Final Performance Report

Diesel Exhaust Exposure and Occupational Lung Cancer Risk

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List of Abbreviations

DF	diesel fraction
EAF	emission adjustment factor
MSHA	Mine Safety and Health Administration
NDI	National Death Index
NIOSH	National Institute for Occupational Safety and Health
RRB	US Railroad Retirement Board
WHO	World Health Organization
USEPA	US Environmental Protection Agency

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Abstract

Objective: The purpose of this research program was to address uncertainties in the exposure data previously used to define the relationship between lung cancer and diesel exhaust exposure in a cohort of over 55,000 US railroad workers. It was hypothesized that historical information regarding railroad-specific diesel locomotive use in the US railroad industry could be used to estimate lung cancer risk.

Importance to Occupational Safety and Health: Overall, a 20% to 50% excess lung cancer risk has been observed in occupations where diesel exhaust exposure was likely, including in studies where it was possible to adjust for cigarette smoking. Since miners in dieselized underground mines are exposed to levels of diesel particles 10 to 20 times greater than other occupational groups, MSHA is concerned about the assessment of risk in underground miners and potential lung cancer risk in other occupational cohorts. Comprehensive mortality studies assessing the risk attributable to diesel exhaust in miners are not yet available. Therefore, there has been interest in assessing lung cancer risk by examining other existing diesel exhaust exposed occupational cohorts

Approach: Previous risk assessments, including work done by NIOSH, relied heavily on a cohort originally studied by our research group. Lung cancer mortality was assessed for 55,407 U.S. railroad workers from 1959 through 1980. Whether or not a meaningful quantitative risk assessment can be done to estimate the potential lung cancer risk attributable to diesel exhaust is controversial due to inadequate information regarding historical exposure measurements and an ill-defined linkage between job title and personal exposure.

The railroad industry changed from steam to diesel locomotives starting in the late 1940's, such that by 1959 based on aggregate data, 95% of the locomotives in service were powered by diesel. However, the date that an individual worker started working with diesel equipment is uncertain because there was wide variation in the acquisition of diesel locomotives by individual railroads. Based on locomotive testing and on differences in engine design and maintenance, it is likely that earlier generations of diesel locomotives (used in the 1950's and 1960's) had greater particulate emissions than later locomotives. No information about job-specific historical exposure to diesel exhaust is available. It was proposed that extensive information about the number and design of older locomotives used by each railroad could be linked with emission data to estimate relative differences in historical and current exposures. This information would permit the development of a profile of exposure for jobs in each railroad which could be assigned to each worker and possibly permit improved estimates of lung cancer risk per unit of exposure.

The yearly locomotive roster of each railroad was obtained, which identified the make, model, and horsepower of each locomotive in service. From this, the number and type of locomotives that were diesel for each year could be calculated for each railroad. USEPA emission inventory guidance documentation provides emission factors for many locomotives. The emission factor times the locomotive's horsepower gives an estimate of total emissions. It was possible to estimate an average annual emission factor for each railroad weighted by the proportion of diesel locomotives. The assumption is that train crews' exposures will be roughly proportional to an average emission factor.

Findings: Prior to the development of the historical profile of diesel locomotive use in the US railroad industry it was necessary to update the mortality experience of the railroad worker cohort between 1959 and 1980 since mortality was not completely ascertained in the original analysis. With the cooperation of the US Railroad Retirement Board, it was possible to obtain additional mortality information on 54,973 (99.2%) subjects.

Although there were over 500 railroads listed in this railroad worker database, the sample studied was limited to 93 railroads that contributed at least 0.1% of the subjects to the cohort. This sample captured 96% of the eligible cohort (52,812 subjects), with 22 larger railroads (each contributing $\geq$1% of the cohort) accounting for 76%. Diesel exhaust exposure weighting factors were determined by examination of railroad equipment rosters between 1945-1980 by calculating a measure of the magnitude of exposure (an emission adjustment factor) and a measure of exposure probability (diesel fraction). The average emission adjustment factor for each railroad was based on railroad-specific number and type of locomotives. Since there have been a large number of mergers among the railroads, to account for service prior to a railroad merger, a weighted average of the emission adjustment factors of precursor railroads was calculated. The last railroad employer for each worker was available and provided the linkage between the railroad roster derived factors and work history. Examination of more detailed work histories for a subset of workers indicated

that it was unusual for workers to change railroad employers. A yearly index exposure was defined based on the product of months of service for subjects who worked on operating trains (train riders: brakemen, conductors, engineers, firemen, or hostlers), the average railroad emission adjustment factor, and the diesel fraction. Analyses were also based on duration of work as a train rider weighted by the probability of diesel exposure. Yearly job code was available between 1959 and 1980, and job title before 1959 was based on 1959 job. Mortality from lung cancer was assessed using Cox proportional hazard regression methods.

Between 1959-1980 there were 21,639 deaths out of 54,973 subjects, and it was possible to identify underlying cause of death in 21,116 (98%). Since lung cancer is usually fatal within several years following diagnosis, lung cancer cases were identified based on both underlying cause of death and if lung cancer was noted elsewhere on the death report (either death certificate or National Death Index report). There were 2,123 lung cancer cases identified overall, and 2,050 lung cancer cases were available for analysis using historical railroad information.

In analyses not using railroad specific emissions data where diesel exposure was assumed to start in 1959, subjects who had the greatest duration of work as train riders had the lowest risk of lung cancer mortality. In efforts to consider the healthy-worker survivor effect, a condition where subjects who remain employed tend to be healthier than those who leave employment, analyses were repeated adjusting mortality for years of employment and time after leaving work. Regression models excluding exposure in the year of death and the preceding 5 and 10 years before death were also explored. The relative risk of lung cancer mortality for subjects with <5, 5 to <10, 10 to <15, and ≥ 15 years of work in diesel exposed jobs ranged from 1.55 to 1.18 without evidence of an increased risk with greater years of work. There was no increase in lung cancer risk in shop workers.

Based on the distribution of railroad-specific diesel fraction, the duration of exposure to diesel exhaust for the train riders was estimated starting in 1945. Adjusting for years of employment and time after leaving work, there was no evidence for an increase in lung cancer with increasing years of exposure. With exposure in the 5, 10, and 15 years before death excluded, the risk of dying of lung cancer ranged from 1.13 to approximately 1.40 to 1.45, with a modest increase in risk with increasing years of exposure in some models. Based on quintiles of a cumulative exposure index (the summation of the product of railroad specific average emission adjustment factor multiplied by months of yearly work and diesel fraction), a consistent relationship between cumulative exposure and lung cancer risk was not noted, even after adjustment for the healthy worker survivor effect.

<u>Conclusions:</u> The use of railroad locomotive rosters to estimate historical exposure to diesel exhaust did not significantly improve the estimation of lung cancer risk associated with work as a train rider when compared to analyses based on exposure assumed to start in 1959. There was no consistent relationship between railroad specific indices of cumulative exposure and lung cancer risk, although train-riders in diesel exhaust exposed jobs had a greater risk of lung cancer compared to workers in unexposed jobs, and in some models, workers with a greater duration of exposure had a greater risk. Workers in shop-related jobs did not have an increased risk of lung cancer. When examined closely, the codes selected for inclusion as shop workers also included workers in non-diesel shops, so the extent that all workers in the shop worker category had significant exposure to diesel was uncertain. The relationship between intensity and duration of exposure remains uncertain using the exposure weighting estimates developed in this study.

Limitations to this approach include: the uncertainty in a single railroad-specific value that was used to weight exposure for all train riders on a single railroad; limited source data for emission factor values; and the uncertainty in personal exposures estimated by emission factors obtained from testing a few engines and expecting them to represent emissions from locomotives operated over a variety of real-life conditions. Although exposures to diesel particulate were predicted to increase with engine emissions in this exposure model, there was no validation of the model. Nor was there information regarding how the characteristics of emissions (such as particle size, organic content) changed over time, or how previous exposure to coal fired locomotive emissions influenced lung cancer risk. Additional follow-up of the mortality experience of this cohort through 1996 is underway that may provide additional insight into lung cancer risk.

Significant Findings

In this research project we sought to improve estimates of the quantitative relationship between diesel exhaust exposure and lung cancer by reexamining lung cancer risk in a large cohort of railroad workers previously studied by our research group. We proposed that the creation of a railroad specific profile of diesel locomotive use could aid in the estimation of exposures. The probability of exposure to diesel exhaust (diesel fraction) between 1945-1980 was estimated by considering the total number of diesel locomotives in service each year, locomotive-specific emission factors, and locomotive-specific horsepower. The probability of exposure to diesel exhaust was found to vary considerably during the 1950's and depended on the railroad studied. Although 50% of the industry had a similar probability of exposure (or rate of transition to diesel locomotives), for the other half the rates varied considerably. This indicates the use of a single probability function based on the overall distribution of the industry transition to diesel locomotives would lead to considerable exposure misclassification.

A railroad emissions adjustment factor was calculated for each railroad for each year. This index was the product of horsepower (a surrogate for fuel consumption) and engine emission factor (mass of particulate matter per unit fuel or energy consumed). The average emissions adjustment factor in a given year was the single unit EAF values for different locomotive models in service in a given railroad weighted by the number of units. An index of diesel exhaust exposure was obtained by multiplying the average emissions adjustment factor by the yearly diesel fraction. This index can be interpreted as a yearly indicator of particulate matter emissions based on railroad employer. Examination of this index of exposure as a function of calendar year revealed that there was little variation once the transition to diesel locomotives was nearly complete. Between 1959 and 1980, the average locomotive horsepower increased but emission factors decreased, thereby keeping the average estimated railroad-specific diesel exhaust particulate emissions relatively uniform. The greatest variation in emissions index was attributable to the years of conversion to from steam to diesel power.

