

# Diesel Engine Exhaust and Lung Cancer Mortality: Time-Related Factors in Exposure and Risk

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To develop a quantitative exposure-response relationship between concentrations and durations of inhaled diesel engine exhaust (DEE) and increases in lung cancer risks, we examined the role of temporal factors in modifying the estimated effects of exposure to DEE on lung cancer mortality and characterized risk by mine type in the Diesel Exhaust in Miners Study (DEMS) cohort, which followed 12,315 workers through December 1997. We analyzed the data using parametric functions based on concepts of multistage carcinogenesis to directly estimate the hazard functions associated with estimated exposure to a surrogate marker of DEE, respirable elemental carbon (REC). The REC-associated risk of lung cancer mortality in DEMS is driven by increased risk in only one of four mine types (limestone), with statistically significant heterogeneity by mine type and no significant exposure-response relationship after removal of the limestone mine workers. Temporal factors, such as duration of exposure, play an important role in determining the risk of lung cancer mortality following exposure to REC, and the relative risk declines after exposure to REC stops. There is evidence of effect modification of risk by attained age. The modifying impact of temporal factors and effect modification by age should be addressed in any quantitative risk assessment (QRA) of DEE. Until there is a better understanding of why the risk appears to be confined to a single mine type, data from DEMS cannot reliably be used for QRA.

**KEY WORDS:** Diesel exhaust; lung cancer; multistage carcinogenesis parametric models; quantitative risk assessment

## 1. INTRODUCTION

Concern that exposure to diesel engine exhaust (DEE) might cause adverse health effects developed soon after the technology was discovered and introduced more than a century ago. With rapid expansion of the use of diesel engines post-World War II, this concern intensified, with attention focused on the potential for prolonged exposure to DEE to cause lung cancer.<sup>(1,2)</sup> The approach to studying this issue has been multifaceted, including the conduct of epidemiological investigations, laboratory animal bioassays, and mechanistic studies using various models. Of these approaches, the epidemiological studies have received particular attention because the results are directly applicable to human populations without extrapolation across species or from *in vitro* settings.

Two influential papers describing the results of a cohort and a nested case-control analysis of the Diesel Exhaust in Miners Study (DEMS) recently

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reported a statistically significant increase in lung cancer mortality among both underground and surface miners exposed to DEE.<sup>(3,4)</sup> Based on these results and others, the International Agency for Research on Cancer (IARC) concluded in June 2012 that there is sufficient evidence of carcinogenicity for DEE in humans and upgraded its classification of DEE from “probably carcinogenic” (Group 2A) to “carcinogenic to humans” (Group 1).<sup>(5)</sup>

No quantitative risk assessment (QRA) has been conducted after the publication of the results of DEMS, and the issue of the suitability of these results for QRA remains open. Prior to 2012, that is, before the DEMS results had been published, only one government agency, the California Air Resources Board (CARB), had conducted a QRA for DEE.<sup>(6–10)</sup> It is noteworthy that three federal agencies, the National Institute of Occupational Safety and Health (NIOSH),<sup>(11)</sup> the Mine Safety and Health Administration (MSHA),<sup>(12)</sup> and the U.S. Environmental Protection Agency (EPA),<sup>(13)</sup> evaluated the epidemiological literature available pre-2000 and deemed it inadequate for QRA. However, all three agencies issued guidance or regulations intended to limit exposure to DEE.

Despite regulations and technological advances in diesel technology, there remains substantial interest from government agencies and the private sector in the potential for conducting QRA for DEE from all technology diesel engines. QRA is of keen interest to multiple government agencies, including U.S. EPA, NIOSH, and MSHA, as well as the private sector. This article analyzes the DEMS cohort data using methods that complement the approach used by Attfield *et al.*<sup>(3)</sup> We hope that the results of our analyses will contribute to the understanding of the relationship between DEE and lung cancer in DEMS, and to the use of this important study for QRA for DEE.

Two related issues have recently received attention in the epidemiologic literature. First, although summary measures of exposure, such as cumulative exposure, have been widely used in epidemiology and have led to important insights into risk factors for human disease, it is becoming increasingly clear that such summary measures of exposure cannot capture the impact of complex temporal patterns of exposure on disease risk.<sup>(14,15)</sup> The second, related issue has to do with the measure of effect. Recent papers<sup>(16,17)</sup> have emphasized the limitations inherent in focusing on hazard ratios in epidemiologic studies. For cohort

data, both issues can be addressed simultaneously by using parametric methods to estimate hazard functions instead of relative hazards. Tammemagi *et al.*<sup>(18)</sup> used a purely statistical approach to estimate hazard functions in cohort data. They used logistic regression models with time-related factors being modeled by cubic splines modifying the impact of pack-years of smoking on the risk of lung cancer. A more biologically motivated approach is based on concepts of multistage carcinogenesis.<sup>(19–21)</sup> These ideas have a long history.<sup>(22–27)</sup> In this approach, parametric hazard functions derived from multistage models of carcinogenesis that explicitly incorporate patterns of exposure are used to directly estimate the hazard functions. In an early application to DEE, Dawson and Alexeeff<sup>(10)</sup> used the multistage model of Armitage and Doll<sup>(28)</sup> to estimate unit risks for DEE-associated lung cancer in a cohort of railroad workers. Statistical approaches that modify the effect of cumulative exposure on the odds ratio have been proposed for analyses of case-control data by Lubin *et al.*<sup>(29–31)</sup> and more recently by Vlaanderen *et al.*<sup>(32)</sup>

With detailed information on patterns of exposure and a relatively large data set, the DEMS provides an excellent opportunity to examine the impact of patterns of exposure to REC on lung cancer risk. In this article, we extend the Attfield *et al.*<sup>(3)</sup> analyses of the DEMS cohort data by exploring the impact of temporal factors, such as duration of exposure and time since cessation of exposure, on lung cancer mortality following exposure to DEE. To assure ourselves that we were analyzing identical data sets, we first reproduced the Cox proportional hazards analyses reported in Attfield *et al.*,<sup>(3)</sup> including the results in their Supplementary Materials. We then explored time-related factors in DEMS by using a version of the multistage clonal expansion model<sup>(33–41)</sup> to directly estimate hazard functions instead of hazard ratios.

