American Journal of Industrial Medicine 14:403–415 (1988)

Diesel Exhaust Exposure and Mortality Among Males in the American Cancer Society Prospective Study

Paolo Boffetta, MD, Steven D. Stellman, PhD, and Lawrence Garfinkel, MA

In 1982, the American Cancer Society enrolled over 1.2 million American men and women in a prospective mortality study of cancer and other causes in relation to different risk factors. The 2-year mortality of 461,981 males aged 40–79 years with known smoking habit has been analyzed in relation to exposure to diesel exhaust (DE) and to employment in selected occupations related to DE exposure. The relative risk (RR) for all causes of death for those exposed was 1.05 (95% confidence interval [CI]: 0.97–1.13). For lung cancer, the RR was 1.18 (95% CI: 0.97–1.44). A dose-response effect was present. Railroad workers, heavy equipment operators, miners, and truck drivers had a higher mortality both for all causes and for lung cancer when compared with subjects with other occupations and no exposure to DE. Truck drivers exposed to DE were not at excess risk of lung cancer if compared with truck drivers unexposed to DE, but a trend of increasing risk with duration of exposure was suggested. DE exposure was also associated with increase in mortality for accidents, cerebrovascular disease, arteriosclerosis, and cirrhosis of the liver. An association based on small numbers was also present for Hodgkin's disease and lymphoid leukemia. No association with chronic non-neoplastic pulmonary diseases or with bladder cancer was found.

Key words: railroad workers, heavy equipment operators, miners, truck drivers, lung cancer, cerebrovascular disease

INTRODUCTION

Evidence for a carcinogenic effect of diesel exhaust (DE) exposure, both in experimental models and in humans, is not conclusive at present.

DE contains large quantities of carbonaceous particulates to which are adsorbed polynuclear aromatic hydrocarbons and other heterocyclic compounds (mostly nitroarenes), known to be mutagenic as well as carcinogenic both in animals and in humans [International Agency for Research on Cancer, 1973]. Data from animals exposed to DE [International Agency for Research on Cancer, 1983; Schenker, 1980; Kotin et al., 1955; Wei and Shu, 1983; Pepelko and Peirano, 1983] are conflicting, but studies in which animals were exposed to high levels for long periods show positive results [Steenland, 1986].

Department of Epidemiology and Statistics, American Cancer Society, Inc., New York (P.B., S.D.S., L.G.).
Cattedra di Epidemiologia dei Tumori, Università di Torino, Torino, Italy (P.B.).
Address reprint requests to Lawrence Garfinkel, Vice President, Epidemiology and Statistics, American Cancer Society, Inc., 1180 Avenue of the Americas, New York, NY 10036.
Accepted for publication May 15, 1988.

Quantitative assessment of exposure is a major problem in epidemiologic studies on DE. Epidemiological studies on effects of DE exposure have concerned four job categories: truck drivers [Leupker and Smith, 1978; Milne et al., 1983], bus drivers and mechanics [Rushton et al., 1983; Harris, 1981], railroad workers [Howe et al., 1983; Schenker et al., 1984; Garshick et al., 1987], and heavy equipment operators [Wong et al., 1985]. One case-control study has addressed the association between DE exposure and lung cancer, without regard to occupation [Hall and Wynder, 1984]. Three critical reviews of this subject have recently been published [Higgins, 1984; Steenland, 1986; Wynder and Higgins, 1986].

Results of these studies are conflicting and inconclusive. Negative studies often had low power to detect any association, had insufficient latency periods, or compared incidence or mortality rates among workers to national rates only, resulting in possible biases caused by the "healthy worker effect." Positive studies often did not control for smoking or other occupational exposures.

We report here interim results of a long-term prospective mortality study, in which 2-year death rates were determined for subjects in target occupations and for DE-exposed subjects, controlling for smoking and other possibly confounding variables.

MATERIALS AND METHODS

In the fall of 1982, more than 77,000 American Cancer Society (ACS) volunteers enrolled over 1,200,000 men and women from all 50 States, the District of Columbia, and Puerto Rico, in a long-term cohort study, Cancer Prevention Study II (CPS-II). Enrolled subjects were usually friends, neighbors, or relatives of the volunteers; enrollment was by family groups with at least one person in the household 45 years of age or older: all members of the household over 30 years of age were asked to participate. Subjects filled out a four-page confidential questionnaire, and returned it in a sealed envelope.