Analyses conducted based on the tabulation of years of exposure starting in 1959 and not accounting for the transition period to diesel locomotives revealed an inverse relationship between lung cancer mortality and exposure duration. This relationship suggested that a healthy worker survivor effect was present in these data. Additional models incorporating time since hire and time since leaving the job did not change these exposure-response relationships. With the use of diesel fraction and adjusting for the healthy worker survivor effect considering time since hire, time since leaving the job, and not including more recent exposure in the assessment of risk resulted in a modest increase in risk with increasing years of exposure in some models. Analyses with emissions adjustment factor values (a surrogate for particulate matter emissions) did not result in a consistent exposure-response relationship with lung cancer mortality. As a result of job-specific smoking data previously collected by our research group for a case-control study of lung cancer mortality in US railroad workers, it was possible to estimate the potential effect of smoking on the relative risks of lung cancer observed. Adjustment factors were calculated based on the distribution of cigarette smoking in diesel exposed (train riders) and unexposed workers (Axelson 1980, Larkin, et al. 2000, Schlesselman 1978). Assuming a true relative risk of lung cancer attributable to diesel exhaust of 1.40 (a 40% excess risk), smoking adjusted values can be obtained by dividing by smoking adjustment factors of 1.10 to 1.20 (Larkin, et al. 2000), resulting in relative risks of 1.17 to 1.27 for the risk of lung cancer attributable to diesel exposure. These risks are within the range attributable to diesel exhaust reported in the literature but lower than previously noted in this cohort. It was not possible to refine the risk further based on the knowledge of railroad rosters or exposure duration.

Usefulness of Findings

Examination of railroad rosters between 1945-1980 provided insight into the variability in the estimation of the start of diesel exposure in the railroad industry. Exposure models based on engine emission factors, engine horsepower, and diesel fraction were not useful in providing insight into the quantitative relationship between lung cancer and diesel exhaust exposure. Results obtained from this cohort still suggest that there is an increased risk of lung cancer in workers with a greater duration of work in jobs associated with diesel exhaust exposure. However, the quantitative exposure response relationship between diesel exhaust exposure and lung cancer remains uncertain. It is possible that exposure to other particles from steam engines contributed to the elevated lung cancer risk observed. Additional follow-up of the mortality experience of this cohort through 1996 is underway that will provide additional insight into lung cancer risk.

Scientific Report

A. Background

Introduction

Diesel exhaust is a complex mixture of soot particles and gases. The particles have mutagenic and carcinogenic compounds adsorbed to a carbon core that aggregate into respirable clusters, and are readily inhaled deep into the lung. Overall, a 20% to 50% excess lung cancer risk has been observed in occupations where diesel exhaust exposure was likely to have occurred, including in studies where it was possible to adjust for cigarette smoking (Bhatia, et al. 1998, California Environmental Protection Agency 1998, Diesel Working Group 1995, Lipsett and Campleman 1999, Office of Research and Development 2002). Based on the consistency of the elevated risk in studies conducted across time and in different cohorts, these results are unlikely to be explained by bias or confounding. MSHA also determined that regulation of diesel exhaust exposure in mines is needed based on this evidence (Mine Safety and Health Administration and Department of Labor 1998).

Although California has considered diesel exhaust to be a lung carcinogen (California Environmental Protection Agency 1998) with a unit risk estimated based on analyses conducted in a cohort of 55,407 US railroad workers that was originally studied by our research group, this assessment is controversial. Given the lack of historical exposure measurements and an ill-defined linkage between job and personal exposure in this cohort, the USEPA has listed diesel exhaust as a likely or probable carcinogen rather than as a definite carcinogen (Office of Research and Development 2002). Although mortality in this cohort was determined between 1959 through 1980 in the original publication (Garshick, et al. 1988), it was later noted that the assessment of mortality after 1976 was incomplete. A reanalysis conducted by a working group sponsored by the Health Effects Institute subsequently assessed lung cancer mortality between 1959 and 1976 (Diesel Epidemiology Expert Panel 1999). They concluded that years of exposure were inversely proportional to lung cancer risk and therefore the US railroad worker cohort had limited utility for risk assessment. Since this reanalysis, mortality in the cohort has been updated through 1980, supported by an interagency agreement with the Risk Evaluation Branch at NIOSH. In the current report, we describe the effects of considering methodology that might improve the assessment of personal exposure to diesel exhaust and the assessment of lung cancer risk in this cohort.

Lung Cancer in Animals Exposed To Diesel Exhaust

Rats exposed to diesel exhaust develop lung tumors in a dose-related manner, although after exposure to much higher concentrations of particles than found in occupational environments (Brightwell, et al. 1989, Heinrich, et al. 1986, Ishinishi, et al. 1986, Mauderly, et al. 1987, Nikula, et al. 1995, Takaki, et al. 1989). In rat inhalation experiments, the levels of exposure that resulted in lung cancer were at 7000 $\mu g/m^3$, 3500 $\mu g/m^3$, and 2500 $\mu g/m^3$. The occurrence of cancer in rats is specifically due to the inhalation of the diesel particles rather than the gases since rats exposed to filtered diesel exhaust do not develop lung cancer. At levels at approximately 2000 $\mu g/m^3$ or less, no increase in lung tumors was noted (Mauderly, et al. 1987, Nikula, et al. 1995). However, in 12 underground coalmines studied by MSHA, mean levels of diesel exhaust were much higher than in railroad workers, and exceeded 500 $\mu g/m^3$ in 8 mines and 1000 $\mu g/m^3$ in 4 mines. In 1 mine, the mean concentration was 2000 $\mu g/m^3$. Similar measurements were obtained in underground metal and nonmetal mines (Mine Safety and Health Administration and Department of Labor 1998). Exposures in other occupations, including railroad workers, were much lower than levels that resulted in cancer in rats and lower than in underground miners (Woskie, et al. 1988a, Woskie, et al. 1988b, Zaebst, et al. 1991).

At high exposure levels that results in lung cancer, particles accumulate in rat lung as clearance mechanisms become saturated (called particle overload). Inflammation and fibrosis are noted, as well as malignant tumors in the alveolar portion of rat lung. In rats exposed at lower concentrations of diesel exhaust where the risk of lung cancer was not increased, the histologic changes of particle overload do not occur. In humans, lung cancer usually starts in the airway rather than in the alveolar region and the histologic changes indicative of particle overload do not occur. Thus, although malignant lung tumors occur in rats due to diesel exhaust exposure, it is likely that the mechanisms through which diesel exhaust produces lung tumors in rats are not the same mechanisms producing lung cancer in humans.

Elemental carbon with little associated organic material, and other inorganic particles without associated organic matter inhaled at high levels also results in inflammation, fibrosis, and a dose-related occurrence of lung cancer in rats at levels similar to the diesel exhaust inhalation studies (Mauderly, et al. 1994). These experiments suggest that the particles alone are responsible for lung cancer observed in the diesel exhaust inhalation experiments in rats. Results of inhalation experiments in other animals, including in other rodents such as mice, do not indicate that lung cancer occurs after high-level exposure. This indicates that the positive result in rats is species-specific (Diesel Working Group 1995, Office of Research and Development 2002). However, after diesel exhaust inhalation experiments, DNA adducts are found in rat lung in similar amounts after both high and low level diesel exhaust exposures (Bond, et al. 1990). This suggests that genetic damage from the organic compounds alone (known to be carcinogenic and mutagenic) is not the cause of cancer noted in animal models, but may contribute in combination with the cellular response observed. The organic compounds could be important to neoplasia that occurs in non-particle overload conditions, such as would occur in humans occupationally exposed to diesel exhaust. However, the role of the adsorbed organics in contributing to lung cancer both in rats and humans remains speculative (Diesel Working Group 1995).

Nevertheless, the relationship between rat lung particle burden and lung cancer was used to estimate the lifetime risk of developing lung cancer in humans by WHO (World Health Organization 1996). The use of these rat-specific data for risk assessment was contrary to the advice of the EPA Clean Air Advisory Committee and a principle author of the animal inhalation experiments (1995). The purpose of conducting quantitative risk estimates is to guide the establishment of policy to regulate diesel exhaust emissions. However, it is likely that these rat-based estimates of risk are erroneous since humans do not achieve particle overload conditions. There is a need for epidemiologic studies with accurate assessments of personal exposure to permit regulatory agencies to quantitatively estimate the risk of lung cancer in humans who may be exposed to diesel exhaust.

Epidemiologic Studies in Humans

The study of lung cancer and diesel exhaust exposure in humans has been limited by the lack of exposure measurements and successful linkage of these measurements to an epidemiologic database. Such exposure data are limited to the U.S. railroad industry (Woskie, et al. 1988a, Woskie, et al. 1988b) and the trucking industry (Steenland, et al. 1990, Zaebst, et al. 1991). In other epidemiological studies, job title (without quantitative exposure estimates obtained by an industrial hygiene survey) or an exposure index based on fuel consumption or time on the job have been used to indicate exposure. In studies based on hospital or registry based-cases, exposure was based on self-report of work in a diesel-exposed job or based on a single job title. Lack of precision in the ascertainment of exposure has made it difficult to determine a relationship between exposure and outcome. In addition, the relatively recent introduction of diesel powered equipment in railroads and other industries means that in past studies few workers had a long duration of exposure (> 20 years). A population with >20 or more years of exposure and with at least 20 years after first exposure is preferable to adequately study the relationship between lung cancer and exposure to an occupational carcinogen.