## 2. METHODS

The data used in our analyses are those acquired by the DEMS team, including their estimates of the respirable elemental carbon (REC) exposure metrics. The DEMS effort was conducted by investigators associated with NIOSH and the National Cancer Institute (NCI) and initiated in the early 1990s. The DEMS research is reported in five papers that describe the exposure assessment,<sup>(42–46)</sup> a paper

describing a cohort study,<sup>(3)</sup> and a paper and letter describing a nested case-control study.<sup>(4,47)</sup> A key feature of DEMS, as noted by the DEMS team, is the attention given to constructing retrospective estimates of workers' exposure to REC as a primary surrogate indicator of exposure to DEE.

The DEMS cohort study, which has been described in detail by Attfield *et al.*,<sup>(3)</sup> included 12,315 workers from eight nonmetal mines and associated facilities, as summarized in Table I. The cohort included individuals who worked for at least one year in the mines or related facilities, excluding administrative and managerial employees.

The eight mines and related facilities handled four types of ore: one limestone mine in Missouri, three potash mines in New Mexico, one salt (halite) mine in Ohio, and three trona mines in Wyoming. These nonmetal mines were all considered to produce ore that was thought not to present a carcinogenic hazard on inhalation. The seven potash, salt, and trona mines all had generally similar operations. The ore in those mines was extracted from seams of various heights (on the order of 10–15 ft) at various depths below the surface with the ore transferred, typically by conveyers, to central vertical shaft locations where it was lifted to the surface for further processing. The processing facilities varied in complexity at each mine, dependent on the intended use of the ore and purified and sized products. All seven of these mines had substantial mechanical ventilation supplying large quantities of air to minimize airborne dust concentrations and, in the case of the trona mines, to minimize the build-up of methane, an explosive gas. The mining operations made substantial use of electric-powered equipment and selective use of diesel-powered equipment for various operations, including underground transport of miners.

The limestone mining operation was quite different from that in the seven other mines. It involved mining of limestone on a single plane with ore hauled by large diesel-powered haul units to surface openings at approximately the same elevation as the underground mining operations. The areas where ore was mined were high-ceiling caverns (approximately 40 ft in height) with intermittent support columns of unmined ore. The limestone mine primarily used natural ventilation, with air flowing up or down vertical shafts between the surface and the mining operations.

Demographic and work history information was abstracted from facility personnel records by DEMS study investigators. Mortality follow-up was conducted from the year of introduction of

diesel-powered equipment in each facility (1947–1967) through December 31, 1997, using the National Death Index and the Social Security Administration death files.

The analyses presented in this article are limited to the data, including exposure information, provided by NIOSH under a data-use agreement. We had no access to the original records underlying the data, nor could we use alternative measures of exposure. Each miner's time-varying historical exposure to DEE was quantitatively estimated as REC based on work histories. Fig. 1 shows histograms for the distributions of estimated cumulative REC exposure in the various mine types. It is important to recognize that these histograms are for all workers, both on the surface and underground. The cohort of limestone mine workers clearly had the lowest estimated cumulative exposures. Table 2 from Attfield *et al.*<sup>(3)</sup> shows that the estimated REC concentration was also lowest for the workers (surface and underground) in the limestone mining operation.

