatest DE exposures). Some evidence of an effect on lung cancer from DE exposure was also seen in surface-only workers. The exposure–response relationships were robust to variations in the methodological approach used in exposure assessment and essentially unchanged after adjustment for potential workplace confounders.

The DE–lung cancer associations seen separately for the ever-underground and surface-only workers were not readily apparent in the complete cohort without adjustment for worker location (ever underground vs surface only), which may be attributable to the generally higher lung cancer mortality and relatively low exposures among the surface workers (Tables 3, 5, and 6). In the complete cohort, most of the surface-only workers fell into the reference category, leading to a concomitant reduction in the HRs at higher exposures. After adjustment for worker location, the exposure–response findings were similar to those reported separately for the two worker location groups. (See the companion case–control study (21) for further information on this observation, including the observation that the risk of lung cancer from cigarette smoking differed by worker location.)

Some differences possibly remain between the two worker locations. As noted earlier, a formal test of significance of the ever-underground vs surface-only HR slopes indicated a statistically significant difference between the two location groups at the 5% level for log average REC intensity (1.26 vs 2.60). The surface-only HR for untransformed cumulative REC exposure was also greater than that for ever-underground workers, although the difference was statistically nonsignificant. This result may be attributable to aging and transformation of DE by sunlight, ozone, and other factors. During these processes, some exhaust components become more toxic (31,32). For example, secondary and unique nitro-PAHs are produced by atmospheric reactions of DE (33).

We found that the HRs were generally greater after exclusion of workers with shorter tenures, which was true for both ever-underground and surface-only workers. Shorter-term employees include transient workers, who may take lower-paid more hazardous jobs, have less access to health care, smoke more, and generally have more lifestyle and occupational risk factors for disease than workers who work for extended periods with the same employer. Such factors have been shown to affect mortality (34,35). Younger short-term workers may go on to receive hazardous exposures elsewhere after leaving employment in the study facilities, whereas workers who enter the study at older ages may have had extensive prior experience in hazardous jobs. Information pertinent to prior or later workplace exposures was not available for most individuals in the cohort study, nor sufficiently reliable, and therefore, we could not take it into account formally in the cohort analysis. Lifetime occupational histories were obtained in the companion case–control study (21), in which a relationship between long-term employment in high-risk occupations for lung cancer was associated with increased lung cancer mortality.

We explored the short-term worker effect further by adding terms for tenure and a REC by tenure interaction to the proportional hazard models for ever-underground workers instead of excluding workers with less than 5 years tenure (data not shown). This analysis led to virtually the same findings, showing that those with the longer tenure had lower absolute risk but greater REC exposure–response slopes compared with short-term workers. In addition, we examined the effect of limiting the less than 5-year tenure worker exclusion by age of starting work at the study facilities. This analysis showed that individuals with short tenures who started work after age 40 had the largest REC exposure–response HRs. Because older workers would have had the greatest potential for prior work in other hazardous jobs, the findings suggest that previous exposures for some individuals may have affected the findings in this cohort and that exclusion of short-term workers may be a partial surrogate for adjustment for prior hazardous exposures. As noted above, lifetime work histories were acquired and used in the analyses for the companion case–control study.

It should be noted, however, that it was not necessary to restrict the analyses on tenure for statistically significant exposure–response findings to arise. For example, the cumulative REC exposure HR for ever-underground workers including all tenures and restricted to less than 1280 μg/m³-y was 2.79 (P < .001). Moreover, statistically significant findings were found for other models in

which tenure was not restricted (Supplementary Table 7, available online). Furthermore, in proportional hazard models using time since entry into cohort and adjusting for age instead of using age as the underlying time variable, similar findings as shown in Table 4 were found without any tenure restriction (Supplementary Table 17, available online).

Among the ever-underground workers, the HRs rose fairly consistently over the REC exposure range but declined or reached a plateau at the higher levels of exposure [Table 4 and case–control findings (21)]. Given the clear evidence of increasing risk with increasing exposure for the lower part of the exposure range, we undertook analyses omitting the highest exposures to provide risk estimates pertinent to the lower range. However, given that the findings (Table 4) could also be interpreted as showing a plateau similar to that seen for average REC intensity (ie, apart from the HR of 5.01, the rest fall in the range 2.21–2.69 from 80 μg/m^3-y and higher), we also fitted log cumulative REC exposure for the full exposure range. However, the log transformation model fitted the data less well than the restricted exposure model. Declines and plateaus have frequently been reported for other occupational exposures, and a variety of plausible explanations have been proposed, for example, misclassification at high exposures, worker selection effects, and enzyme saturation (36).

