Crump successfully replicated Garshick's major findings. He reproduced the original finding of increased lung cancer mortality risk related to the subject's age in 1959 and to cumulative exposure defined dichotomously, as described above (see discussion of Railroad Retirement Board Cohort Study: Garshick and Colleagues 1988) and in Table 4. Crump compared lung cancer mortality with the job held in 1959, which corresponded to the career exposure groups defined by Woskie and associates (1988a,b; and Table 2). He found increased lung cancer mortality among engineers and firemen (RR = 1.7, 95% CI 1.2, 2.4) and among brakemen, conductors, and hostlers (RR = 1.6, 95% CI 1.2, 2.1) ages 40 through 44 in 1959, whose presumed exposures and potential induction times were the greatest when compared with the unexposed clerks and signal maintainers. However, the expected inverse relation with age in 1959 was not present for the brakemen, conductors, and hostlers. In addition, among shopworkers, the group with the highest estimated exposures, the risk elevations were smaller than those for the unexposed clerks and signal maintainers, presumably the less-exposed jobs (e.g., RR = 1.1, 95% CI 0.8, 1.6 for shop workers ages 40 through 44 in 1959). These latter observations were interpreted by Crump as evidence against an effect of diesel exhaust. However, Garshick (1991) notes that exposure misclassification might well explain these apparent inconsistencies.[9]

Crump also discovered an important limitation of the data. Whereas Garshick and associates (1988) had compared lung cancer mortality rates only between exposed and unexposed railroad workers within the cohort, Crump also compared the lung cancer mortality of the cohort to that of the U.S. population; this comparison revealed evidence that deaths that occurred between 1976 and 1980 had been underascertained by the Railroad Retirement Board. This underascertainment did not affect the major findings because analyses limited to the years 1959 through 1976 still revealed excess lung cancer mortality risk.[10] However, this discovery implies that reanalyses of these data, particularly analyses of induction time, might well be compromised because the data from the later, and potentially most informative, years of follow-up are incomplete. It is clear that future follow-up of this important cohort will need to use more reliable sources of mortality data (e.g., the National Death Index) in addition to, or instead of, the Railroad Retirement Board.

Table 5. Lung Cancer Relative Risk Estimates for the Railroad Retirement Board Case-Control Study[a]

	Diesel-Years of Cumulative Exposure (cases/controls)			
Relative Risk	0 (120/272)	1–10 (45/77)	11–19 (53/122)	20 (117/166)
Younger Workers				
Crude	(1.0)	1.36	0.99	1.60
Age-adjusted	(1.0)	1.10	1.28	1.39
		(NA)	(NA)	(1.05, 1.83)
Age-, smoking-, asbestos-adjusted	(1.0)	1.11	1.29	1.41
		(NA)	(NA)	(1.06, 1.88)
Older Workers				
Crude	(1.0)	1.09	1.03	0.93
Age-adjusted	(1.0)	1.01	1.01	1.02
Age-, smoking-, asbestos-adjusted	(1.0)	0.97	0.93	0.91
				(0.71, 1.17)
	Diesel-Years of Cumulative Exposure			
		0–4	5–19	20+
Younger Workers				
Age-, smoking-, asbestos-adjusted		(1.0)	1.02	1.64
			(0.72, 1.45)	(1.18, 2.29)

[a] Data are from Garshick et al. (1987). NA = not available.

When Crump attempted to use the average respirable particulate levels for railroad worker job categories estimated by Woskie and colleagues (1988a,b) to calculate relative risks, the results were difficult to interpret. Crump constructed several different exposure metrics that combined measures of particulate levels with information on regional climate for the various areas of the U.S., and used these metrics and age to fit 50 regression models to the lung cancer data. All but two models showed inverse relations between lung cancer mortality and the various exposure metrics; that is, the subjects with the highest estimated exposures had the lowest risk of lung cancer mortality. He attributed these surprising findings to inadequate exposure data.[11] As he noted in his report, "... there are many limitations in using the data on markers of diesel exposure ... to estimate exposure in the cohort of railroad workers studied by Garshick.... These limitations are potentially of sufficient magnitude to obscure any relationship between exposure to [diesel exhaust] and lung cancer that might exist in the cohort" (Crump et al. 1991).