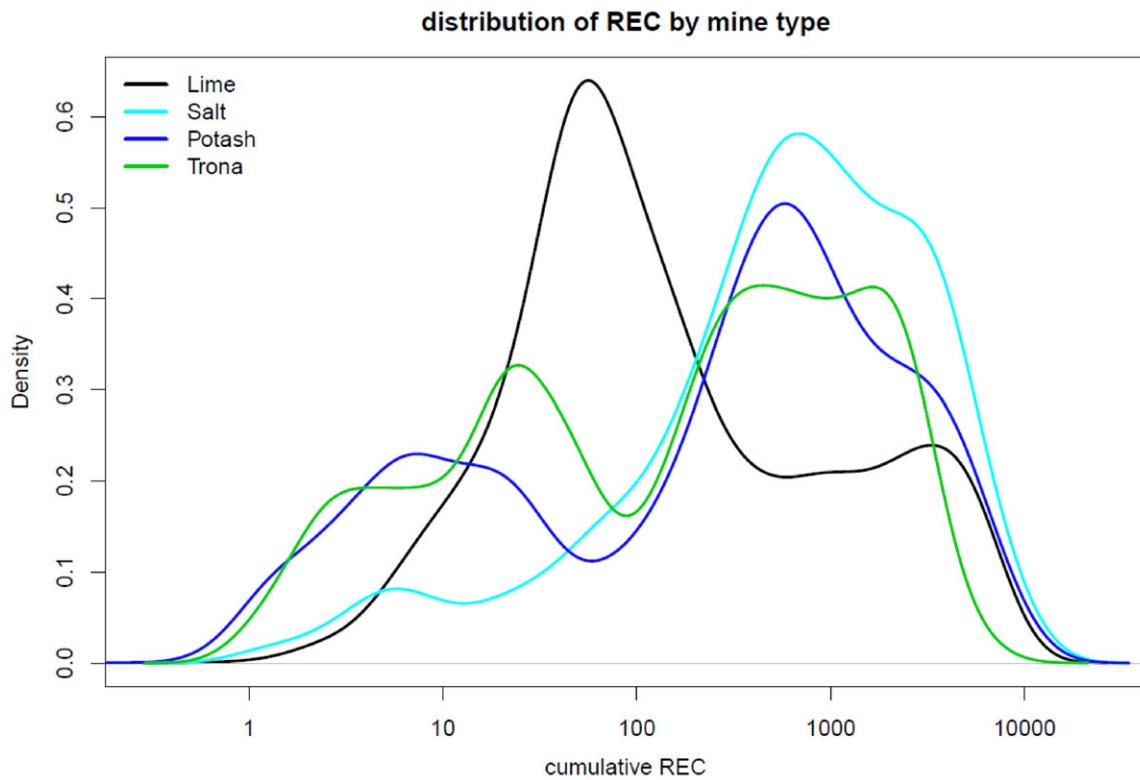
## 2.1. DEMS Data

In response to our request for the data set for the DEMS internal cohort analysis, NIOSH provided three de-identified data files with demographic, occupational, and death outcome data, which we combined into a single data set. The death outcome file identified miners who died of lung cancer or esophageal cancer as an underlying or contributing cause, but did not provide specific cause-of-death codes for any other deceased miners in the cohort. By the end of the mortality follow-up period, 2,185 deaths were ascertained, including 200 deaths from lung cancer as the underlying cause and an additional 12 deaths from lung cancer as a contributing cause. Cigarette smoking histories were not available for analysis of the cohort data. In addition, at the time our analyses were conducted, we had not been provided accurate radon exposure data on the mines and workers.

To accommodate the time-varying nature of the exposure, we constructed a data set with monthly average REC intensity and cumulative REC starting from the date of first exposure until the date of last known follow-up or death, with exposure estimates indexed at the end of each month. Lagged exposure on a given date was calculated by retrieving the exposure during the same month a set number of years earlier. If no work record existed at that time, then the lagged exposure was set to zero. Age attained at the beginning and end of each month was used

**Table I.** Number of Miners and Lung Cancer Deaths by Worker Location and Mine Type in the DEMS Cohort

Mine Type	Ever-Underground Workers							
	Surface-Only Workers		Underground-Only Workers		Surface and Underground Workers		Complete Cohort	
	Miners	Deaths	Miners	Deaths	Miners	Deaths	Miners	Deaths
Limestone	730	15	123	12	823	10	1,676	37
Potash	1,293	38	1,951	46	1,327	18	4,571	102
Salt	50	<5	208	9	289	<5	547	<19
Trona	1,935	23	1,798	15	1,788	11	5,521	49
Entire Cohort	4,008	<81	4,080	82	4,227	<44	12,315	200



**Fig. 1.** Distribution of cumulative respirable elemental carbon (REC) exposures in the various mine types. Note that the cumulative REC exposure is shown on a logarithmic scale.

as the primary time scale. An event was recorded if a worker died from lung cancer during a particular monthly period. Other causes of death and loss to follow-up were represented as right-censoring times.

**2.2. Standardized Mortality Ratio (SMR) Analyses and Cox Proportional Hazards Regression**

We replicated the results in Attfield *et al.*<sup>(3)</sup> and performed additional analyses as described in the

Supporting Information. In particular, we performed extensive new analyses to explore the shape of the exposure-response relationship and the role of temporal factors in determining risk.

**2.3. Multistage Carcinogenesis Parametric Models**

Dawson and Alexeeff<sup>(10)</sup> estimated unit risks for DEE-associated lung cancer in a cohort of railroad workers using the multistage model of Armitage and

Doll.<sup>(28)</sup> In this article, we used two versions of multistage clonal expansion models, the two-stage clonal expansion model (2SCE) and the three-stage clonal expansion model (3SCE), to analyze the DEMS cohort data. Note that because we set the first two “mutation” rates equal in the 3SCE model, we estimate the same number of parameters in the 2SCE and 3SCE models. Both models yielded very similar results, but the 3SCE had a higher likelihood model. Therefore, we present only the results using the 3SCE model. The two main advantages of using multistage models are direct estimation of hazard functions rather than relative hazards, and explicit consideration of temporal patterns of exposure, such as ages at exposure initiation and cessation and time-dependent patterns of exposure.

A pictorial depiction of the main features of this model is shown in Fig. 2. Details can be found in the published literature.<sup>(21,33–36)</sup> The parameters of the model are treated as functions of the exposures of interest, in this case the concentration of REC. The hazard function, the probability of lung cancer by age  $t$ , denoted  $P(t)$ , and the survival function,  $S(t) = 1 - P(t)$ , are therefore also functions of REC concentration. In terms of these quantities, the likelihood function is given as follows. Assuming independence between individual response probabilities, the cohort likelihood is the product of individual likelihoods over all subjects  $j$ ,  $\mathcal{L} = \prod \mathcal{L}_j$ . Individual likelihoods  $\mathcal{L}_j = \mathcal{L}_j(s_j, t_j, (\dots))$  depend on age at entry into the study  $s_j$ , censoring or failure age  $t_j$ , and detailed exposure histories in conjunction with general exposure-response models for the biological parameters in the TSCE model, and possibly on a lag time or distribution of lag times.