Every 2nd year through 1988 the volunteers are asked to check whether their enrollees are alive or dead and to record the date and the place of all deaths. Death certificates are subsequently obtained from State Health Departments and coded by a trained nosologist according to a simplified system based on the International Classification of Diseases, 9th revision (92 categories).

The questionnaire included history of cancer and other diseases, use of medicines and vitamins, menstrual and reproductive history, occupational history, diet, drinking, smoking, and other habits.

The occupational section of the questionnaire included three questions on occupation: the current occupation; the last occupation, if retired; the job held for the longest period of time, if different from the other two.

Occupations were coded according to an ad hoc two-digit classification (70 categories) developed from a preliminary manual tally of several thousand questionnaires, to identify broad categories of job or branches of activities. A more specific classification, such as a three-digit SIC code, was impractical for the large number of ambiguous responses derived from a self-administered questionnaire.

Exposures at work or in daily life to any of 12 groups of substances were also investigated, as well as their durations: asbestos; chemicals/acids/solvents; coal or stone dusts; coal tar/pitch/asphalt; diesel engine exhausts; dyes; formaldehyde; gaso-

line exhausts; pesticides/herbicides; textile fibers/dusts; wood dusts; X-rays/radioactive materials.

The analysis reported here consists of three parts: 1) mortality for all causes and lung cancer in relation to DE exposure; 2) mortality for all causes and lung cancer and employment in selected occupations with high DE exposure; 3) mortality from other causes in relation to DE exposure. In the first two parts, the measure of association used is the incidence density ratio [Kleinbaum et al., 1982], with test-based confidence limits calculated according to Miettinen [1976]; the Mantel and Haenszel [1959] estimator and the chi-square test for linear trend proposed by Mantel [1963] are used in the stratified analysis. Chi-square goodness-of-fit test for multiplicative and additive models of interaction are calculated according to Thomas and Whittemore [1988]. In the third part of the analysis, the cumulative incidence ratio [Kleinbaum et al., 1982] is the measure of association, and the direct method of standardization [Fleiss, 1981] is used, the standard population being the unexposed study population. In both stratified analysis and direct standardization, four 10-year strata of age, five strata of smoking (never smoker, current 1–20/day cigarette smoker, current 21+/day cigarette smoker, ex-cigarette smoker, only pipe and/or cigar smoker), and two strata for occupational exposure (ever/never exposed to asbestos, coal, tar, pitch, or gasoline exhaust) are used.

RESULTS

The analysis has been restricted to men aged 40–79 years at enrollment whose vital status was known at the end of the first 2-year follow-up (September, 1984): in Table I the numbers of people involved are reported, and in Table II the number of deaths that occurred in the period of follow-up are reported, by wide categories of causes.

A total of 14,667 (3.1%) subjects had unknown smoking status, and were excluded in all the analyses that involved controlling for smoking; 98,026 (20.6%) subjects did not give information about DE exposure. (Table III). Subjects without information regarding DE exposure, compared with subjects with exposure status known, are older, have a higher proportion of missing information on other variables (especially on other occupational exposures), and show a higher mortality rate. Among 461,981 subjects with known smoking status, 92,038 did not give information about DE, 62,800 were exposed, and 307,143 were unexposed. The group with no information about DE has been excluded from analysis regarding DE.

All-Cause and Lung Cancer Mortality and DE Exposure

In Tables IV–VI, subjects who reported DE exposure are compared with subjects who did not, without regard to occupation.

TABLE I. Subjects in the Analysis

Enrolled male cohort	508,580
Lost to follow-up	3,863
Age under 40 or over 79	28,069
Analyzed subjects	476,648
Person years of exposure to risk	939,817

TABLE II. Number of Deaths at 2 Years Follow-up, by Causes of Death

Cause of death	ICD-9	No.	%
All cardiovascular diseases	390–459	5,475	49.6
All respiratory diseases	010–012, 460–519	539	4.9
Accidents	E800–E999	402	3.6
All other non-neoplastic diseases[a]	001–009, 013–139, 210–389, 520–779	792	7.2
Malignant tumors	140–208	3,757	34.0
Lung cancer	162	1,266	11.5
Colon cancer	153	389	3.5
Prostate cancer	185	332	3.0
Pancreas cancer	157	227	2.1
Ill-defined causes of death	780–799	79	.7
Total deaths		11,044	100.0

[a]Twenty benign tumors included.