Diesel trucks were introduced into the U.S. in the 1950's and 1960's. Steenland and coworkers (Steenland, et al. 1990, Zaebst, et al. 1991) studied 994 lung cancer deaths in 1982 and 1983 in male Teamsters who had filed claims for pension benefits (requiring at least a 20 year Teamster membership). Work history and smoking history were obtained from next-of-kin, and job history was also available from Teamster records. Since diesel particles have a carbon core, exposure was estimated in current trucking industry workers by measuring elemental carbon in respirable particles (Zaebst, et al. 1991). However, the intensity of diesel exposure in the trucking industry in the past is not known nor is it known how long drivers included in the epidemiologic database actually drove diesel trucks. Many drivers would have spent 20 years or less in a diesel truck. Larger trucking companies completed the transition to diesel by 1960, while independent drivers and other non-trucking companies completed the transition later (Steenland, et al. 1990). The uncertainty about past exposure levels in the trucking industry and the possibility that many drivers could have been driving diesel powered trucks for a relatively short time make these data unsuitable for quantitative risk assessment.

In the US railroad industry, diesel locomotives replaced steam locomotives following World War II and during the 1950's. In 1949, 20% of the locomotives in service were diesel, but by 1952 50%, and by 1959 95% of the locomotives in service were diesel powered. The US RRB maintains computerized work and mortality records of railroad workers, with yearly job title (based on a 3-digit code) available starting in 1959. These records were utilized as a death registry and as a registry of work in jobs associated with diesel exhaust exposure from 1959 (when the transition from steam to diesel locomotives was nearly complete) through 1980 in a retrospective cohort study of 55,407 railroad workers. An industrial hygiene survey was conducted between 1981 through 1983 in 530 workers in four small, northern U.S. railroads (Garshick, et al. 1988, Woskie, et al. 1988a, Woskie, et al. 1988b). Exposure assessment was limited to workers in 39 out of over 150 railroad job codes who were selected for inclusion in the retrospective cohort. Jobs with regular exposure to diesel exhaust were workers on operating trains (engineers, firemen, brakemen, conductors) and workers engaged in the repair and maintenance of diesel locomotives (shop workers). Workers with little or no exposure to diesel exhaust were clerks and signal maintainers. Concentrations of respirable particles were measured over a work shift and adjusted for environmental tobacco smoke. These measurements were used to characterize exposure in each job.

Diesel exhaust exposure in the railroad industry changed as new diesel locomotives were introduced. Diesel engines first introduced in the late 1940's and throughout the 1950's were said to be "smokier" than locomotives introduced later (Woskie, et al. 1988a). These first locomotives were in service through the early 1960's when a second generation was introduced. In the 1980's newer models (third generation) were introduced with similar overall emission characteristics to the second generation of locomotives. Because the railroads in our industrial hygiene survey were small, they used mostly first and second-generation diesel engines. There was no difference in air levels measured among the railroads attributable to the generation of locomotive. Furthermore, diesel locomotives are used for many years before being retired. For example, in 1992, 22% of the engines in service were built before 1970, and an additional 43% were built between 1970 and 1979 (Association of American Railroads 1993). Therefore, our industrial hygiene data, although obtained after the establishment of the cohort, may be representative of the exposure received by the cohort between 1959 and the 1980's. However, it is possible that exposure associated with the early diesel engines in the 1950's was greater than later exposures. It is also possible that the large railroads had lower exposures because they more rapidly updated their fleets and purchased the newest locomotives with the lowest emissions.

In the original analysis of the railroad worker, exposure was considered to start in 1959 when the transition from steam to diesel power was nearly complete. Since the U.S. railroad industry gradually changed from steam to diesel locomotives during the 1950's, many U.S. railroad workers would have been exposed to diesel exhaust prior to 1959. Previously, it has not been possible to construct a profile of exposure for each worker. As a result, there is an error of 1 to 15 years in the onset and duration of exposure for the subjects, which could be a substantial fraction of the total duration. Such information is needed if the relationship between exposure and lung cancer is to be assessed. It is not known if workers who worked with diesel locomotives early in the 1950's had the greatest lung cancer risk, thereby accounting for lung cancer approximately 20 years or more after exposure (in the mid 1970's and thereafter).

B. Specific Aims

The specific aims of this proposal were:

a. To better estimate the onset and duration of exposure to diesel exhaust for each member of the cohort starting in the 1940's by constructing a profile for the introduction of diesel locomotives by each railroad where subjects worked;

b. To use estimates of emissions based on locomotive design to estimate the impact of changes in locomotive fleet composition on the profile of each worker's personal exposure.

c. To use these modified estimates of personal exposure to assess the relationship between diesel exhaust exposure and lung cancer risk.

C. Procedures and Methodology

Population Description

In a computerized data extraction originally provided by the RRB in 1981 to our laboratory, male workers in selected job categories age 40-64 with 120 to 240 service months of creditable railroad service by 1959 were selected for study (Garshick, et al. 1988). The workers were grouped into four categories, based on characteristics of their exposure. The three groups of workers originally classified as exposed to diesel exhaust were (1) "engineers" (engineers and firemen); (2) "conductors" (conductors, brakemen and hostlers); and (3) "shop workers" (shop supervisors, machinists, and electricians). Workers with infrequent or no exposure to diesel exhaust included clerks, ticket agents, station agents, and signal maintainers. Every third engineer, fireman, brakemen, conductor, hostler, and shop worker as defined above, and every fourth clerk was selected from the RRB database such that approximately 75% of the cohort had potential diesel exposure and 25% were considered unexposed. Since mortality was under reported in the original data extraction between 1977 and 1980, in 1998, the RRB graciously provided an updated work history and mortality data tape for all individuals meeting the original search criteria. Linkage between the original 1959-1980 data (n=56,208) and new data tape (n=125,833) was possible because both sets of data were provided in a specific record sequence based on Social Security number. Of the 55,407 white males in the original cohort, follow-up was available on 55,016 subjects (99.2%). Forty-three subjects were found to have less than 10 years of railroad service or were not working in 1959, and were dropped from the cohort, leaving 54,973 white males in the updated cohort.

Cause of Death Determination

The National Death Index (NDI) was used to obtain *International Causes of Death Version 9* (ICD-9) coded cause of death for deaths between 1979 and 1980. A match was considered acceptable if the sex, last name, social security number, and month and year of death exactly matched the RRB records. Efforts were made to obtain a death certificate from each state for deceased subjects without a valid NDI match, for newly identified deaths between 1959-1978, and for subjects between 1959-1978 where a death certificate was not available previously.

Exposure Characterization

During and after the transition from steam to diesel locomotives individual railroads maintained different locomotive fleet purchasing and modernization policies. Cumulative exposure was calculated from 1945 through 1980 based on factors weighted by the distribution of diesel powered locomotives in an effort to quantify the differences in start dates, speed of diesel transition, and individual railroad locomotive fleet characteristics. To estimate the effects of the transition to diesel as well as the effects of different locomotive fleets by company, we composed two exposure-weighting factors. These factors were determined by examination of yearly railroad rosters starting in 1945 leading to a factor that was an indicator of the magnitude of exposure (EAF, or an emission adjustment factor) and a measure of exposure probability (DF, or diesel fraction). Although were over 500 railroads listed in the railroad worker database, the each railroad selected for study had to contribute at least 0.1% to the cohort. This limited the sample to 93 railroads that captured 96% of the eligible cohort (52,812 subjects) There were 22 larger railroads that each contributed $\geq$1% of the cohort that accounting for 76% of the subjects.

The EAF was the basic exposure parameter calculated, and was the product of horsepower (a surrogate for fuel consumption) and engine emission factor. An emission factor is expressed in units of mass of particulate matter emitted per gallon of fuel burned. Emission factors are based on analysis of exhaust during engine tests under constant loads (or throttle positions). Actual locomotive operation requires a mix of various throttle notch positions based on engine activity. Brake specific (or power specific) fuel consumption is considered to be constant as recommended by EPA (Office of Air and Radiation and Office of Air Quality Planning and Standards 1996). Each load level has its own emission factor, and the overall factor is a weighted average of all the individual throttle-specific factors based on whether an engine is used in the railroad yard or in road service. The average EAF in a given year is the single unit EAF values for different models in service during the year in a given railroad weighted by the number of units. Emission factor data were available from EPA's emission inventory guidance documentation (Office of Air and Radiation and Office of Mobile Sources 1991), and included emission factors for essentially all EMD and GE locomotives, 80% to 90% of the engine designs used by U.S. railroads from the 1940's through 1980. Builder's records and company specific railroad rosters served as records of railroad rosters between 1945 and 1980. If an EPA emission factor was not available for a given locomotive type, it was assigned an extrapolated value based on locomotives and diesel engine designs with similar engine characteristics. Once an EAF was assigned to each locomotive in the fleet, a company-specific emission adjustment factor was created using a weighted average of all unit emission EAFs.

The railroad-specific DF, representing the probability of exposure in a specific year, was calculated by considering the product of the total number of diesel locomotives in service, locomotive specific emission factors, and the horsepower for each locomotive type in each railroad. If the first year of 100% diesel locomotive use was reliably available from historical sources, the product of the total number of diesel locomotives in service, the locomotive specific emission factor, and the horsepower for each locomotive type in that year was selected as the denominator and DF in the preceding years was calculated based on the yearly ratio. If the first year of all locomotive use was not available, the railroad-specific product of the total number of diesel locomotives in service, the locomotive specific emission factor, and the horsepower for each locomotive type were examined and the asymptotic (essentially average maximal) value used in the calculation of DF. An additional approach considered for DF calculation was to compile numbers of steam, electric, and diesel-electric units for each year, and to calculate a yearly direct percent (DP) of diesel locomotives. This approach was undertaken for a subset of railroads, and provided similar percentages to the DF. Therefore, the DF, and not the DP was used in all calculations. In the years prior to conversion to 100% diesel locomotives, the average EAF (based on diesel locomotive data in a given year) was multiplied by the diesel fraction in that year.