The individual likelihoods for cases and survivors, accounting for left-truncation, are given by:

$$\mathcal{L}_j(t_j, s_j) = \begin{cases} P'(t_j)/S(s_j) & \text{if diagnosed with} \\ & \text{cancer,} \\ S(t_j)/S(s_j) & \text{otherwise.} \end{cases} \quad (1)$$

Furthermore, let  $h_m(u)$  represent the individual TSCE model hazard and  $S_m(u)$  represent the TSCE model survival at some age  $u$ . For a fixed lag time from the first malignant cell to cancer death,  $t_{lag}$ , individual likelihoods in Equation (1) are calculated using  $S(t_j) = S_m(t_j - t_{lag})$ ;  $S(s_j) = S_m(s_j - t_{lag})$ ;  $P'(t_j) = h_m(t_j - t_{lag})S_m(t_j - t_{lag})$ . Here we used lag = 0 or lag = 15, in accordance with the approach used by Attfield *et al.*<sup>(3)</sup> Left-truncation requires calculation

of the survival probability,  $S(s_j)$ , at entrance into the study.

Identifiability of parameters of multistage clonal expansion models is discussed in Heidenreich *et al.*<sup>(48)</sup> and Little *et al.*<sup>(33)</sup> For the analyses here, the identifiable parameters are “slope” =  $\mu_0\mu_1(g/\alpha)$ ; “promotion” =  $g = \alpha - \beta - \mu_2$ ; and  $\mu_2$ , which is a mutation rate and therefore very small, on the order of  $10^{-7}$ ; therefore,  $g \sim \alpha - \beta$ . The interpretation of these parameters in terms of the shape of the cancer incidence curve is described in recent papers.<sup>(34,37)</sup> In addition, a dose-response parameter for exposure to DEE is estimated, as described later. Had smoking and other covariate information been available, it could have been included in the analyses by modeling its effects on these parameters. Explicitly, each of the identifiable parameters can be made a time-dependent function of the estimated concentrations of REC. We found that the REC intensity impacted only the promotion parameter,  $g$ . We used the following dose-response relationship for  $g$  through its dependence on the cell division rate  $\alpha$ :

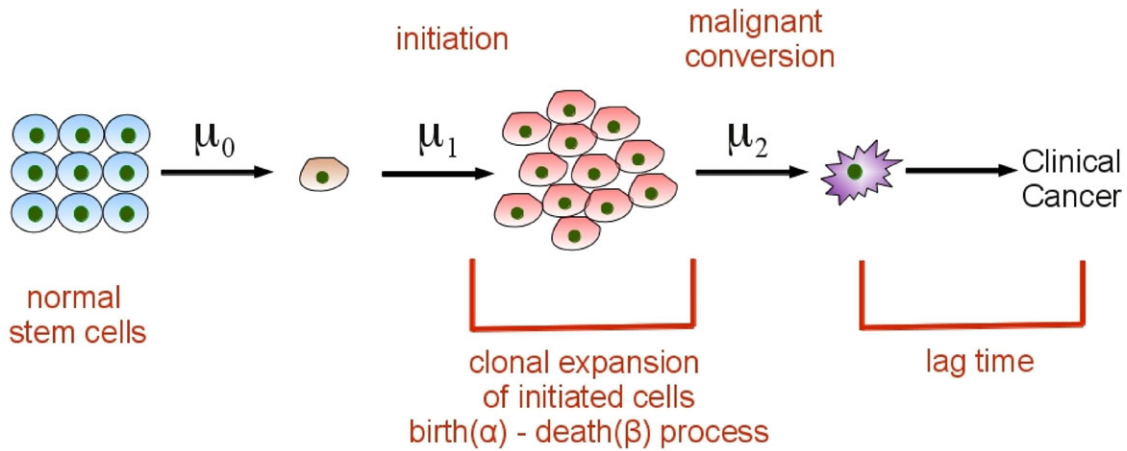
$$\alpha(\text{REC}) = a_0 \times [1 + \log(1 + a_1 x \text{REC})],$$

where  $a_0$  is the background rate of initiated cell division and REC is the age-dependent concentration of REC in  $\mu\text{g}/\text{m}^3$ . Confidence intervals for the parameters are based on the Wald statistic and also on Markov chain Monte Carlo (MCMC) methods. These two approaches yielded similar results; however, we believe that the MCMC results are more reliable. We used the Metropolis-Hastings algorithm for our MCMC samples. We ran eight independent chains, each for several thousand cycles. We concluded that the cycles had converged when there was little evidence of drift in means and variances of the parameter estimates. We conducted these analyses for the entire cohort and also separately for each of the mine types. We used likelihood-based methods to test for equality of exposure-response parameters across mine types.

### 3. RESULTS

We successfully replicated the analyses described by Attfield *et al.*,<sup>(3)</sup> yielding results that were virtually identical to those reported in the main article and Supplementary Materials (data not shown; results of these and other analyses described herein are available upon request if not shown). In doing so, we confirmed that the data set that we analyzed was essentially the same as that used by Attfield *et al.*<sup>(3)</sup>





**Fig. 2.** Three-stage clonal expansion model. The model assumes that initiation requires the biallelic inactivation of a (tumor suppressor) gene. The parameters are  $X$ , the number of susceptible stem cells;  $\mu_0$ , the first mutation rate;  $\mu_1$ , the second mutation rate;  $\alpha$ , the division rate of initiated cells;  $\beta$ , the death rate of initiated cells; and  $\mu_2$ , the rate of malignant conversion. The time between the first malignant cell and death from tumor is modeled as a constant lag (here, 0 or 15 years, following Attfield *et al.*<sup>3</sup>).