TABLE III. Characteristics of Subjects by Information on Diesel Exhaust (DE) Exposure*

	DE exposure known	DE exposure unknown
Mean age (years)	54.7	57.7
% smoking[a]		
Yes	25.2	21.2
No	72.4	73.2
Unknown	2.4	5.6
% race[a]		
White	95.1	90.9
Non-white	4.4	8.3
Unknown	.5	.8
% sick at enrollment[a]		
Yes	9.2	11.1
No	89.1	84.7
Unknown	1.7	4.2
% exposure unknown[a]		
Asbestos	4.7	83.6
Coal stone dusts	4.7	89.9
Coal tar pitch	5.5	95.8
Gasoline exhausts	2.3	87.9
Mortality rate (1,000 per year)[a]	23.0	28.8
No. of subjects	378,622	98,026
Person years	747,521	192,296

*$p < .01$ in all subsets of data.
[a]Age-standardized.

TABLE IV. Relative Risk for All Causes of Death and for Lung Cancer*

	All causes	Lung cancer
No. of deaths among those exposed to diesel exhaust[a]	1,242	174
Person years at risk among those exposed to diesel exhaust[a]	124,053	124,053
No. of deaths among unexposed[a]	6,257	669
Person years at risk among unexposed[a]	606,397	606,397
Crude RR	1.11	1.40
95% CI[b]	1.05–1.18	1.19–1.66
Adjusted RR[c]	1.05	1.18
95% CI[b]	.97–1.13	.97–1.44

*Subjects with diesel exhaust exposure unknown and subjects with smoking habit unknown excluded.
[a]With no regard to occupation.
[b]CI, test-based confidence interval.
[c]RR adjusted for age, smoking, other occupational exposures, according to Mantel-Haenszel method.

TABLE V. Relative Risk for All Causes of Death and for Lung Cancer, by Duration of Diesel Exhaust Exposure*

Duration of diesel exhaust exposure (yr)	Cause of death	RR[a]	95% CI[b]	Chi-square test for trend p-value[c]
1–15	All Causes	.94	(.85–1.05)	
	Lung Cancer	1.05	(.80–1.39)	
16+	All Causes	1.09	(.99–1.20)	$p > .10$
	Lung Cancer	1.21	(.94–1.56)	$.05 < p < .10$

*Subjects with unknown duration of diesel exhaust exposure excluded.
[a]Reference category: unexposed to diesel exhaust, with no regard to occupation. RR controlled by age, smoking, other occupational exposures, according to Mantel-Haenszel method.
[b]CI, test-based confidence interval.
[c]Chi-square test according to Mantel. Scores: 0 (unexposed), 7.5, and 20.

Table IV shows the relative risks (RR) for exposed subjects for all causes and for lung cancer mortality. Adjustment for smoking habit and other occupational exposures (asbestos, coal and stone dusts, coal tar and pitch, gasoline exhausts) reduced the stength of the association between lung cancer and total mortality and DE exposure. If exposed subjects are divided by duration of exposure (13.1% of them did not report this information), a dose-response effect is suggested for lung cancer mortality, but not for total mortality (Table V).

Table VI shows the risk of lung cancer associated with DE exposure in the different smoking categories. These data suggest an additive rather than a multiplicative interaction between DE and smoking.

Lung Cancer Mortality and Selected Occupations Related to DE Exposure

Railroad worker, truck driver, and heavy equipment operator were the job categories most frequently exposed to DE in our cohort (Table VII). They were analyzed in more detail, together with the miners, some of whom can be heavily exposed to DE as indicated by other studies [Steenland, 1986]. A preliminary analysis

TABLE VI. Relative Risk and No. of Deaths (N) for All Causes of Death and for Lung Cancer (by Diesel Exhaust [DE] Exposure and Smoking)*

	Nonsmokers	Exsmokers	Current smokers
DE unexposed			
RR	1.00 (–)[a]	1.53 (1.42–1.63)	2.32 (2.15–2.49)
N	1,115	2,868	1,827
All causes			
DE exposed			
RR	1.18 (.97–1.43)	1.80 (1.56–2.08)	2.71 (2.32–3.16)
N	189	549	429
Chi-square goodness-of-fit test for interaction			
Additive model	Chi-square (2 d.f.) = 0.4, $p > .10$		
Multiplicative model	Chi-square (2 d.f.) = 6.6, $p > .025$		
DE unexposed			
RR	1.00 (–)[a]	7.53 (5.32–10.66)	17.99 (13.15–24.08)
N	25	318	315
Lung cancer			
DE exposed			
RR	1.73 (.60–4.95)	11.06 (6.27–19.53)	19.82 (11.20–35.07)
N	7	85	78
Chi-square goodness-of-fit test for interaction			
Additive model	Chi-square (2 d.f.) = 3.2, $p > .10$		
Multiplicative model	Chi-square (2 d.f.) = 6.0, $p > .025$		

*RR controlled for age and other occupational exposures. In parentheses, 95% test-based confidence intervals.
[a]Reference category: Nonsmokers not exposed to DE, with no regard to occupation.