The last railroad employer for each worker was available and provided the linkage between the railroad roster derived factors and work history. Examination of more detailed work history in a subset of workers indicated that it was unusual for workers to change railroad employers. To account for railroad service prior to a railroad merger, a weighted average of the emission adjustment factors of precursor railroads was calculated for the years prior to the merger. Exposure in a given year was defined by the product of months of service for subjects who worked on operating trains (train riders: brakemen, conductors, engineers, firemen, or hostlers) and either the average railroad emission adjustment factor or diesel fraction. Yearly job code was available between 1959 and 1980, and months of service in each year were available starting in 1947. Between 1945 and 1947, it was assumed that each subject worked 12 months. Job classification before 1959 was based on 1959 job title.

Statistical analysis

To assess the relationship of exposure to diesel exhaust with lung cancer mortality, we conducted Cox proportional hazard analyses with calendar year used as the time axis. Mortality follow-up began on January 1, 1959. Each subject contributed person-time to the analysis up until December 31, 1980, or until the date of death, whichever came earlier. We calculated relative risks (RR) and 95% confidence intervals (CI) for workers identified as train riders compared to other railroad industry workers ("unexposed"). Because an additional review of the original industrial hygiene survey indicated that job codes selected for the shop category were not specific for diesel repair shop jobs, but also included workers in other repair shops, we modeled this group separately in all models. All models described here and subsequently were performed in SAS (SAS Institute Inc 1996).

We assessed the effect of cumulative exposure to diesel exhaust (as a train rider) by calculating total years of work in an exposed job, from the yearly information on months of work and job title. We modeled cumulative exposure as time varying variables for 5-year exposure categories, again compared to the unexposed group. We also constructed models where the exposure in the year of death and the previous 4, 9, and 14 years were excluded (5 year, 10 year, and 15 year lag models, respectively). Similar models were constructed using years of exposure that included years worked as a train rider before 1959 using yearly DF to indicate the probability of diesel exposure. The yearly EAF times the number of months in each year was summed in a time-dependent manner and examined as a predictor of lung cancer mortality.

For all workers exposed and unexposed we estimated their start data from information provided by the RRB on total months of service prior to 1959, assuming each person worked a 12-month year. In some models, to adjust for the healthy worker survivor effect, we included a time-varying variable for years on the job, either modeled continuously or in 5-year categories. We also assessed the effect on lung cancer mortality risk of time off the job for all workers. The purpose of these two variables was to address a possible healthy worker survivor effect.

Results

There were 21,639 deaths identified out of 54,973 subjects, and it was possible to identify underlying cause of death in 21,116 (98%). In the original publication (Garshick, et al. 1988), 19,396 deaths were noted, and underlying cause of death was unavailable in approximately 12%. Since lung cancer is usually fatal within several years following diagnosis, in order to more completely ascertain lung cancer mortality, a lung cancer death was defined based on the underlying cause of death or if lung cancer was listed elsewhere on the death report (death certificate or the NDI). There were 2,123 lung cancer cases identified using these criteria, and for the 52,812 subjects with EAF or DF data available, there 2,050 lung cancer cases identified. As expected, workers who were younger in 1959 were more likely to have a greater duration of work in jobs with potential exposure to diesel exhaust between 1959 and retirement compared to older workers, and had a greater duration of service (Table 1). Date of initial railroad work (Table 1) was estimated based on total years of railroad service.

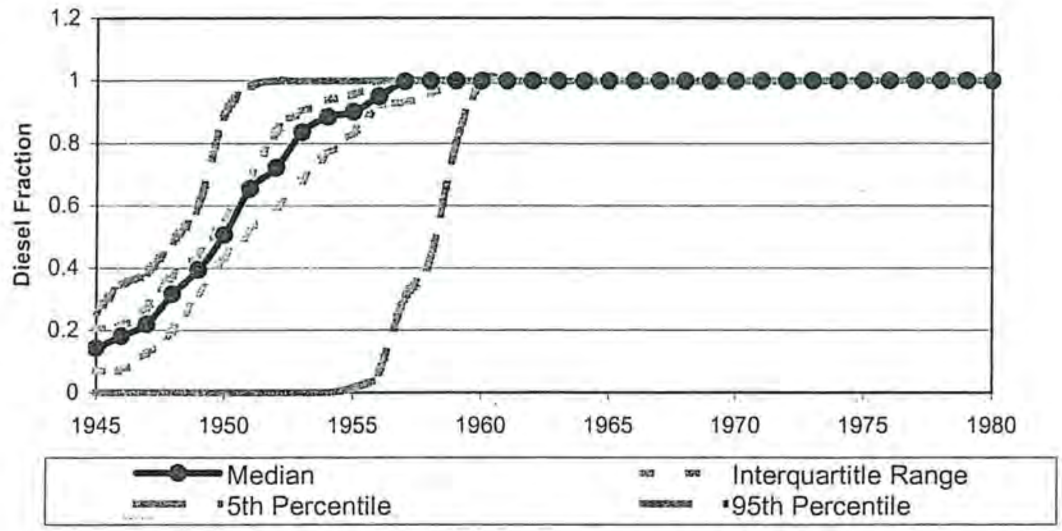
Table 1: Distribution of the entire cohort by exposure categories, duration of service and exposure presented by age at baseline (1959)

	Age in 1959 40-44 (n=19,794)	45-49 (n=13,874)	50-54 (n=9,820)	55-59 (n=7,216)	60-64 (n=4,269)	Total (n=54,973)
1959 Job Groups						
Engineers[1]	4,002	2,834	1,855	1,394	836	10,921
Conductors [2]	7,204	5,074	2,898	1,916	971	18,063
Shop[3]	3,677	2,834	2,466	1,917	1,148	12,042
Unexposed	4,911	3,132	2,601	1,989	1,314	13,974
Lung Cancer Deaths						
Engineers	110	107	108	81	37	443
Conductors	191	193	147	134	73	738
Shop	67	98	96	132	69	462
Unexposed	87	95	110	110	78	480
Total	455	493	461	457	257	2,123
Years of exposure 1959-1980 [4]						
≥ 20	3,191	265	11	0	0	3,467
15-<20	4,539	4,119	451	6	0	9,115
10-<15	1,458	1,727	2,670	791	47	6,693
5-<10	1,081	1,005	946	1,694	647	5,373
>0-<5	985	831	689	842	1,115	4,462
Any Shop Work 1959-1980	3,793	2,911	2,523	1,941	1,158	12,326
Duration of Employment						
Retirement Year:						
Median	1977	1974	1971	1966	1963	
IQR	1972-1979	1970-1975	1967-1972	1964-1969	1961-1965	
Hire Date ≥1945 (%)	10.4	5.6	3.7	2.3	1.1	
Yrs of service (mean±sd)	30.9±6.6	28.7±5.8	25.7±5.1	22.8±4.2	20.2±3.6	

[1]Engineers, firemen; [2]Conductors, brakemen, hostlers; [3]Shopworkers; [4]Years of work in engineer or conductor group; 'Any Shop' refers to any work in a shop job between 1959 and retirement. IQR=interquartile range, 25th to 75th percentile.

A graph of the distribution of DF in the cohort revealed that probability of exposure to diesel exhaust (the ratio of product of number of number of locomotives, unit specific emission factor, and horsepower) varied considerably by railroad during the 1950's. Five percent of the railroads achieved 100% diesel locomotives by 1952, 25% by 1956, 50% by 1957, 75% by 1958, and 95% by 1961 (Figure 1).

Figure 1: Distribution of diesel fraction based on calendar year, 1945-1980.



For approximately 50% of the industry the rate of conversion to diesel was similar, as indicated by the narrow DF interquartile range, but others, the rates varied considerably. With years of exposure weighted using DF, it was estimated that 26% (n=7,311) of the 27,655 subjects who worked as a train rider with railroad roster information available worked for 25 years or more, and 30% worked between 20 and 25 years (Table 2).

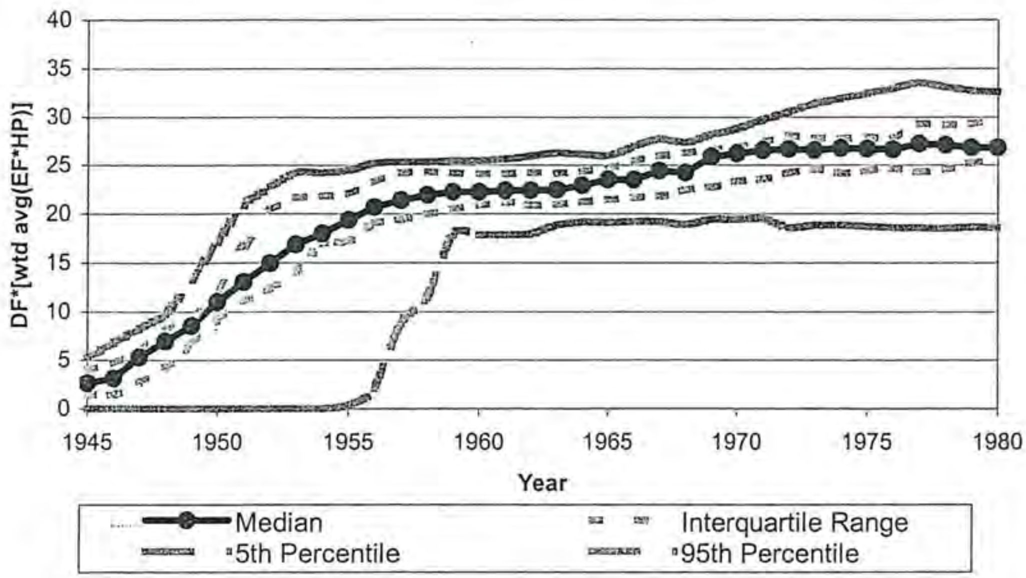
Table 2: Distribution of years of exposure based on yearly diesel fraction (1945-1980), number of unexposed subjects, and subjects with work in any shop job 1959-1980. Presented by age at baseline (1959).