Canadian Railroad Workers

The RRB studies corroborate the results of an earlier study of Canadian railroad workers. Howe and colleagues (1983) studied the mortality of 43,826 retired male pensioners of the Canadian National Railway Company from 1965 through 1977. Individuals were classified as unexposed, possibly exposed, and probably exposed to diesel exhaust, though neither the jobs included in each category nor any further details of the classification scheme were described. No information was collected on cigarette smoking. The investigators observed a standardized mortality ratio (SMR) for lung cancer in the entire cohort of 1.06 (95% CI 0.99, 1.13) relative to the Canadian male population. Relative risks comparing possibly and probably exposed workers with unexposed workers were calculated as the ratios of their respective SMRs: 1.23 for possibly exposed workers and 1.40 for probably exposed workers. Excluding from the analysis individuals who were likely to have been exposed to asbestos left the results basically unchanged. The apparent effect of diesel exhaust exposure on lung cancer mortality may have been due to confounding by cigarette smoking; indeed, the authors note that certain other smoking-related causes of death were elevated.

National Institute for Occupational Safety and Health Teamsters Study

Steenland and colleagues (1990) conducted a case-control study of lung cancer mortality in the Central States Teamsters Union. Cases and control subjects were selected from among 10,699 male union members who died in calendar years 1982 and 1983 and who had filed for pension benefits. Cases (n = 1,288) comprised all deaths from lung cancer, defined as an underlying or contributing cause of death coded as ICD 162 or ICD 163. Control subjects (n = 1,452) consisted of every sixth death in the decedents file. Deaths from cancer of the lung or bladder and motor vehicle accidents were excluded as control subjects. As with the RRB case-control study, nonmalignant respiratory disease deaths were included as control subjects, but the likely effect of their inclusion is small for the reasons discussed above.[12]

Diesel exhaust exposure was ascertained from two sources. Interviews with the next of kin were conducted with family members of 82% of cases and 80% of control subjects to obtain a life-long work history. Study subjects were classified according to the job category in which they had worked the longest: diesel truck driver, gasoline truck driver, driver of both types of trucks, truck mechanic, or dockworker (i.e., people who work on truck loading docks and in warehouses). Subjects who had never worked in any of the above categories were defined as unexposed to diesel exhaust. The second source of exposure information consisted of Teamsters Union pension applications completed by the study subjects, which listed each occupation, employer, and dates of employment. As with the data provided by next of kin, study subjects were categorized according to the job held the longest: long-haul drivers, short-haul or city drivers, truck mechanics, and dockworkers. The Teamsters Union work histories indicated that most subjects had worked in only one job category. The Teamsters Union data provided no information on the type of truck driven. The concordance between exposure classification based on Teamsters Union records and the next-of-kin data was generally high, but varied among job categories.[13] Information on the amount and duration of cigarette smoking was obtained from the next of kin, as was information on asbestos exposure and diet.

When exposure was considered as a dichotomous variable (i.e., ever employed in any of the index job categories versus nonexposed), imprecise elevations were seen in all major categories except dockworkers (Table 6). Teamsters Union work histories for the period beginning in 1959 were used to characterize exposure because the industrial hygiene study had revealed that dieselization was complete in the trucking industry by approximately 1960. Relative risk estimates appear to increase with duration of employment after 1959 for both long- and short-haul truckers, although the individual estimates are imprecise;[14] and a similar but less pronounced pattern was discerned in analyses based on the length of employment as a driver of diesel trucks, using job histories provided by the next of kin. Employment as a diesel truck driver for 35 or more years

Table 6. Lung Cancer Relative Risk Estimates for Teamsters Union Job Categories

Job Category[a]	Elemental Carbon[b] ($\mu g/m^3$)	Crude Estimate[c] (cases)	Adjusted Estimate[d] (95% CI)
Unexposed[e]	1.1-2.5[f]	(1.0) (45)	(1.0)
Truckers:			
Long-haul	3.8	1.68 (609)	1.27 (0.83, 1.93)
City	4.0	1.51 (121)	1.31 (0.81, 2.11)
Mechanics	12.1	2.25 (50)	1.69 (0.92, 3.09)
Dockworkers	13.8	1.27 (70)	0.92 (0.55, 1.55)
Other exposed	NA	1.15 (99)	1.44 (0.88, 2.39)

[a] From Steenland et al. (1990), Table 1. Teamsters Union data, jobs ever held.