TABLE VII. Diesel Exhaust Exposure by Occupation

Occupation[a]	No. of subjects	Diesel exhaust exposure (%) Yes	No	Not stated
Railroad worker	1,828	49.7	34.0	16.3
Truck driver	9,738	47.0	33.4	19.6
Heavy equipment operator	613	46.5	36.4	17.1
Farmer	22,571	45.7	33.5	20.9
Fireman	2,026	36.3	37.2	26.6
Auto mechanic	13,399	28.2	46.8	25.1
Shipyard worker	211	24.6	40.3	35.1
Foreman	5,626	21.3	50.0	28.7
Construction worker	6,843	20.8	54.3	24.9
Welder	2,145	20.2	45.9	33.9
Laborer	398	17.3	53.5	29.1
Policeman	4,202	14.9	61.9	23.2
Machine operator	6,203	14.9	54.3	30.7
Steel mill operator	1,683	14.7	46.4	38.9
Military	4,654	14.6	66.2	19.2
Electrician	6.598	14.6	60.0	25.5
Miner	1,233	14.4	41.4	44.2
All others specified	281,275	8.7	74.1	17.2
Unspecified[b]	105,402	11.9	61.7	26.4
All categories	476,648	13.5	65.9	20.6

[a]Main job during life. Only categories with over 100 subjects and proportion of exposed over 13.5 are listed separately.
[b]Eleven thousand four hundred sixty-one unemployed included.

TABLE VIII. Relative Risk for Lung Cancer in Selected Occupations

Occupation[a]	No. of subjects[b]	No. of deaths	RR-MH[c]	95% CI
Railroad worker	2,973	14	1.59	(0.94–2.69)
Truck driver	16,208	48	1.24	(0.93–1.66)
Heavy equipment operator	855	5	2.60	(1.12–6.06)
Miner	2,034	15	2.67	(1.63–4.37)

[a]Any period during life.
[b]No. of subjects in the job categories are higher than in Table VII, because any employment is considered here, while in Table VII only the current job—or the job held for the longest period during life—was considered. Reanalysis of this table according to the criteria of definition of job used in Table VII does not produce different results.
[c]Reference category: subjects with occupation different from those listed and not exposed to DE. RR controlled by age and smoking, according to Mantel-Haenszel method.

showed no increase in risk among farmers. Therefore, they were not investigated further.

Table VIII shows the mortality for lung cancer in these four occupational categories: the reference category consists of subjects with other occupations and unexposed to DE. All-cause mortality was also elevated among railroad workers (RR 1.43, 95% confidence internal [CI]: 1.20–1.72), heavy equipment operators (1.70, 1.19–2.44), miners (1.34, 1.06–1.68), and truck drivers (1.19, 1.07–1.31). A further analysis restricted to truck drivers only showed a similar lung cancer risk among those reporting DE exposure (RR = 1.22, 95% CI: 0.77–1.95, 18 cases) and those

who did not report DE exposure (RR = 1.19, 95% CI: 0.74–1.89, 18 cases; the remaining 12 lung cancer cases among truck drivers had no information on DE). When truck drivers unexposed to DE are used as a reference category, no overall association with DE (RR = 1.03) is shown, but if duration of DE exposure for truck drivers is analyzed, a dose-response effect is shown (duration 1–15 years: RR = 0.87, 95% CI: 0.33–2.25, six exposed cases; duration 16+ years: RR = 1.33, 95% CI: 0.64–2.75, 12 exposed cases; reference category unexposed truck drivers). Other occupational categories have been excluded from this step because too few exposed cases were observed.

Mortality for Other Causes and DE Exposure

An analysis regarding mortality of exposed subjects for each major cause of death, after adjustment for age, smoking, and other occupational exposures, using unexposed subjects, without regard to occupation, as reference group, is shown in Table IX. Results on mortality for lung cancer and for all causes are almost identical with results in Table IV; the difference is explained by the different measures of association (incidence density ratio in Table IV, cumulative incidence ratio in Table IX). Mortality for all malignant tumors (ICD-9 140–208) was nonsignificantly in excess: RR = 1.07, 95% CI: 0.97–1.17. No deaths from chronic bronchitis were observed; 1.6 were expected according to the rate among unexposed. Significant ($p < .05$) excesses of deaths were observed in the following categories: cerebrovascular disease (ICD-9 430–438), arteriosclerosis (ICD-9 440) pneumonia and influenza (ICD-9 480–489), cirrhosis of the liver (ICD-9 571), and accidents (ICD-9 E800–E949, E970–E999).