**Table II.** Log-Likelihoods for Fits of the Three-Stage Clonal Expansion Model to the Entire Cohort and to Each Mine Type Separately

Mine Type	Null Max Log-Likelihood	Dose-Response Max Log-Likelihood	$2 \times \text{LLR}$
Limestone	-258.6	-254.7	<b>7.8; <math>p = 0.005</math></b>
Potash	-700.2	-700.2	0
Salt	-79.9	-79.9	0
Trona	-370.7	-369.2	3.0; $p = 0.08$
Entire Cohort	-1,418.0	-1,415.4	<b>5.2; <math>p = 0.02</math></b>

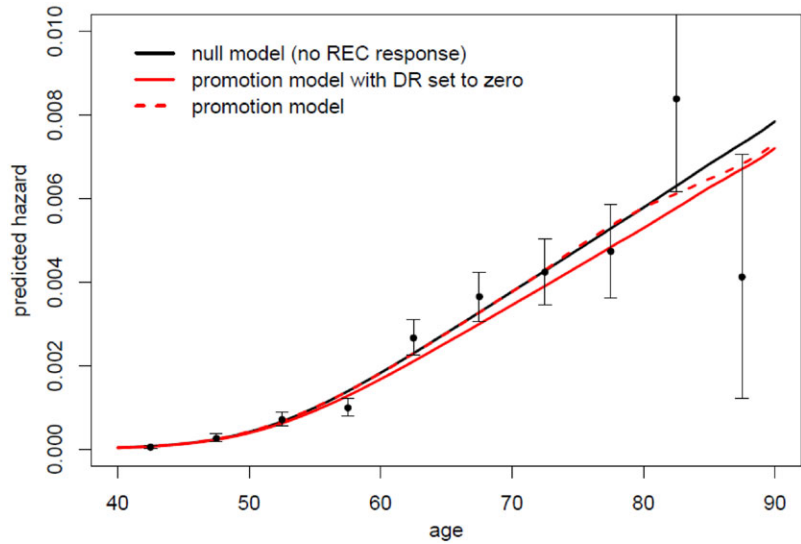
*Note:* Maximum log-likelihoods are reported for both the null model (no dose-response parameter for respirable elemental carbon) and the model with dose response on promotion (see text for details). LLR = log of the likelihood ratio.  $2 \times \text{LLR} > 3.84$  is significant at the 0.05 level. Significant results are shown in bold font (limestone mine and the entire cohort).

The results of fitting the 3SCE model to the overall DEMS cohort and to individual mine types are shown in Tables II and III and in Figs. 3–6. Table II shows that the impact of REC is statistically significant in the limestone mine and in the entire cohort. Table III shows the parameter estimates together with the Wald 95% confidence intervals and the 95% credibility intervals based on 2,500 MCMC cycles. Fig. 3 indicates that the 3SCE model describes well the observed hazard function for lung cancer mortality in the DEMS cohort. Fig. 4 shows that the hazard function for lung cancer mortality after exposure to REC stops approaches the hazard function among the unexposed, as is the case for the hazard function among ex-smokers. Fig. 5 shows that the relative risk (RR) associated with a given cumulative exposure depends upon how the exposure was accumulated, as is the case for smoking and lung cancer.<sup>(14,15)</sup>

Fig. 6 shows the RR as a function of age for continuous exposure to REC starting at birth. The strong effect modification of the RR by age is of particular note. This figure shows also that, for the same exposure concentration, the RR in the limestone mine is considerably higher than in the combined cohort, with the excess relative risk (ERR) associated with a  $1\text{-}\mu\text{g}/\text{m}^3$  exposure to REC starting at birth being about five-fold higher in the limestone mine than in the entire cohort at age 45. In these analyses, the RR and therefore the ERR are age-dependent for a given continuous exposure concentration. The RR of cigarette smoking on lung cancer risk is similarly modified by age.<sup>(15,20,49)</sup>

Results were similar when the model was fit to ever-underground miners, whereas among surface-only workers, REC exposure was not associated with lung cancer mortality (data not shown). A model

**Fig. 3.** Fit of the three-stage clonal expansion model to the observed hazard rates from the entire DEMS cohort. The observed hazard rates were estimated by dividing the observed number of lung cancer deaths in five-year age groups by the total person-years of risk in the age group. The predicted hazard function was calculated by summing up the predicted hazard functions for each individual in the data at any given age. The graph shows three distinct fits. First, the null model assumes that respirable elemental carbon (REC) has no impact on risk of lung cancer mortality. The hazard function is shown by the black solid line. The dashed red line shows the hazard function for the model that incorporates a dose-response (DR) for REC (see text for details). The red solid line shows the hazard function from this model, but with the dose-response parameter ( $a_1$ ) set to 0. Although introduction of a dose-response parameter significantly improves the fit as judged by the likelihood ( $p = 0.02$ ; Table II), this figure shows that the hazard functions for the model with a dose-response parameter and the null model are virtually identical.



**Table III.** Results of Fitting the Three-Stage Clonal Expansion Model with Dose-Response on Promotion to the Entire DEMS Cohort and to the Cohort of Workers Employed in the Limestone Mine