	Age in 1959					
	40-44 (n=19,060)	45-49 (n=13,393)	50-54 (n=9,437)	55-59 (n=6,885)	60-64 (n=4,037)	Total (n=52,812)
Years of exposure 1959-1980 based on diesel fraction[4]						
≥ 25	5,320	1,888	100	3	0	7,311
20-<25	2,411	3,079	2,052	313	16	7,871
15-<20	1,614	1,431	1,279	1,409	312	6,045
10-<15	872	813	750	968	894	4,297
5-<10	401	325	323	394	431	1,874
>0-<5	77	60	29	50	41	257
Unexposed	4,717	2,983	2,477	1,877	1,234	13,288
Any Shop Work 1959-1980	3,648	2,814	2,427	1,871	1,109	11,869

[1]Engineers, firemen; [2]Conductors, brakemen, hostlers; [3]Shopworkers; [4]Years of work in engineer or conductor group; 'Any Shop' refers to any work in a shop job between 1959 and retirement. IQR=interquartile range, 25th to 75th percentile.

The yearly average EAF (an estimate of diesel locomotive particulate emissions) for each railroad was multiplied by DF to reflect the probability of exposure prior to complete conversion to diesel. A plot of this product versus calendar year (Figure 2) indicates that after the late 1950's when most of the industry had converted to diesel locomotives, there was little variability in emissions over time. Although the PM emissions per gallon of fuel or horsepower generally decreased, the typical horsepower rating grew, offsetting this difference. The main reason for lower EAF values in the years prior to the late 1950's was due to the conversion to diesel locomotives, not increases in the product of horsepower and emission factor.

Figure 2: Distribution of emission adjustment factor weighted by diesel fraction based on calendar year, 1945-1980



Analysis of lung cancer mortality based on exposure starting in 1959 was compared to results based on using DF and EAF to include pre-1959 exposure in the analysis of lung cancer risk. Based on exposure considered to start in 1959, there was no evidence of an increasing risk of lung cancer mortality with greater years of exposure. With exposure in year of death and work as a train rider in the preceding 4 (5-year lag) or 9 years (10-year lag) not included in the calculation of years of exposure, the risk of lung cancer still decreased with increasing years of exposure (Table 3). Subjects who worked as a shop worker for any time between 1959-1980 did not have an increased risk of lung cancer (OR=1.07; 95%CI=0.94,1.21). The finding that subjects who work the longest have a lower lung cancer risk is consistent with a healthy worker survivor effect (Arrighi and Hertz-Picciotto 1993, Choi 1992, Sheikh 2000). Since subjects in an occupational cohort must be healthier to work for longer periods of time, there is an inverse relationship with years of work. Additional regression models were constructed that included total years worked for all subjects in order to adjust for time on the job, and also included time off the job to adjust the risk of lung cancer mortality for time since last worked. For each year of railroad work there was on average a 3.2% (95%CI=1.7% to 4.9%) decrease in lung cancer mortality. In the first year after leaving work, there was a 5.51 (95% CI=4.72-6.41) increased risk of dying of lung cancer. After 10 years or more following the last year worked regardless of exposure status, the risk of dying of lung cancer was still elevated by approximately 30 to 40%.

Table 3: RR of lung cancer mortality 1959-1980 and cumulative years of work in an engineer or conductor job group, with exposure 5 and 10 years before death excluded (lag models) as cumulative exposure, adjusting for age and work in any shop category.

			Years of Work as Engineer or Conductor				
Lag Model		Not Exposed	0-<5	5-<10	10-<15	15-<20	≥20
None	Cases	462	247	360	364	206	14
	Person years	246,907	160,840	157,470	126,290	78,127	7,699
	RR	ref	1.63	1.52	1.29	0.93	0.48
	95% CI		1.38-1.92	1.32-1.76	1.12-1.49	0.78-1.10	0.28-0.82
5 years	Cases	548	304	376	316	109	0
	Person years	389,278	139,033	130,480	93,730	24,812	0
	RR	ref	1.58	1.35	1.19	1.14	
	95% CI		1.34-1.85	1.17-1.56	1.02-1.39	0.90-1.45	
10 years	Cases	751	361	369	172	0	0
	Person years	522,589	116,353	104,176	34,214	0	0
	RR	ref	1.57	1.22	1.24		
	95% CI		1.34-1.83	1.05-1.41	1.01-1.52		

However, after adjustment for time off the job and total years of work, the inverse gradient between years of exposure and lung cancer mortality persisted in the no lag, 5-year, and 10-year lag models (Table 4). The magnitude of the inverse relationship was less as more recent exposure was excluded from the exposure models. There was more uniformity of the relative risks, but greater years of exposure assessed from 1959 was still not associated with a greater risk of lung cancer

Table 4: RR of lung cancer mortality 1959-1980 and cumulative years of work in an engineer or conductor job group, with exposure 5 and 10 years before death excluded (lag models) from cumulative exposure, adjusting for age and work in any shop category. Models are adjusted for the Healthy Worker Survivor Effect using years of employment and time since last worked as time dependent covariates.

Lag Model		Not Exposed	Years of Work as Engineer or Conductor 0-<5	5-<10	10-<15	15-<20	≥20
None	Cases	462	247	360	364	206	14
	Person years	246,907	160,840	157,470	126,290	78,127	7,699
	RR	ref	1.33	1.52	1.49	1.08	0.73
	95% CI		1.12-1.57	1.32-1.75	1.29-1.72	0.89-1.30	0.42-1.27
5 years	Cases	548	304	376	316	109	0
	Person years	389,278	139,033	130,480	93,730	24,812	0
	RR	ref	1.45	1.48	1.31	1.18	
	95% CI		1.23-1.70	1.28-1.71	1.11-1.53	0.92-1.51	
10 years	Cases	751	361	369	172	0	0
	Person years	522,589	116,353	104,176	34,214	0	0
	RR	ref	1.55	1.29	1.27		
	95% CI		1.32-1.81	1.11-1.50	1.02-1.57		

Similar regression models were constructed using DF to estimate years of exposure (Table 5). In the regression model without a lag for recent exposure, the risk of lung cancer mortality was essentially uniform with less than 20 years of exposure, and with a lower risk for workers with 20 to <25 and 25 or more years of exposure. With introduction of a 5, 10 , and 15-year exposure lag, lung cancer mortality risk also became more uniform.

Table 5: RR of lung cancer mortality 1959-1980 based on diesel fraction weighted cumulative years of work in an engineer or conductor job group, with exposure 5, 10, and 15 years before death excluded (lag models) from cumulative exposure, adjusting for age and work in any shop category.

Lag Model		Not Exposed	Years of Work as Engineer or Conductor 0-<5	5-<10	10-<15	15-<20	20-<25	≥25
None	Cases	463	12	94	269	362	292	101
	Person years	242,649	8,623	58,031	154,502	139,760	104,310	39,654
	RR	ref	1.32	1.50	1.53	1.37	1.09	0.85
	95% CI		0.74-2.34	1.20-1.89	1.31-1.78	1.19-1.58	0.94-1.27	0.68-1.07
5 years	Cases	463	37	156	319	335	256	27
	Person years	244,595	42,276	144,633	135,637	109,625	64,631	6,132
	RR	ref	1.32	1.25	1.33	1.26	1.26	1.05
	95% CI		0.93-1.89	1.02-1.51	1.15-1.55	1.09-1.46	1.07-1.49	0.70-1.58
10 years	Cases	464	136	277	334	324	58	0
	Person years	251,232	163,630	133,564	111,606	77,894	9,600	2
	RR	ref	1.23	1.34	1.26	1.31	1.31	
	95% CI		0.99-1.53	1.14-1.57	1.09-1.46	1.12-1.53	0.97-1.77	
15 years	Cases	494	333	325	363	78	0	0
	Person years	287343	249,732	114,282	83,588	12,582	2	0
	RR	ref	1.19	1.23	1.34	1.36		
	95% CI		1.02-1.39	1.06-1.43	1.16-1.56	1.04-1.7		

With adjustment including time off the job and total years of work (Table 6), the relationship between years of exposure with the 5, 10, and 15-year lag models suggested a modest increase in risk with increasing years of exposure. In the 5-year lag model, the relative risk increased from 1.13 to 1.15 for workers with 0-<5 and 5-<10 years of exposure to 1.43 to 1.42 in workers with 15-<20 and 20-<25 years of exposure. Although the relative risk for workers with 25 or more years of exposure was 1.12,, there were relatively few cases and person-years of follow-up in this group on which to draw a meaningful conclusion. For models with a 10 and 15-year lag of recent exposure and adjusting for time on and off the job, the relative risk increased from approximately 1.20 to 1.40 to 1.45 when exposure in lowest and highest categories are examined.