DISCUSSION

The population under study is not representative of the adult male U.S. population: CPS-II subjects are healthier and less frequently exposed to important risk factors such as smoking and alcohol. The mortality ratio for all causes in the male CPS-II cohort is 58, compared to the total U.S. white male population. External comparisons on the occurrence of disease and death are therefore inappropriate, but the internal comparisons upon which the foregoing analyses are based are not affected strongly by selection biases.

Quality of information on exposure is a major problem in self-administered questionnaires. To assess the accuracy of the information on occupational exposures in this cohort, an analysis was performed on a well-established association: asbestos and lung cancer. After controlling for age, smoking, and other occupational exposures, a RR of 1.5 (95% CI: 1.2–1.8) was found for exposure to asbestos. This result is lower than the risk of lung cancer among workers heavily exposed to asbestos, such as insulation workers, as cited in the literature [Hammond et al., 1979], and it is similar to the risk found among shipyard workers [Blot et al., 1978; Blot et al., 1980] who had mainly indirect exposure to asbestos. When duration of exposure to asbestos is analyzed, however, no evidence of a trend with duration is suggested. Two other checks on self-reported information on occupational exposures to substances without evidence of lung carcinogenicity showed no increased risk of lung cancer among the exposed—RR for exposure to pesticides and herbicides: 1.11 (95% CI: 0.84–1.46, 55

TABLE IX. Diesel Exhaust Exposure and Mortality for Selected Causes

Cause of death	ICD-9	No. of deaths	RR[a]
Ischemic heart disease	410–414	398	0.98
Hypertensive heart disease	401–405	21	1.34
Other heart disease	390–398, 415–429	75	0.94
Cerebrovascular disease	430–438	62	1.61*
Arteriosclerosis	440	10	3.12*
Other vascular disease	441–459	15	0.72
Diabetes mellitus	250	13	1.03
Emphysema	492	10	1.21
Chronic obstructive pulmonary disease	496	23	1.18
Pneumonia and influenza	480–489	14	1.97*
Other pulmonary disease	460–479, 490–491, 493–495, 500–519	5	0.43
Cirrhosis of liver	571	18	1.79*
Other digestive disease	520–570, 572–579	12	0.71
Genitourinary disease	580–629	7	0.95
Accidents	E800–E949, E970–E999	46	1.56*
Suicide, homicide	E950–969	15	0.63
All other causes[b]	001–139, 210–246, 251–389, 680–779	28	0.93
Ill-defined causes	780–799	10	3.44*
Non-Hodgkin lymphomas and Hodgkin's disease	200–202	20	0.92
Multiple myeloma	203	14	1.21
All leukemias	204–208	17	1.29
Esophagus cancer	150	7	0.61
Stomach cancer	151	16	0.86
Colon cancer	153	41	1.03
Rectum cancer	154	10	0.98
Liver and bile ducts cancer	155–156	7	1.13
Pancreas cancer	157	27	1.39
Lung cancer	162	174	1.17
Melanoma	172	11	1.67
Prostate cancer	185	33	0.93
Bladder cancer	188	13	1.04
Other urinary organs cancer	189	14	1.18
Brain cancer	191	12	0.90
Cancer of all other specified sites	140–149, 152, 158–161, 163–171, 173–174, 186, 187, 190, 192–194	26	0.78
Cancer of unspecified sites	199	18	1.03
All malignant tumors	140–208	460	1.07
All other causes	001–139, 210–799, E800–E999	782	1.05
All causes		1,242	1.06

[a]Relative risks, standardized by age, smoking, other occupational exposures. Reference category, subjects unexposed to diesel exhaust, with no regard to occupation.
[b]Ill-defined causes and malignant tumors excluded.
*$P < .05$.

exposed cases); RR for exposure to dyes: 0.93 (95% CI: 0.55–1.57, 14 exposed cases).