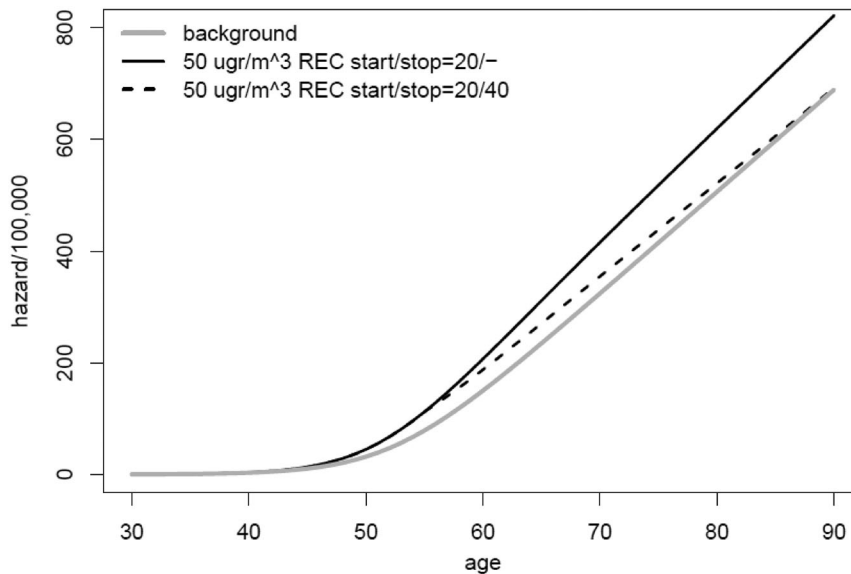
Mine Type	Parameter	MLE (95% Wald-Based CI)	MCMC Median (MCMC 95% CI)
Entire cohort			
	Max log-likelihood = -1,415.4		
	$g_{0,u}$	0.254 (0.163, 0.374)	0.235 (0.166, 0.356)
	$g_{0,s}$	0.297 (0.183, 0.443)	0.275 (0.192, 0.427)
	$a_1 \times 10^4$	0.556 (0.020, 1.092)	0.544 (0.112, 1.091)
	Slope $\times 10^3$	0.183 (0.127, 0.263)	0.169 (0.130, 0.269)
	$\mu_2 \times 10^7$	4.926 (0.490, 35.28)	7.970 (0.583, 29.75)
Limestone			
	Max log-likelihood = -254.7		
	$g_{0,u}$	0.207 (0.100, 0.380)	0.191 (0.117, 0.297)
	$g_{0,s}$	0.239 (0.097, 0.478)	0.231 (0.112, 0.387)
	$a_1 \times 10^4$	0.226 (0.0, 0.451)	0.237 (0.050, 0.717)
	Slope $\times 10^3$	0.186 (0.082, 0.422)	0.151 (0.068, 0.486)
	$\mu_2 \times 10^7$	6.55 (0.128, 79.28)	16.75 (1.39, 47.10)

*Note:* The parameters are defined as follows:  $g_{0,u}$ , background underground promotion rate;  $g_{0,s}$ , background surface promotion rate;  $g_1$ , dose-response promotion parameter as defined in the text; slope, identifiable parameter as defined in the text. MLE, maximum likelihood estimate; MCMC, Markov chain Monte Carlo; CI, confidence interval.

with a 15-year lag fit substantially better than a model with no lag. In both the overall cohort and ever-underground miners, a small but statistically significant impact of REC was observed on the promotion of initiated cells, resulting in increased lung cancer mortality among miners exposed to REC. The background hazard in the absence of

exposure to REC was higher in surface-only than ever-underground workers, but worker location did not modify the relationship between REC exposure and lung cancer mortality.

Separate analyses by mine type show that REC is significantly associated with lung cancer mortality in only the limestone mine (Table II). We tested the



**Fig. 4.** Age-specific lung cancer mortality curves generated by the three-stage clonal expansion model for the entire DEMS cohort. The solid curves show, respectively, the background age-specific mortality curve among those not exposed to respirable elemental carbon (REC), and the age-specific mortality curve for a  $50\text{-}\mu\text{g}/\text{m}^3$  continuing exposure starting at age 20 years. The dashed curve shows the age-specific mortality curve if the exposure, that started at age 20 years stopped at age 40 years. Note that the mortality among those whose exposure stopped at age 40 years approaches that among those not exposed, just as in the case of cigarette smoking and lung cancer.

hypothesis that the exposure-response parameter for the entire cohort is driven by the limestone mine by removing the limestone mine and analyzing the other mine types together. The result was highly insignificant; that is, the null hypothesis that the exposure-response parameter in the entire cohort minus limestone is zero cannot be rejected (likelihood ratio test for the hypothesis that the dose-response parameter in the entire cohort minus limestone is zero = 1.86 on 1 degree of freedom [*df*];  $p = 0.17$ ). We analyzed the entire cohort with a single exposure-response parameter and with two exposure-response parameters, one for the limestone mine and the second for the other mine types. The likelihood ratio test rejected the hypothesis that the two exposure-response parameters were equal (likelihood ratio test = 4.56 on 1 *df*;  $p = 0.03$ ). Finally, in the model with two exposure-response parameters, we tested the hypothesis that the parameter for the non-limestone mine types was equal to 0. This null hypothesis was not rejected (likelihood ratio test = 3.0 on 1 *df*;  $p = 0.08$ ).

As we report in the Supporting Information, the Cox proportional hazards regression analysis also demonstrated that the risk in the entire cohort is driven by the increased risk in the limestone mine.

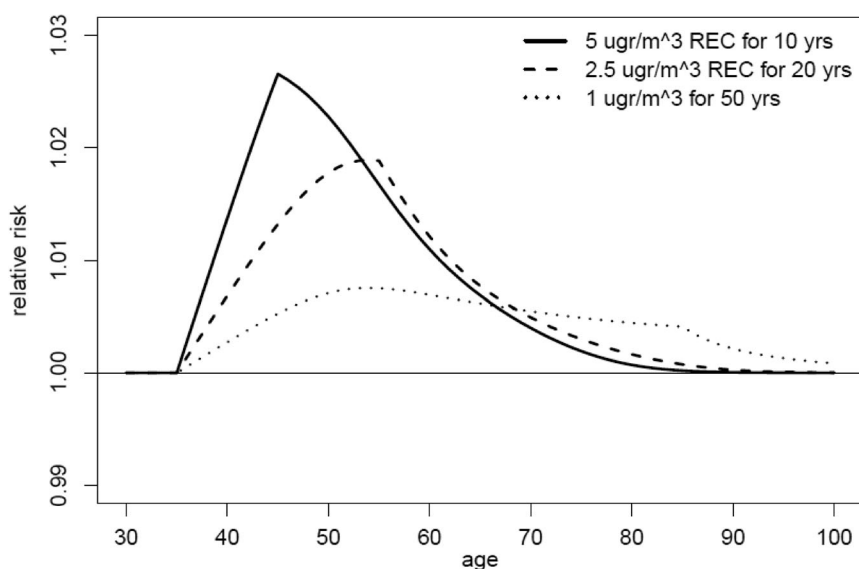
#### 4. DISCUSSION

Because it is now abundantly clear that that temporal patterns of exposure are important in determining the risk of lung cancer,<sup>(14,15,19,21,36)</sup> and in light of the valuable opportunity to investigate this issue in the DEMS cohort data, we conducted extended analyses of this cohort using both time-dependent proportional hazards models and biologically-based multistage clonal expansion models.