Table 6: RR of lung cancer mortality 1959-1980 and diesel fraction weighted cumulative years of work in an engineer or conductor job group, with exposure up to 5, 10, and 15 years before death excluded (lag models) from cumulative exposure, adjusting for age and work in any shop category. Models are adjusted for the Healthy Worker Survivor Effect using years of employment and time since last worked as time dependent covariates.

			Years of Work as Engineer or Conductor					
Lag Model		Not Exposed	0-<5	5-<10	10-<15	15-<20	20-<25	≥25
None	Cases	463	12	94	269	362	292	101
	Person years	242,649	8,623	58,031	154,502	139,760	104,310	39,654
	RR	ref	1.06	1.20	1.40	1.47	1.27	1.07
	95% CI		0.59-1.88	0.95-1.51	1.19-1.63	1.28-1.69	1.09-1.49	0.84-1.35
5 years	Cases	463	37	156	319	335	256	27
	Person years	244,595	42,276	144,633	135,637	109,625	64,631	6,132
	RR	ref	1.13	1.15	1.35	1.43	1.42	1.12
	95% CI		0.79-1.61	0.95-1.40	1.17-1.57	1.23-1.65	1.20-1.69	0.74-1.69
10 years	Cases	464	136	277	334	324	58	0
	Person years	251,232	163,630	133,564	111,606	77,894	9,600	2
	RR	ref	1.20	1.36	1.35	1.43	1.40	
	95% CI		0.96-1.49	1.16-1.59	1.16-1.56	1.22-1.68	1.03-1.89	
15 years	Cases	494	333	325	363	78		
	Person years	287,343	249,732	114,282	83,588	12,582	2	
	RR	ref	1.21	1.30	1.43	1.45		
	95% CI		1.04-1.41	1.12-1.51	1.23-1.66	1.11-1.90		

Exposure was also estimated by the time-dependent summation of EAF and division of cumulative exposure into quintiles. The risk of lung cancer mortality in each quintile of cumulative exposure was compared to unexposed workers and adjusted for time on and off the job (Table 7). There was no suggestion of an increased risk of lung cancer mortality with increasing exposure, including in the no exposure lag, 5-year, 10-year, or 15-year lag. With more recent exposure disregarded, the relative risk varied from 1.20 to 1.40 without any obvious relationship with cumulative exposure.

Table 7: RR of lung cancer mortality 1959-1980 based on emission factor weighted cumulative exposure in an engineer or conductor job group. Cumulative exposure is divided into quintiles, with exposure up to 5, 10, and 15 years before death excluded (lag models) from cumulative exposure, adjusting for age and work in any shop category. Models are adjusted for the Healthy Worker Survivor Effect using years of employment and time since last worked as time dependent covariates.

Lag Model		Not Exposed	Quintiles of cumulative emission factor				
			Q1	Q2	Q3	Q4	Q5
None	Cases	463	328	358	222	152	70
	Person years	242,649	189,528	148,489	84,722	54,748	27,392
	RR	ref	1.38	1.45	1.26	1.18	1.05
	95% CI		1.19-1.61	1.26-1.67	1.06-1.48	0.97-1.43	0.80-1.37
5 years	Cases	463	355	387	229	111	48
	Person years	244,595	257,593	136.409	65,678	31,519	11,734
	RR	ref	1.28	1.42	1.39	1.24	1.14
	95% CI		1.10-1.48	1.23-1.63	1.17-1.65	0.99-1.55	0.83-1.57
10 years	Cases	464	428	369	214	68	50
	Person years	251232	301,074	117,992	50,867	16,361	10,002
	RR	ref	1.32	1.37	1.45	1.22	1.30
	95% CI		1.14-1.52	1.19-1.58	1.22-1.73	0.93-1.61	0.95-1.79
15 years	Cases	494	467	373	154	59	46
	Person years	287,343	300,495	102,736	35,546	11,903	9,506
	RR	ref	1.27	1.40	1.32	1.28	1.19
	95% CI		1.11-1.45	1.22-1.62	1.09-1.61	0.96-1.71	0.86-1.65

Discussion

In this research project we sought to improve estimates of the quantitative relationship between diesel exhaust exposure and lung cancer by collecting previously missed cancer deaths and improving the estimates of diesel exposure onset and intensity. Cause of death information obtained by a mortality update reduced the number of subjects with missing cause of death information from 12% to 2%, and an additional 1,700 deaths were noted. In the specific aims we proposed that the creation of a profile diesel locomotive use based on the distribution of the railroads in the cohort could be used to estimate the start of diesel exposure for each subject. We further proposed that estimates of emissions based on locomotive design could be used to estimate the impact of changes in locomotive fleet composition on the profile of each worker's personal exposure. It was hypothesized that these modified estimates of personal exposure could be used to refine the quantitative relationship between diesel exhaust exposure and lung cancer risk and refine existing estimates of lung cancer risk based in this cohort. We first conducted analyses as in our previous publication that assessed lung cancer risk based on exposure starting in 1959 (Garshick, et al. 1987, Garshick, et al. 1988). By 1959, 95% of the railroad industry had converted to diesel use. The results of these analyses were compared to the results obtained when railroad roster data was used primarily to estimate pre-1959 exposure.

Specific Aim A: To better estimate the onset and duration of exposure to diesel exhaust starting in the 1940's by constructing a profile for the introduction of diesel locomotives by each railroad where subjects worked

The probability of exposure to diesel exhaust (DF) was estimated by examining of the product of the total number of diesel locomotives in service each year, the locomotive specific emission factor, and the horsepower for each locomotive type in each railroad. The DF was calculated based on how this product changed starting in 1945. It was estimated that 26% (n=7,311) of the 27,655 subjects who worked as a train rider with railroad roster information available worked for 25 years or more, and 30% worked between 20 and 25 years. The probability of exposure to diesel exhaust was found to vary considerably during the 1950's and depended on the railroad studied. Although 50% of the industry had a similar rate of transition to 100% diesel locomotives, for the other half the rates varied considerably (Figure 1).

Specific Aim B: To use estimates of emissions based on locomotive design to estimate the impact of changes in locomotive fleet composition on the profile of each worker's personal exposure

The average railroad EAF, the product of horsepower (a surrogate for fuel consumption) and engine emission factor (mass of particulate matter per unit fuel or energy consumed), was weighted by the diesel fraction and the months each subject worked in each year to obtain a diesel exhaust exposure index. Since horsepower is proportional to fuel consumption, the product of horsepower and emissions per unit energy consumed yields an index that serves to weight exposure. This index can be interpreted as an indicator of particulate matter emissions that was hypothesized to vary by railroad and calendar year as newer locomotive engines were introduced. However, examination of EAF (Figure 2) as a function of calendar year revealed that there was little variation in average railroad EAF once the transition to diesel locomotives was complete. Rather than predicting a fall in particulate matter emissions due to improvements in engine design, the increase in horsepower, also a determinant of emissions resulted in a relatively constant EAF over time. The greatest variation in EAF was due to the adjustment using DF during the years of conversion to diesel power. It was necessary to use the DF to weight the railroad specific EAF values to indicate the probability of diesel particulate matter exposure during the transition to diesel.

Specific Aim C: To use these modified estimates of personal exposure to assess the relationship between diesel exhaust exposure and lung cancer risk.

Analyses conducted based on the tabulation of years of exposure starting in 1959 and disregarding the transition period to diesel locomotives revealed an inverse relationship between lung cancer mortality and exposure duration. Since the cellular events that result in lung cancer take years to result in clinical disease, additional exposure models were constructed that did not include more recent exposure in the assessment of lung cancer risk. The inverse relationship was also noted with 5-year and 10-year exposures before death excluded from the risk models. This relationship further suggested that it was likely that the healthy worker survivor effect was present in these data. This effect refers to the continuing selection process such that those who remain employed tend to be healthier than those who leave employment (Arrighi and Hertz-Picciotto 1994). Methods proposed to adjust for this effect so that a true exposure-response relationship can be considered includes excluding recent exposure from risk models and controlling for time since hire (Arrighi and Hertz-Picciotto 1995). Additional models incorporating time since hire and time since leaving the job were used together with exposure-lag models. The inverse relationship with duration of exposure persisted (Table 3).

With pre-1959 exposure included based on DF weighted exposures and adjusting for the healthy worker survivor effect, there was a modest in risk with increasing years of exposure if more recent exposure was disregarded This modest increase in lung cancer risk with years of exposure was noted for the 5-year, 10-year, and 15-year lag models. The relationship between maximal risk and duration of exposure varied considerably since the relative risk was maximal (relative risk approximately 1.4, Table 6) for subjects between 10 to 25 years of exposure depending on the exposure model. Analyses with adjusted EAF values (a surrogate for diesel exhaust related particulate matter emissions) did not result in a consistent exposure-response relationship (Table 7).

It was not possible to model lung cancer risk attributable to diesel exhaust exposure in shop workers in a similar fashion. When examined closely, the codes selected for shop workers included in the cohort also included workers in non-diesel shops. The shop worker group did not have an increased risk of lung cancer. The extent that all workers in the shop worker category included in the cohort had significant exposure to diesel is uncertain.