The high proportion of individuals whose DE exposure status is unknown could introduce a substantial bias in the estimate of the association. This possibility is reinforced by the fact that they experienced a higher mortality—for all causes as well as for lung cancer—than both the exposed and the unexposed groups (RR for total mortality: 1.2 and RR for lung cancer: 1.4; reference category: unexposed subjects). A very conservative estimate of the effect of this bias is given by an alternative RR, in which all subjects with unknown exposure status are considered unexposed and are added in the reference category. The results of this analysis are as follows: RR (all causes): 0.98 (95% CI: 0.91–1.04); RR (lung cancer): 1.03 (95% CI: 0.86–1.23). This value is a lower limit of the estimate of the RR for exposed subjects. The assessment of the outcome (living status and cause of death) was carried out in a very accurate way: only 0.8% of subjects were lost at follow-up, and the death certificate was obtained for all dead individuals; 8.7% of subjects stated they were sick at the date of the enrollment (89.7% were not sick, and 1.5% did not answer that question). Restriction of the analysis to nonsick people, however, does cause only minor modifications of RRs for exposure to DE: RR (all causes): 1.06 (95% CI: 0.97–1.17); RR (lung cancer): 1.20 (95% CI: 0.92–1.56). This shows that illness at time of enrollment was not a source of recall bias (exposure overreported by cases aware of lung cancer), that may introduce nondifferential misclassification.

Medical information provided by death certificates has been criticized [Comstock and Markush, 1986]. Cancers noted on death certificates in CPS-II are routinely checked by histological confirmation from physicians or cancer registries (less frequently from hospitals). Up to now, 24.1% of all cancer deaths have been verified, and the accuracy of the cause of death recorded in death certificates is very high: for lung cancer the specificity was 98.3%, and the sensitivity was 93.3% (the actual sensitivity might be slightly lower, because some lung cancers might have been recorded on death certificate as non-neoplastic disease, and therefore were not checked).

The association between DE and lung cancer was confounded by age, smoking, and other occupational exposures (such as asbestos). The age-adjusted RR was 1.41 (95% CI: 1.19–1.66). After controlling for smoking only it showed a decrease to 1.31 (95% CI: 1.10–1.54). The relative risk for smoking and lung cancer found in this analysis (Table VI) is high in comparison with findings of other large prospective studies [U.S. Department of Health, Education and Welfare, 1979] and the previous ACS Cancer Prevention Study [Hammond, 1966]. The full explanation of this result requires further analyses and is beyond the scope of the present report.

After the confounders have been controlled for, an excess risk of about 20% still remains. This result is similar to that from the Hall and Wynder [1984] case-control study (RR = 1.4, 95% CI: 0.8–2.4, controlling for smoking). The dose-response effect (Table V) and the higher risk among nonsmokers and exsmokers (Table VI) support the suggestion of a causal association among DE and lung cancer.

This analysis also shows an association between employment as miner or as heavy equipment operator and lung cancer mortality; a weak, nonsignificant effect for railroad workers and truck drivers was present; a small dose-response effect was also suggested for truck drivers. These results were partially concordant with previous studies [Leupker and Smith, 1978; Milne et al., 1983; Rushton et al., 1983; Howe et

al., 1983; Schenker et al., 1984; Wong et al., 1985; Morton and Treyve, 1982; Menck and Henderson, 1976; Williams et al., 1977; Garshick et al., 1987].

Diesel exposure was significantly associated with several other causes of death. An association with mortality from accidents was found in Leupker and Smith's study on truck drivers [1978]. The higher risk of dying from accidents in the group exposed to DE in this study is largely explained by the confounding effect of those occupations that have a high proportion of DE-exposed subjects and a high death rate from accidents: looking at subjects in occupations with high DE exposure rates listed in Table VII (railroad workers through miners), there is only a small and nonsignificant increase of risk of dying from accidents associated with DE exposure (RR 1.28, 95% CI: 0.72–2.25).

The association with cerebrovascular disease has not been reported in previous studies: in this analysis, a dose-response effect is also present: RR for duration of DE exposure 1–15 years: 1.43 (95% CI: 0.89–2.29); RR for duration over 15 years: 1.68 (95% CI: 1.06–2.66). A possible explanation of this result might involve the high level of carbon monoxide in diesel exhaust. Gasoline engine exhausts may have carbon monoxide concentration as high or higher than DE exhausts; however, in this study, the relative risk for death from cerebrovascular disease among auto mechanics likely to be exposed to gasoline as well as diesel engines exhausts, was not elevated (RR = 0.84, 95% CI: 0.48–1.49, 12 cases among 12,951 automechanics; reference category: other occupations, excluding those listed in Table VIII), and further investigations are needed on this subject to reach a conclusion about a causal link.