[b] From Zaebst et al. (1991), Table III. Geometric mean submicrometer elemental carbon levels.

[c] From Steenland et al. (1990), Table 1. Teamsters Union data.

[d] Adjusted for age, smoking, and asbestos exposure using logistic regression. From Steenland et al. (1990), Table 2.

[e] Reference category.

[f] Range of background levels (residential and highway background) from Zaebst et al. (1991), Table III.

was associated with an 89% increase in lung cancer mortality (RR = 1.89, 95% CI 1.04, 3.42), although this estimate is quite imprecise. The same relation between duration of employment and excess lung cancer mortality was not evident for mechanics (Table 7), although apparent increases in lung cancer mortality were observed in all categories of duration of employment as a truck mechanic after 1959, with the highest risk observed for 12 to 17 years (RR = 2.1, 95% CI 0.78, 5.52).[15]

More recently, Steenland and colleagues (1992) discussed the case-control study results in the context of a National Institute of Occupational Safety and Health (NIOSH) industrial hygiene survey of the jobs included in the teamsters study. Present-day levels of elemental and organic carbon associated with each job were measured (Zaebst et al. 1991). Elemental carbon measurement is considered to be the most specific method for determining diesel exhaust particle levels (see background papers by Watts and by Busby and Winer, this report). Steenland and colleagues noted that the elemental carbon measurements are generally consistent with the epidemiologic results (Table 6) in that mechanics have the highest exposures and the highest relative risk, followed by long-haul and local drivers.[16] The elemental carbon results for the dockworkers are apparently inconsistent with the epidemiologic findings. Diesel-powered forklifts, however, were introduced in the

Table 7. Lung Cancer Relative Risk Estimates[a] and 95% Confidence Intervals by Duration of Employment in Selected Job Categories

	Years of Employment Since 1959			
Teamsters Job Category[b]	0[c]	1–11	12–17	18+
Long-haul driver	(1.0)	1.08 (0.68, 1.70)	1.41 (0.90, 2.21)	1.55 (0.97, 2.47)
Short-haul driver	(1.0)	1.11 (0.61, 2.03)	1.15 (0.63, 2.43)	1.79 (0.94, 3.92)
Truck mechanic	(1.0)	1.83 (0.80, 4.19)	2.08 (0.78, 5.52)	1.50 (0.59, 3.40)
	Total Years of Employment			
Next-of-Kin Job Category[d]	0[c]	1–24	25–34	35+
Diesel truck driver	(1.0)	1.27 (0.70, 2.27)	1.26 (0.74, 2.16)	1.89 (1.04, 3.42)
Truck mechanic	(1.0)	1.69 (0.61, 4.67)	1.39 (0.63, 3.07)	1.09 (0.44, 2.66)

[a] Adjusted for age, smoking, and asbestos exposure using logistic regression. From Steenland et al. (1990).

[b] From Steenland et al. (1990), Table 3.

[c] Reference category.

[d] From Steenland et al. (1990), Table 4.

United States in the 1980s—too short an interval for any carcinogenic effect to have been detected in this study. The present-day elemental carbon levels for truckers do not differ greatly from highway background levels (Table 6); however, truckers spend a larger proportion of their time on and around the highway than nontruckers. Moreover, levels of diesel exhaust in the truck cabs may have been higher in years past due to differences in the design of exhaust systems (Ziskind et al. 1977; Steenland 1986). If one can assume that the relative exposure rankings as indicated by the elemental carbon measurements have remained constant over time, then the industrial hygiene study results support the exposure classification used in the epidemiologic study. As noted above, however, the industrial hygiene measurements were not made on the actual study subjects and reflect contemporary conditions, not the conditions that may have obtained 10 to 30 years before; thus, making a more quantitative inference is difficult.