We did not deal with the fundamental question of whether the back-extrapolated exposure estimates used in DEMS are reliable estimates of actual exposure to DEE, which has been questioned.<sup>(50-53)</sup> We could not use the smoking history data used in the case-control analysis of Silverman *et al.*<sup>(4)</sup> Therefore, the analyses reported here focused on other vital issues, namely, the temporal patterns of exposure-response relationships and the dependence of these relationships on specific mining facilities.

We achieved three principal goals in the analyses of these data. First, we successfully reproduced the results reported in Attfield *et al.*<sup>(3)</sup> Second, we explored temporal aspects of exposure and the evolution of lung cancer risk following exposure more carefully by focusing on hazard functions, rather than hazard ratios, using parametric models based on





**Fig. 5.** Relative risk of lung cancer mortality as a function of age in the entire DEMS cohort for the identical cumulative exposure ( $50 \mu\text{g}/\text{m}^3 \cdot \text{year}$ ) accumulated in different ways starting at age 20 years:  $5 \mu\text{g}/\text{m}^3$  over 10 years;  $2.5 \mu\text{g}/\text{m}^3$  for 20 years;  $1 \mu\text{g}/\text{m}^3$  for 50 years. It is quite clear that the temporal pattern of the relative risk depends strongly on how total dose is accumulated. All exposures were lagged 15 years.

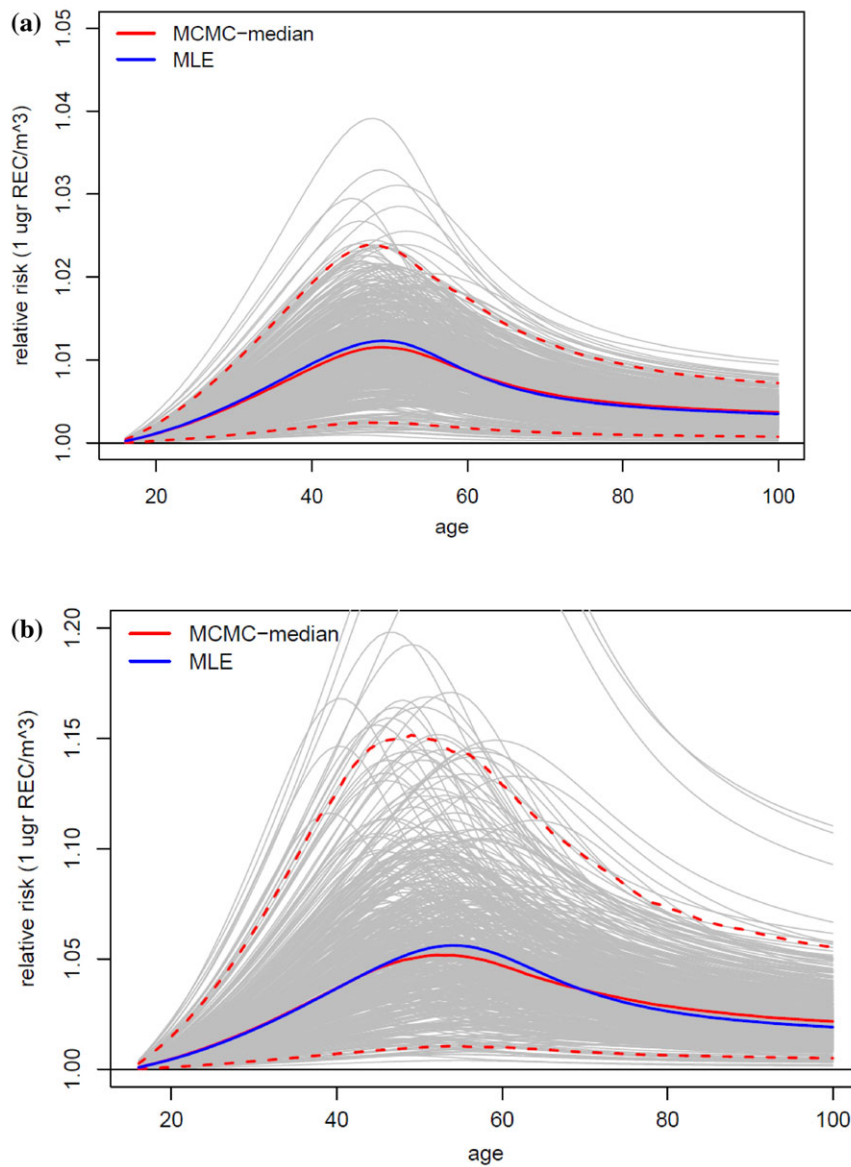
concepts of multistage carcinogenesis. Finally, we repeated these analyses for individual mine types, and performed a variety of sensitivity analyses and extended analyses using alternative statistical models, as detailed in the Supporting Information.