No association was found between DE exposure and mortality for non-neoplastic pulmonary diseases. A problem of lack of statistical power is likely to be present here: the power to detect an increase of 50% in the mortality rate from chronic obstructive lung disease in this analysis was slightly lower than 60%, and other pulmonary diseases are even rarer. Further analysis, with a larger cohort, or a longer period of follow-up are needed before excluding a causal association.

Nor was an association found between DE exposure and bladder cancer mortality. An analysis by duration of DE exposure showed no dose-response effect: RR for duration of DE exposure 1–15 years: 1.43 (95% CI: 0.61–3.33, seven exposed cases); RR for duration over 15 years: 0.94 (95% CI: 0.35–2.51, five exposed cases). Several recently published case-control studies on bladder cancer showed an increase in risk associated with DE exposure (odds ratios [OR] between 1.7 and 2.8) [Howe et al., 1980; Wynder et al., 1985] or with related occupations: truck driving (OR between 1.5 and 2.5) [Silverman et al., 1983; Hoar and Hoover, 1985; Silverman et al., 1986], railroad work (OR between 1.9 and 9.0) [Howe et al., 1980; Silverman et al., 1983], and taxi and bus driving [Silverman et al., 1986]. This analysis had a power of about 85% to detect a RR of 2 for bladder cancer among those ever exposed to DE but only a power of about 38% to detect the same association among those exposed 16 or more years to DE. Since most positive studies were restricted to subjects with long duration of exposure, the possibility of low power in this analysis cannot be dismissed. Mortality from Hodgkin's disease and lymphoid leukemia was increased among those exposed, in comparison with those unexposed. No excess was found for non-Hodgkin lymphomas or for leukemias other than lymphoid. An association between leukemia and railroad work has been suggested by one study [Schenker et al., 1984]. In the 1983 report on the 1967–1975 follow-up on workers at London Transport bus garages, a standardized mortality ratio of 151 for leukemia was reported [Rushton et al., 1983],

and a study on mortality of a cohort of heavy equipment operators indicated an increase in mortality for lymphoma and Hodgkin's disease [Wong et al., 1985]. Other studies did not confirm this association [Leupker and Smith, 1978; Howe et al., 1983; Williams et al., 1977]. Inference from the results of this analysis must be cautious, given the small number of deaths: four cases of Hodgkin's disease (ICD-9 201, RR = 3.8), nine cases of lymphoid leukemia (ICD-9 204, RR = 2.1).

The association between lung cancer and DE is plausible according to current biological and toxicological knowledge. The exact quantification of the risk of lung cancer associated with DE exposure is, as in the study of all "weak" associations, difficult for two main reasons: 1) exact quantification of the level of exposure, 2) identification of a true unexposed comparison group. Further analyses of the CPS-II cohort, with longer period of follow-up and increasing number of cases, can lead to more powerful analysis. This first analysis supported some evidence of a causal association between DE exposure and lung cancer. The association between DE and several other outcomes represents an original finding.

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance of Margaret Mushinski and Melody Davis in organizing and training researchers and managing the quantities of data. We especially thank the 77,000 American Cancer Society volunteers for their role in data collection. Richard Hayes, Paolo Vineis, Kyle Steenland, and Benedetto Terracini provided useful comments and advice.

REFERENCES

Blot WJ, Harrington JM, Toledo A, Hoover R, Heath CW, Fraumeni JF (1978): Lung cancer after employment in shipyards during World War II. N Engl J Med 299:620–624.

Blot WJ, Morris LE, Stroube R, Tagnon I, Fraumeni JF (1980): Lung and laryngeal cancers in relation to shipyard employment in Coastal Virginia. JNCI 65:571–575.

Comstock GW, Markush RE (1986): Further comments on problems in death certification. Am J Epidemiol 124:180–181.

Fleiss JL (1981): "Statistical Methods for Rates and Proportions." New York: Wiley.

Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Woskie SR, Hammond K, Speizer FE (1987): A case-control study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 135:1242–1248.

Hall NEL, Wynder EL (1984): Diesel exhaust exposure and lung cancer: A case-control study. Environ Res 34:77–86.

Hammond EC (1966): Smoking in relation to the death rates of one million men and women. Natl Cancer Inst Monogr 19:127–204.

Hammond EC, Selikoff IJ, Seidman H (1979): Asbestos exposure, cigarette smoking and death rates. Ann NY Acad Sci 330:473–490.

Harris JE (1981): "Potential Risk of Lung Cancer From Diesel Engine Emissions. Report to the Diesel Impacts Study Committee, Assembly of Engineering, National Research Council." Washington: National Academy Press.

Higgins ITT (1984): Air pollution and lung cancer: Diesel exhaust, coal combustion. Prev Med 13:207–218.