It was also not possible to directly adjust for the effect of cigarette smoking in these analyses since these data are taken from a retrospective mortality assessment where it is not possible to obtain smoking histories directly. However, the degree that cigarette smoking will be a confounder in the cohort depends on the extent that smoking is related to both lung cancer mortality and diesel exhaust exposure. In blue-collar cohorts such as railroad workers, the difference in smoking behavior among jobs is expected to be minimal. Job (exposure)-specific smoking rates from next-of-kin were obtained from a case-control study of lung cancer in US railroad workers and were used to calculate adjustment factors to apply to the relative risk of lung cancer in the current retrospective cohort study (Garshick, et al. 1987, Larkin, et al. 2000). The method of Schlesselman and Axelson (Axelson 1980, Schlesselman 1978) was used to obtain an adjusted relative risk based on the distribution of cigarette smoking in diesel exposed (train riders) and unexposed workers. In a previous analysis of these data, workers in diesel exhaust exposed jobs had a slightly greater prevalence of smoking resulting in smoking adjustment factors of approximately 1.10 to 1.20, depending on specific age and exposure group (Larkin, et al. 2000). Assuming a true relative risk of lung cancer attributable to diesel exhaust of 1.40 (a 40% excess risk), the smoking adjusted values would be obtained by dividing by these factors, resulting in relative risks of

1.17 to 1.27 for the risk of lung cancer attributable to diesel exposure. These risks are within the range attributable to diesel exhaust reported in the literature but lower than previously noted in this cohort. It was not possible to refine the risk further based on the knowledge of railroad rosters or exposure duration obtained in this study.

Conclusions

The use of railroad locomotive rosters to estimate the duration and potential intensity of historical exposure to diesel exhaust and assess its effect on lung cancer mortality between 1959 and 1980 did not improve the estimation of lung cancer risk associated with work as a train rider when compared to analyses based on exposure assumed to start in 1959. In some models based on duration of exposure, the risk of lung cancer increased with greater cumulative exposure. However, there was no consistent relationship between indices of cumulative exposure and lung cancer risk, although train-riders in diesel exhaust exposed jobs had a greater risk of lung cancer compared to workers in unexposed jobs. The relationship between exposure intensity and duration of exposure remains uncertain using the exposure weighing estimates developed in this study. The risk of lung cancer attributable to work as a train rider was elevated as in previous analyses using these data. It was not possible to conduct a quantitative risk assessment in this cohort.

Limitations to this approach include: the uncertainty in a single railroad-specific value that was used to weight exposure for all train riders on a single railroad; limited source data for emission factor values; and the uncertainty in personal exposures estimated by emission factors obtained from testing a few engines and expecting them to represent emissions from locomotives operated over a variety of real-life conditions. Although exposures to diesel particulate were predicted to increase with engine emissions in this exposure model, there was no validation of the model. Nor was there information regarding how the characteristics of emissions (such as particle size, organic content) changed over time, or how previous exposure to coal fired locomotive emissions influenced lung cancer risk. Additional follow-up of the mortality experience of this cohort through 1996 is underway that may provide additional insight into lung cancer risk.

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References

Arrighi HM and Hertz-Picciotto I: Definitions, sources, magnitude, effect modifiers, and strategies of reduction of the healthy worker effect. J Occup Med 35:890-2., 1993.

Arrighi HM and Hertz-Picciotto I: The evolving concept of the healthy worker survivor effect. Epidemiology 5:189-96., 1994.

Arrighi HM and Hertz-Picciotto I: Controlling for time-since-hire in occupational studies using internal comparisons and cumulative exposure. Epidemiology 6:415-8., 1995.

Association of American Railroads. Railroad Facts. 1993.

Axelson O: Aspects of confounding and effect modification in the assessment of occupational cancer risk. J Toxicol Environ Health 6:1127-31, 1980.

Bhatia R, Lopipero P and Smith AH: Diesel exhaust exposure and lung cancer. Epidemiology 9:84-91, 1998.

Bond JA, Mauderly JL and Wolff RK: Concentration- and time-dependent formation of DNA adducts in lungs of rats exposed to diesel exhaust. Toxicology 60:127-35, 1990.

Brightwell J, Fouillet X, Cassano-Zoppi AL, Bernstein D, Crawley F, Duchosal F, Gatz R, Perczel S and Pfeifer H: Tumours of the respiratory tract in rats and hamsters following chronic inhalation of engine exhaust emissions. J Appl Toxicol 9:23-31, 1989.

California Environmental Protection Agency. Health Risk Assessment for Diesel Exhaust: Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant. 1998.

Choi BC: Definition, sources, magnitude, effect modifiers, and strategies of reduction of the healthy worker effect. J Occup Med 34:979-88., 1992.

Clean Air Scientific Committee. Letter to the administrator of EPA , July. 1995.

Diesel Epidemiology Expert Panel. Diesel emissions and lung cancer: Epidemiology and quantitative risk assessment. 1999.

Diesel Working Group. Diesel exhaust: A critical analysis of emissions, exposure, and health effects. 1995.

Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Woskie SR, Hammond SK and Speizer FE: A case-control study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 135:1242-8, 1987.

Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Woskie SR, Hammond SK and Speizer FE: A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 137:820-5, 1988.

Heinrich U, Muhle H, Takenaka S, Ernst H, Fuhst R, Mohr U, Pott F and Stober W: Chronic effects on the respiratory tract of hamsters, mice and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. J Appl Toxicol 6:383-95, 1986.

Ishinishi N, Kuwabara N, Nagase S, Suzuki T, Ishiwata S and Kohno T: Long-term inhalation studies on effects of exhaust from heavy and light duty diesel engines on F344 rats. Dev Toxicol Environ Sci 13:329-348, 1986.

Larkin EK, Smith TJ, Stayner L, Rosner B and Speizer FE: Diesel exhaust and lung cancer: Adjustment for the effects of smoking in a retrospective cohort study. Am J Ind Med 38:399-409, 2000.

Lipsett M and Campleman S: Occupational exposure to diesel exhaust and lung cancer: a meta- analysis. Am J Public Health 89:1009-17, 1999.

Mauderly JL, Jones RK, Griffith WC, Henderson RF and McClellan RO: Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. Fundam Appl Toxicol 9:208-21, 1987.

Mauderly JL, Snipes MB, Barr EB, Belinsky SA, Bond JA, Brooks AL, Chang IY, Cheng YS, Gillett NA, Griffith WC, Henderson RF, Mitchell CE, Nikula KJ and Thomassen DG. Pulmonary Toxicity of Inhaled Diesel Exhaust and Carbon Black in Chronically Exposed Rats: Part I: Neoplastic and Nonneoplastic Lung Lesions. 1994.

Mine Safety and Health Administration and Department of Labor. Underground coal miners; proposed rule. Federal Register 1998; 30 CFR Part 72 and 75. 1998.

Nikula KJ, Snipes MB, Barr EB, Griffith WC, Henderson RF and Mauderly JL: Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. Fundam Appl Toxicol 25:80-94., 1995.

Office of Air and Radiation and Office of Air Quality Planning and Standards. Compilation of Air Pollution Emission Factors, Volume 1: Stationary Point and Area Sources. 1996.

Office of Air and Radiation and Office of Mobile Sources. Nonroad Engine and Vehicle Emission Study-Report. PB92-126960INZ. 1991.

Office of Research and Development. HEALTH ASSESSMENT DOCUMENT FOR DIESEL ENGINE EXHAUST. 2002.

SAS Institute Inc. SAS Statistical Software 6.12. 1996.

Schlesselman JJ: Assessing effects of confounding variables. Am J Epidemiol 108:3-8, 1978.

Sheikh K: A review of the healthy worker effect in occupational epidemiology. Occup Med (Lond) 50:146., 2000.

Steenland NK, Silverman DT and Hornung RW: Case-control study of lung cancer and truck driving in the Teamsters Union. Am J Pub Health 80:670-674, 1990.

Takaki Y, Kitamura S, Kuwabara N and Fukuda Y: Long-term inhalation studies of exhaust from the diesel engine in F-344 rats: the quantitative relationship between pulmonary hyperplasia and anthracosis. Exp Pathol 37:56-61, 1989.

World Health Organization. Diesel fuel and exhaust emissions. 1996.

Woskie SR, Smith TJ, Hammond SK, Schenker MB, Garshick E and Speizer FE: Estimation of the diesel exhaust exposures of railroad workers: I. Current exposures. Am J Ind Med 13:381-94, 1988a.

Woskie SR, Smith TJ, Hammond SK, Schenker MB, Garshick E and Speizer FE: Estimation of the diesel exhaust exposures of railroad workers: II. National and historical exposures. Am J Ind Med 13:395-404, 1988b.

Zaebst DD, Clapp DE, Blade LM, Marlow DA, Steenland K, Hornung RW, Scheutzle D and Butler J: Quantitative determination of trucking industry workers' exposures to diesel exhaust particles. Am Ind Hyg Assoc J 52:529-41, 1991.

Publications

Current:

Laden F, Eschenroeder A, Smith TJ, Gagnon D, Jackson SL, Dockery DW, Speizer FE, Garshick E. Historical estimation of diesel exhaust exposure in a cohort study of railroad workers and lung cancer. Am J Respir Crit Care Med 2001;163:A717.

Garshick E, Laden F, Smith TJ, Gagnon D, Jackson SL, Dockery DW, Speizer FE, Garshick E. Retrospective cohort study of diesel exhaust exposure and lung cancer in US railroad workers. Am J Respir Crit Care Med 2001;163:A718.

Proposed (In preparation):

Eschenroeder A, Laden F, Smith TJ, Hart J, Garshick E. Estimation of historical exposures to diesel exhaust for a retrospective cohort study of railroad workers.

Garshick E, Laden F, Smith TJ, Gagnon D, Rosner B, Hart J, Dockery DW. Diesel exhaust exposure and lung cancer mortality 1959-1996 in US railroad workers.

Laden F, Hart J, Eschenroeder A , Smith TJ, Gagnon D, Rosner B, Dockery DW, Garshick E. Effects of historical estimation of diesel exhaust exposure on lung cancer mortality in US railroad workers.