The extended analyses using multistage models confirmed that time-related exposure patterns are of critical importance in the DEMS cohort data. Fig. 3 shows the fit of the 3SCE model to the entire DEMS cohort. This figure shows also that, although the impact of REC is statistically significant in this data set, the inclusion of REC makes only a small difference in the estimated hazard function. We could not construct a similar figure for the limestone mine because, with only 37 lung cancer deaths in that subgroup, we could not estimate the observed age-specific hazard function. Fig. 4 shows that after exposure to REC stops, the hazard function approaches that among the unexposed, similar to the pattern seen among ex-smokers after they quit. Fig. 5 shows that the impact of REC on lung cancer mortality depends on how exposure is accumulated, and does not remain constant after exposure stops. Fig. 6 shows age-related effect modification of the RR associated with continuous lifetime exposure of  $1 \mu\text{g}/\text{m}^3$  both for the full DEMS cohort (Fig. 6a) and the limestone cohort (Fig. 6b). Clearly, these dependencies should be explicitly considered when using the DEMS cohort data for a

QRA. Finally, these analyses show that the risk in the entire cohort is driven by the limestone mine.

For regulatory purposes, there is considerable interest in developing a QRA for DEE. Hitherto, only CARB has estimated a unit risk for DEE, as mentioned above. The U.S. EPA initiated its preparation of a health assessment for DEE soon after IARC concluded its first review in 1988. The EPA report went through five drafts that were subjected to external review before a final assessment was published.<sup>(13)</sup> A major contentious issue during the prolonged review process was whether the epidemiological evidence was sufficiently robust to use for a QRA. The final EPA assessment<sup>(13)</sup> concluded that DEE was a probable human carcinogen, but deemed the data insufficient for QRA. Thus, the DEMS data now have a pivotal role in any QRA for DEE, and it is therefore imperative that the association between DEE and lung cancer in these data be carefully and critically evaluated using multiple analytic techniques.

In light of the growing evidence that time-related factors are important in determining risk, they should not be ignored in the development of a unit risk. Effect modification by age should be accounted for in any unit risk estimation using life tables. The results from the 3SCE parametric analyses suggest one approach to the development of a unit risk for lung



**Fig. 6.** Relative hazard of lung cancer mortality as a function of age generated by the three-stage clonal expansion model for continuous exposure to  $1 \mu\text{g}/\text{m}^3$  respirable elemental carbon (REC) starting at birth. The red solid line represents the relative hazard generated by the maximum likelihood estimates (MLE) of the parameters. The blue solid line represents the point-wise median of the relative hazards generated by 2,500 Markov chain Monte Carlo (MCMC) cycles. The red dashed lines show the point-wise 95% credible intervals for the relative hazards generated by the MCMC runs. Individual outputs of the MCMC runs are shown in gray. Note the strong effect modification of the relative hazard by age. (a) Lung cancer mortality in the entire DEMS cohort. (b) Lung cancer mortality in limestone mine workers.

cancer mortality in association with DEE exposure. An analysis that effectively addressed effect modification could yield a result that differs substantially from the Vermeulen *et al.*<sup>(54)</sup> meta-regression risk estimate. The development of a unit risk may be premature, however, given the many uncertainties surrounding both exposure and analysis issues. In

particular, we need a better understanding of why the risk in DEMS is driven by a single mine type. Only after resolving these complex issues can the exposure-response relationship between DEE and lung cancer be quantified reliably.

Finally, in considering the results of the DEMS analyses as reported by Attfield *et al.*,<sup>(3)</sup> Silverman

*et al.*,<sup>(4)</sup> and now in this article, it is important to recognize the continuous improvements in diesel technology that occurred from 1947, the earliest year of dieselization for any DEMS mine, to the present time.<sup>(2)</sup> Estimates of lung cancer risk associated with DEE from engines through the end of DEMS are probably inappropriate for evaluating risks associated with exposure to DEE from contemporary sources.

In summary, our results show that time-related factors have a crucially important influence on lung cancer mortality in the DEMS cohort data, and ignoring them may yield misleading conclusions. Our analyses show that the RR of lung cancer mortality following DEE exposure is modified by age. Furthermore, in both the Cox model (see Supporting Information) and the 3SCE analyses, a significant positive association of REC with lung cancer mortality is based on a single mine type (limestone), with no obvious explanation for this pattern, given that both cumulative REC levels and average REC levels in that mine were substantially lower than in all other mines studied. Until important questions raised by these findings are adequately addressed, the DEMS data cannot reliably be used for QRA.

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NIOSH reviewed an earlier version of this article to ensure compliance with all provisions of the agreement under which the DEMS data were released to the analytical team. The review by NIOSH was not a review of the technical contents of the article or the scientific conclusions drawn.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Table SI.** Results of Proportional Hazards Regression Analysis for Lung Cancer Mortality in Association with 15-Year Lagged Cumulative Exposure to Respirable Elemental Carbon (REC) and Average Intensity for Underground-Only (i.e., Exclusively Underground) Workers: Quartiles, Expanded Categories, and Continuous Modeling Results

**Table SII.** Results of Proportional Hazards Regression Analysis for Lung Cancer Mortality in Association with Log of 15-Year Lagged Cumulative Exposure to Respirable Elemental Carbon (REC), that is,  $\text{Log}(1 + \text{REC-Lagged } 15 \text{ years})$  for the Entire Cohort, the Entire Cohort Minus the Limestone Mine, and Each Mine Type Separately

**Table SIII.** Results of a Proportional Hazards Regression Analysis for the Cohort of Miners with Total Exposure  $<1,280 \mu\text{g}/\text{m}^3 \cdot \text{year}$ ; All the Covariates in this Model are Highly Statistically Significant

**Fig. S1.** Exposure-response relationship between cumulative respirable elemental carbon (REC;  $\mu\text{g}/\text{m}^3 \cdot \text{yr}$ ) and relative hazard in the entire cohort of ever-underground miners