The overall findings were essentially unchanged after inclusion of silica, asbestos, non-diesel PAHS, and respirable dust in the models. Although radon was associated with lung cancer risk, the observed effect was driven by a small subset of older workers hired before 1947 at facility A. At that facility, the estimated radon exposure levels were about half of those at four other facilities (Table 2). The hazard ratio for cumulative radon exposure was 6.2, considerably greater than the 1.1 predicted from radon-exposed underground miners for the same exposure levels (37). We conclude that the radon finding is anomalous and probably arose from chance or other unknown factors affecting early older workers at that one facility.

Few studies of lung cancer and DE have been conducted in mining operations. A previous mortality study of US potash workers, based on mine tenure, did not find an excess of malignant neoplasms of the respiratory system (38). However, as noted by the authors, the latency period was inadequate to detect elevations in lung cancer mortality associated with DE (at study closure, only two mines used diesel engines, with follow-up of 10 and 18 years, respectively). In a study of German potash miners (5), a statistically significantly higher lung cancer relative risk (2.47, 95% CI = 1.02 to 6.02) was found for miners with 2.04 to less than 2.73 mg/m^3-y total carbon (TC, which includes both EC and organic carbon) exposure, compared with the reference group (<1.29 mg/m^3-y TC). A positive trend in increasing mortality with increasing TC exposure was observed (P = .09).

Apart from those mentioned above, there are no other existing cohort mortality studies of DE and lung cancer in miners, and none of the cohort studies in other industries used quantitative measurements of exposure directly in the epidemiological modeling. A recent study of truckers (6) reported higher hazard ratios (approximately 2) among long-haul drivers and pick-up/delivery drivers with 20 years of work and with adjustment for smoking. Spline analyses also showed evidence of increasing lung cancer risk with increasing tenure in truck driving jobs, with estimated hazard ratios ranging from 2.5 to 4.0 after 40 years exposure. These findings are fairly similar to those from an earlier study of truckers (39), in which an odds ratio of 1.89 was reported for diesel truck drivers with 35 or more years tenure. These hazard ratios, possibly applicable to reported arithmetic mean exposures of 3–5 μg/m^3 for highway and local drivers (40), are similar to what we found for surface-only workers at equivalent levels of exposure (HR of 2.33 at the average REC level for the 2 to <4 μg/m^3 category).

Among causes of death previously reported to be associated with DE exposure, few were higher in this standardized mortality ratio analysis. Standardized mortality ratios for nonmalignant respiratory disease (apart from pneumoconiosis), heart disease, and all-cause mortality were either less than or close to expected values. A statistically nonsignificant increase in the standardized mortality ratio for bladder cancer was seen for surface-only workers, but there was a statistically nonsignificant deficit for the ever-underground workers (who had much higher DE exposures). A similar pattern was observed for leukemia. However, the number of bladder cancer and leukemia deaths was too small to draw meaningful conclusions. The hazard ratios for esophageal cancer were higher in ever-underground workers but not in surface-only workers, and there was a suggestion of a relationship with level of DE exposure. However, the number of esophageal cancers was too small for reliable evaluation (16 for ever-underground and seven for surface-only workers).

We observed 17 deaths from pneumoconiosis, whereas only two were expected. These consisted of 10 coal workers' pneumoconiosis, one asbestosis, one silicosis, and five unspecified. Of the 16 having past work information, 13 had worked in coal mining before employment at the study facilities. Three individuals had worked extensively in jobs with either likely or possible exposure to lung carcinogens, including a power plant (22 years; asbestosis), an auto mechanic (27 years; unspecified), and a mining mill operator (27 years; silicosis). Overall, the development of pneumoconiosis in these workers appears likely to be related to their previous work.