Title: Diesel Exhaust and Occupational Lung Cancer Risk
Investigator: Eric Garshick, M.D.
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Award Number: 5 R01 CC115818-02
Start & End Date: 9/30/1999–9/29/2002
Total Project Cost: $279,815
Program Area: Mixed Exposures
Key Words:

Final Report Abstract:
Objective: The purpose of this research program was to address uncertainties in the exposure data previously used to define the relationship between lung cancer and diesel exhaust exposure in a cohort of over 55,000 US railroad workers. It was hypothesized that historical information regarding railroad-specific diesel locomotive use in the US railroad industry could be used to estimate lung cancer risk.

Importance to Occupational Safety and Health: Overall, a 20% to 50% excess lung cancer risk has been observed in occupations where diesel exhaust exposure was likely, including in studies where it was possible to adjust for cigarette smoking. Since miners in dieselized underground mines are exposed to levels of diesel particles 10 to 20 times greater than other occupational groups, MSHA is concerned about the assessment of risk in underground miners and potential lung cancer risk in other occupational cohorts. Comprehensive mortality studies assessing the risk attributable to diesel exhaust in miners are not yet available. Therefore, there has been interest in assessing lung cancer risk by examining other existing diesel exhaust exposed occupational cohorts.

Approach: Previous risk assessments, including work done by NIOSH, relied heavily on a cohort
originally studied by our research group. Lung cancer mortality was assessed for 55,407 U.S. railroad workers from 1959 through 1980. Whether or not a meaningful quantitative risk assessment can be done to estimate the potential lung cancer risk attributable to diesel exhaust is controversial due to inadequate information regarding historical exposure measurements and an ill-defined linkage between job title and personal exposure.

The railroad industry changed from steam to diesel locomotives starting in the late 1940's, such that by 1959 based on aggregate data, 95% of the locomotives in service were powered by diesel. However, the date that an individual worker started working with diesel equipment is uncertain because there was wide variation in the acquisition of diesel locomotives by individual railroads. Based on locomotive testing and on differences in engine design and maintenance, it is likely that earlier generations of diesel locomotives (used in the 1950's and 1960's) had greater particulate emissions than later locomotives. No information about job-specific historical exposure to diesel exhaust is available. It was proposed that extensive information about the number and design of

older locomotives used by each railroad could be linked with emission data to estimate relative differences in historical and current exposures. This information would permit the development of a profile of exposure for jobs in each railroad which could be assigned to each worker and possibly permit improved estimates of lung cancer risk per unit of exposure.

The yearly locomotive roster of each railroad was obtained, which identified the make, model, and horsepower of each locomotive in service. From this, the number and type of locomotives that were diesel for each year could be calculated for each railroad. USEPA emission inventory guidance documentation provides emission factors for many locomotives. The emission factor times the locomotive's horsepower gives an estimate of total emissions. It was possible to estimate an average annual emission factor for each railroad weighted by the proportion of diesel locomotives. The assumption is that train crews' exposures will be roughly proportional to an average emission factor.

Findings: Prior to the development of the historical profile of diesel locomotive use in the US railroad industry it was necessary to update the mortality experience of the railroad worker cohort between 1959 and 1980 since mortality was not completely ascertained in the original analysis. With the cooperation of the US Railroad Retirement Board, it was possible to obtain additional mortality information on 54,973 (99.2%) subjects.

Although there were over 500 railroads listed in this railroad worker database, the sample studied was limited to 93 railroads that contributed at least 0.1% of the subjects to the cohort. This sample captured 96% of the eligible cohort (52,812 subjects), with 22 larger railroads (each contributing >1% of the cohort) accounting for 76%. Diesel exhaust exposure weighting factors were determined by examination of railroad equipment rosters between 1945-1980 by calculating a measure of the magnitude of exposure (an emission adjustment factor) and a measure of exposure probability (diesel fraction). The average emission adjustment factor for each railroad was based on railroad-specific number and type of locomotives. Since there have been a large number of mergers among the railroads, to account for service prior to a railroad merger, a weighted average of the emission adjustment factors of precursor railroads was calculated. The last railroad employer for each worker was available and provided the linkage between the railroad roster derived factors and work history. Examination of more detailed work histories for a subset of workers indicated that it was unusual for workers to change railroad employers. A yearly index exposure was defined based on the product of months of service for subjects who worked on operating trains (train riders: brakemen, conductors, engineers, firemen, or hostlers), the average railroad emission adjustment factor, and the diesel fraction. Analyses were also based on duration of work as a train rider weighted by the probability of diesel exposure. Yearly job code was available between 1959 and 1980, and job title before 1959 was based on 1959 job. Mortality from lung cancer was assessed using Cox proportional hazard regression methods.

Between 1959-1980 there were 21,639 deaths out of 54,973 subjects, and it was possible to identify underlying cause of death in 21,116 (98%). Since lung cancer is usually fatal within several years following diagnosis, lung cancer cases were identified based on both underlying cause of death and if lung cancer was noted elsewhere on the death report (either death certificate or National Death Index report). There were 2,123 lung cancer cases identified overall, and 2,050 lung cancer cases were available for analysis using historical railroad information.

In analyses not using railroad specific emissions data where diesel exposure was assumed to start in 1959, subjects who had the greatest duration of work as train riders had the lowest risk of lung cancer mortality. In efforts to consider the healthy-worker survivor effect, a condition where subjects who remain employed tend to be healthier than those who leave employment, analyses were repeated adjusting mortality for years of employment and time after leaving work. Regression models excluding exposure in the year of death and the preceding 5 and 10 years before death were also explored. The relative risk of lung cancer mortality for subjects with <5, 5 to <10, 10 to <15, and >15 years of work in diesel exposed jobs ranged from 1.55 to 1.18 without evidence of an increased risk with greater years of work. There was no increase in lung cancer risk in shop workers.

Based on the distribution of railroad-specific diesel fraction, the duration of exposure to diesel exhaust for the train riders was estimated starting in 1945. Adjusting for years of employment and time after leaving work, there was no evidence for an increase in lung cancer with increasing years of exposure. With exposure in the 5, 10, and 15 years before death excluded, the risk of dying of lung cancer ranged from 1.13 to approximately 1.40 to 1.45, with a modest increase in risk with increasing years of exposure in some models. Based on quintiles of a cumulative exposure index (the summation of the product of railroad specific average emission adjustment factor multiplied by months of yearly work and diesel fraction), a consistent relationship between cumulative exposure and lung cancer risk was not noted, even after adjustment for the healthy worker survivor effect.

Conclusions: The use of railroad locomotive rosters to estimate historical exposure to diesel exhaust did not significantly improve the estimation of lung cancer risk associated with work as a train rider when compared to analyses based on exposure assumed to start in 1959. There was no consistent relationship between railroad specific indices of cumulative exposure and lung cancer risk, although train-riders in diesel exhaust exposed jobs had a greater risk of lung cancer compared to workers in unexposed jobs, and in some models, workers with a greater duration of exposure had a greater risk. Workers in shop-related jobs did not have an increased risk of lung cancer. When examined closely, the codes selected for inclusion as shop workers also included workers in non-diesel shops, so the extent that all workers in the shop worker category had significant exposure to diesel was uncertain. The relationship between intensity and duration of exposure remains uncertain using the exposure weighting estimates developed in this study.

Limitations to this approach include: the uncertainty in a single railroad-specific value that was used to weight exposure for all train riders on a single railroad; limited source data for emission factor values; and the uncertainty in personal exposures estimated by emission factors obtained from testing a few engines and expecting them to represent emissions from locomotives operated over a variety of real-life conditions. Although exposures to diesel particulate were predicted to increase with engine emissions in this exposure model, there was no validation of the model. Nor was there information regarding how the characteristics of emissions (such as particle size, organic content) changed over time, or how previous exposure to coal fired locomotive emissions influenced lung cancer risk. Additional follow-up of the mortality experience of this cohort through 1996 is underway that may provide additional insight into lung cancer risk.

Publications

Laden F, Eschenroeder A, Smith TJ, Gagnon D, Jackson SL, Dockery DW, Speizer FE, Garshick E: Historical Estimation of Diesel Exhaust Exposure in A Cohort Study of Railroad Workers and Lung Cancer. Am J Respir Crit Care Med 163:A717, 2001

Garshick E. Laden F, Smith TJ, Gagnon D, Jackson SL, Dockery DW, Speizer FE, Garshick E: Retrospective Cohort Study of Diesel Exhaust Exposure and Lung Cancer in US Railroad Workers. Am J Respir Crit Care Med 163:A718, 2001

Memorandum

Date: January 31, 2003

From: Lee M. Sanderson, Ph.D., Program Official
Office of Extramural Programs, NIOSH, E-74

Subject: Final Report Submitted for Entry into NTIS for Grant 5 R01 CC115818-02.

To: William D. Bennett
Data Systems Team, Information Resources Branch, EID, NIOSH, P03/C18

The attached final report has been received from the principal investigator on the subject NIOSH grant. If this document is forwarded to the National Technical Information Service, please let us know when a document number is known so that we can inform anyone who inquires about this final report.

Any publications that are included with this report are highlighted on the list below.

Attachment
cc: Sherri Diana, EID, P03/C13

List of Publications

Garshick E. Laden F, Smith TJ, Gagnon D, Jackson SL, Dockery DW, Speizer FE, Garshick E: Retrospective Cohort Study of Diesel Exhaust Exposure and Lung Cancer in US Railroad Workers. Am J Respir Crit Care Med 163:A718, 2001

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