Hoar SK, Hoover R (1985): Truck driving and bladder cancer mortality in rural New England. JNCI 74:771–774.

Howe GR, Burch JD, Miller AB, Cook GM, Esteve J, Morrison B, Gordon P, Chambers LW, Fodor G, Winsor GM (1980): Tobacco use, occupation, coffee, various nutrients, and bladder cancer. JNCI 64:701–713.

Howe GR, Fraser D, Lindsay J, Presnal B, Yu SZ (1983): Cancer mortality (1965-77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. JNCI 70:1015-1019.

International Agency for Research on Cancer (1973): "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Volume 3. Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds." Lyon: IARC.

International Agency for Research on Cancer (1983): "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Volume 32. Polynuclear Aromatic Compounds, Part 1, Chemical, Environmental and Experimental Data." Lyon: IARC.

Kleinbaum DG, Kupper LL, Morgenstern H (1982) "Epidemiologic Research: Principles and Quantitative Methods." New York: Van Nostrand.

Kotin P, Falk H, Thomas M (1955): Aromatic hydrocarbons. Arch Ind Health 11:113-120.

Leupker RV, Smith ML (1978): Mortality in unionized truck drivers. J Occup Med 20:677-682.

Mantel N (1963): Chi-square tests with one degree of freedom; extensions of the Mantel-Haenszel procedure. J Am Stat Assoc 58:690-700.

Mantel N, Haenszel W (1959): Statistical aspects of the analysis of data from retrospective studies of disease. JNCI 22:719-748.

Menck HR, Henderson BE (1976): Occupational differences in rates of lung cancer. J Occup Med 18:797-801.

Miettinen O (1976): Estimability and estimation in case-referent studies. Am J Epidemiol 103:226-235.

Milne KL, Sandler DP, Everson RB, Brown SM (1983): Lung cancer and occupation in Alameda County: A death certificate case-control study. Am J Ind Med 4:565-575.

Morton WE, Treyve EL (1982): Histologic differences in occupational risks of lung cancer incidence. Am J Ind Med 3:441-457.

Pepelko WE, Peirano WB (1983): Health effects of exposure to diesel engine emissions. A summary of animal studies conducted by the U.S. Environmental Protection Agency's Health Effects Research Laboratories at Cincinnati, OH. J Am Coll Toxicol 2:253-306.

Rushton L, Alderson MR, Nagarajah CR (1983): Epidemiological survey of maintenance workers in London transport executive bus garages and Chiswick works. Br J Ind Med 40:340-345.

Schenker MB (1980): Diesel exhaust—an occupational carcinogen? J Occup Med 22:41-46.

Schenker MB, Smith T, Munoz A, Woskie S, Speizer F (1984): Diesel exposure and mortality among railway workers: Results of a pilot study. Br J Ind Med 41:320-327.

Silverman DT, Hoover RN, Albert S, Graff KM (1983): Occupation and cancer of the lower urinary tract in Detroit. JNCI 70:237-245.

Silverman DT, Hoover RN, Mason TJ, Swanson GM (1986): Motor exhaust-related occupations and bladder cancer. Cancer Res 46: 2113-2116.

Steenland K (1986): Lung cancer and diesel exhaust: A review. Am J Ind Med 10:177-189.

Thomas DC, Whittemore AS (1988): Methods for testing interactions, with applications to occupational exposures, smoking, and lung cancer. Am J Ind Med 13:131-147.

U.S. Department of Health, Education, and Welfare (1979): "Smoking and Health: A Report of the Surgeon General." Washington: U.S. Department of Health, Education, and Welfare.

Wei E, Shu H (1983): Nitroaromatic carcinogens in diesel soot: A review of laboratory findings. Am J Ind Hyg 9:1085-1088.

Williams RR, Stengens NL, Goldsmith JR (1977): Associations of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. JNCI 59:1147-1185.

Wong O, Morgan RW, Kheifets L, Larson SR, Whorton MD (1985): Mortality among menbers of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. Br J Ind Med 42:435-448.

Wynder EL, Dieck GS, Hall NEL, Lahti H (1985): A case-control study of diesel exposure and bladder cancer. Environ Res 37:475-489.

Wynder EL, Higgins ITT (1986): Exposure to diesel exhaust emissions and the risk of lung and bladder cancer. In Ishinishi N, Koizumi A, McClellan RO, Stoeber W (eds): "Carcinogenic and Mutagenic Effects of Diesel Engine Exhaust." Dublin: Elsevier, pp 489-501.