Steenland notes that exposure to asbestos, presumably occurring during the relining of brakes, may account for some of the observed effect of diesel exhaust exposure in the mechanics, despite attempts at analytic control. The likely extent of such confounding is difficult to estimate, but is probably small.[17]

Other reviewers (Wynder and Higgins 1986; Boffetta et al. 1990) have suggested that differences in diet between truckers and the general population might account for the excess lung cancer observed among truckers. Steenland collected data from the next of kin on the dietary habits of participants in his study. Whereas he observed an inverse relation between the consumption of certain fruits and vegetables and lung cancer risk, dietary habits did not confound the apparent effects of diesel exhaust exposure. Although the reliability of proxy data on diet might be questioned (Samet 1990), Steenland did corroborate the inverse association of fruit and vegetable consumption with lung cancer risk reported by others using more reliable tools (International Agency for Research on Cancer 1990).

Like the studies of the railroad workers discussed above and most epidemiologic studies of diesel exhaust exposure, the study by Steenland and colleagues does not report relative risks for various time intervals after initial exposure. Therefore, the magnitude of the effect among truckers and mechanics, whom one might predict have the highest risks, is unknown.

Swedish Bus Garage Workers

Gustavsson and colleagues (1990) evaluated lung cancer mortality and incidence in a cohort of 695 men who worked as mechanics, servicemen, or hostlers in any of the five bus garages in Stockholm for at least six months between 1945, when the bus companies converted to diesel-powered vehicles, and 1970. Mortality from 1952 through 1986 and cancer incidence from 1958 through 1984 were ascertained from local and national registries.

Industrial hygienists developed a semiquantitative scale for past exposure to diesel exhaust using detailed historical data on bus and fuel characteristics, ventilation in the bus garages, and work practices. The authors provide few details, however, about how they used this information to estimate exposure intensity. Each period of a subject's work history was assigned an exposure intensity score on a six-level scale of intensity. Cumulative exposure was calculated by multiplying the exposure score by the duration in years for every work period in the work history and then summing over the entire history. The investigators divided cumulative exposure into four strata (0 to 10, 10 to 20, 20 to 30, and greater than 30 units). To estimate asbestos exposure, the investigators devised a three-level exposure scale, similar to that for diesel exhaust, using contemporary personal sampling data collected during brake repair operations in the Stockholm bus garages as well as information on similar exposures collected elsewhere. No information was collected on the smoking habits of study subjects.

The investigators compared the cohort's lung cancer mortality rate to an expected rate based on Stockholm's occupationally active population. They observed a 22% excess based on 17 observed deaths (SMR = 1.22, 95% CI 0.71, 1.96) (Table 8). The SMRs did not increase with cumulative exposure, although the standardized mortality difference (SMD), a measure of the absolute excess, did increase.[18] It is not clear whether the occupationally active population of Stockholm included professional and other white-collar (e.g., clerical and administrative) workers. If so, then the small apparent excess may reflect differences in lung cancer mortality rates between social classes due to factors unrelated to diesel exhaust exposure.

Gustavsson and colleagues also conducted a nested case-control study of the cohort that included all individuals identified from either the mortality or incidence records as having primary lung cancer (ICD code 162.1). Six control subjects per case, age-matched within two years, were selected at random from the cohort. Relative risk estimates for three levels of exposure to diesel exhaust were derived from logistic regression models that controlled for both age and asbestos exposure. The relative risk associated with exposure to more than 30 units was 2.4 (95% CI 1.32, 4.47); relative risks of 1.3 (95% CI 1.09, 1.64) and 1.8 (95% CI 1.20, 2.71) were observed for 10 to 20 units and 20 to 30 units of cumulative exposure, respectively (Table 8).

The absence of information on cigarette smoking is the most apparent limitation of this study. The bus garage workers in

the case-control study, however, constitute a socioeconomically homogenous group whose smoking habits would not be expected to differ markedly according to diesel exhaust exposure. Under these conditions, confounding by cigarette smoking sufficient to explain greater than twofold increases in lung cancer occurrence among the most exposed would be unlikely (Axelson 1978).[19] Furthermore, for cigarette smoking to explain fully the observed pattern of apparent diesel exhaust effects over ordered categories of cumulative exposure, the smoking-induced effects must be not only present but also directly correlated with exposure. Levin and colleagues (1990) found that the potential of confounding by cigarette smoking to explain a pattern of monotonically increasing lung cancer risk with duration of employment was minimal, even when the smoking-related relative risks were assumed to be 20 times higher in smokers than in nonsmokers.