This investigation had limitations typical of cohort mortality studies, including the uncertainty commonly encountered in exposure assessment (eg, limited sampling data for some jobs and reliance on surrogate information for extrapolation to the past), incomplete information on potentially hazardous exposures received in other jobs held before or after employment in the study facilities, and lack of information on lifestyle factors (eg, smoking). These limitations pertain to the information for every individual in the study to a greater or lesser extent. Although the study lacked smoking data, the findings from the companion case–control study (21) showed that the REC effect was not attenuated by the inclusion of smoking in the models. Smoking information available from the case–control study and from a morbidity survey of underground metal and non-metal miners undertaken in the mid-1970s that included six of the mines in this mortality study [see (36) for results for the potash miners] did not show any evidence of increased smoking prevalence in the more highly DE-exposed jobs underground. In addition, Hein et al. (37) have pointed out that adjustment for birth year (as undertaken in this study) can partially adjust for confounding from smoking. Taken

overall, this information implies that smoking was unlikely to have caused the observed relationship of lung cancer with DE exposure in the cohort study.

The case–control study also adjusted for other lifestyle factors as well as for employment associated with potentially confounding exposures from work outside of the study mines. As noted above, the exclusion of workers with less than 5 years tenure appears to have been a surrogate for adjustment of other exposures, although it should be noted that the main REC exposure–response findings were evident without any tenure exclusion (Figures 1 and 2).

This study also had strengths, including 90% statistical power to detect a doubling of risk of lung cancer in the highest DE exposed workers, time since first exposure sufficient to detect excess lung cancer mortality, and multiple study facilities in various geographical locations and mining different commodities. DE levels among underground workers in this study were considerably higher on average, and had a wider range, than in virtually all previous investigations, thus increasing the power to detect any DE effects. The study had extensive information on potential workplace confounders for lung cancer, and we chose workplaces largely devoid of known confounders. In addition, the exposure assessment relied on thousands of recent and historical measurements instead of relying solely on surrogate exposure information (23). The anchor measurements (the 1998–2001 DEMS environmental samples) consisted of job-specific means of multiple REC samples. They therefore provided reliable estimates of environmental conditions in 1998–2001. Because the samples were collected for epidemiological use, they were more likely to accurately represent the working environment than samples collected for compliance purposes (compliance measurements may be greater than typical levels because compliance samples are more likely to be taken when environmental levels are suspected to be high). Past exposure extrapolation was based on trends in measurements of CO (along with REC, a major emission from diesel engines) supported by models using indicators of diesel usage and ventilation rates obtained from records and supplemented by local knowledge from workers (25). Although the CO data were based on compliance measurements, we used them only for the development of relative trends, not to estimate absolute levels of exposure.

The exposure assessors (P. A. Stewart, R. Vermeulen, J. B. Coble) were blinded to the mortality outcome data during their development of the exposure estimates. Their estimates were evaluated by comparison with independent data (see "Methods") and showed good agreement (22). Through the use of alternative metrics, we were able to explore the effect of exposure assessment assumptions and demonstrated that similar findings emerged regardless of the REC estimate used (Supplementary Table 13, available online). Importantly, although imprecision in our exposure estimates exists, we feel that it is non-differential (ie, not systematically biased to higher or lower exposure levels across the study), and as such, would lead only to the exposure–response coefficients being biased to the null in expectation (26). Finally, the consistency of the findings across multiple analyses using alternative exposure estimates and modeling approaches demonstrated that the results were robust to different choices of methodological strategy.

We believe that it is unlikely that the results are subject to healthy worker survivor selection effects (41) arising from individuals leaving work because of respiratory disease. We specifically chose the non-metal mining environment for its absence of known lung cancer health effects relating to dust exposures. The earlier morbidity study of underground potash miners, undertaken at most of the facilities participating in this study, showed no obvious severe respiratory problems at the mines (42). Moreover, the respiratory disease findings from this study do not indicate any excess mortality among causes that would lead to the suspicion that workers might have left work because of respiratory disease.

This study was undertaken during a period when, through the efforts of manufacturers, diesel engine emissions were declining (31). These advances continue into the present and imply that future occupational and environmental exposure levels to DE should be less than those encountered during the study. However, there will continue to be legacy of older equipment in operation, the extent and duration of this varying across different countries depending on economic prosperity. Certainly, many workers around the world, in mining and in other industries and jobs, continue to be exposed to REC at levels similar to those observed in this study (43); in addition, environmental exposures have been shown to reach the levels seen for average REC intensity in surface workers in this study (44–48). As a result, the findings from this study suggest that diesel engine exhaust may be, and may continue to be, a public health risk for many workers worldwide.

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Notes

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