Gustavsson and colleagues' study of Swedish bus garage workers provides the first evidence that occupational exposure to diesel exhaust may be associated with lung cancer in bus garage workers. Neither the British Transport Executive Workers studies (Raffle 1957; Waller 1981; Rushton et al. 1983) nor a Swedish study (Edling et al. 1987) found any indication of increased lung cancer occurrence of the magnitude observed by Gustavsson and colleagues, but all these studies were limited by poor exposure characterization,[20] as well as insufficient exposure duration (Raffle 1957; Rushton et al. 1983), populations at low risk of mortality (e.g., active employees) (Waller 1981), and small study size (Edling et al. 1987).

Swedish Marine Dockworkers

Mechanization of work on the Swedish marine docks began in the late 1950s and, over the next decade, led to increasing exposures of dockworkers to diesel exhaust. Diesel-powered vehicles were used increasingly to load and unload freight, entailing exposure to exhaust both on the docks and in the enclosed holds of ships (Gustafsson et al. 1986; Ulfvarson et al. 1987). Two studies, described below, examine the relationship of lung cancer incidence to diesel exhaust exposure in Swedish marine dockworkers.

Cohort Study: Gustafsson and Colleagues (1986). Gustafsson and colleagues (1986) studied cancer incidence and mortality in a cohort of Swedish dockworkers employed for at least six months before 1974. The cohort was assembled from the records of employers and trade unions. Employment as a dockworker was the only information on diesel

Table 8. Cohort and Nested Case-Control Studies of Lung Cancer and Diesel Exhaust Exposure Among Swedish Bus Garage Workers[a]

	Index of Cumulative Diesel Exhaust Exposure			
Cohort Study	0–10	10–30	30+	Total
Observed deaths	5	5	7	17
Expected deaths	5.2	3.3	5.5	13.9
Person-years of follow-up	11,078	5,673	4,567	21,318
Expected rate	47×10^{-5}	58×10^{-5}	120×10^{-5}	65×10^{-5}
Standardized mortality ratio	0.97	1.52	1.27	1.22
Standardized mortality difference	-2.0×10^{-5}	30×10^{-5}	33×10^{-5}	15×10^{-5}

	Index of Cumulative Diesel Exhaust Exposure			
Nested Case-Control Study	0–10	10–20	20–30	30+
Cases	5	2	3	10
Control subjects	45	15	18	42
Crude relative risk	(1.0)	1.20	1.50	2.14
Adjusted relative risk	(1.0)	1.34 (1.09, 1.64)	1.81 (1.20, 2.71)	2.43 (1.32, 4.47)

[a] Gustavsson et al. (1990).

exhaust exposure used in the analysis. No information on cigarette smoking was available. Cancer incidence and mortality were ascertained from national cancer and mortality registries. Standardized morbidity and mortality ratios were calculated using incidence and mortality rates of the Swedish male population based on age and calendar period. A total of 6,063 dockworkers who were alive and free of cancer as of January 1, 1961, were followed until January 1, 1980, death, or cancer diagnosis. The standardized incidence ratio (SIR) for all cancers combined was 1.10 (95% CI 1.01, 1.20, 452 cases), due mainly to excess lung cancer (SIR = 1.68, 95% CI 1.36, 2.07, 86 cases). Lung cancer mortality was also elevated (SMR = 1.32, 95% CI 1.05, 1.66). The average length of employment and the maximum time since first employment were both approximately 20 years.

Case-Control Study: Emmelin and Colleagues (1993). Emmelin and colleagues (1993) conducted a nested case-control study of lung cancer among Swedish male dockworkers in the cohort studied by Gustafsson and colleagues. They used information on diesel exhaust exposure and smoking habits to evaluate further the apparent association between lung cancer and occupation as observed in the cohort study. Review of national data bases on cancer incidence and mortality revealed that 90 cases of lung cancer had occurred in the cohort between 1960 and 1982. Four control subjects were matched to each case based on seaport and date of birth. Ultimately, 50 cases and 154 control subjects were included in the study, after excluding (1) cases among workers at seaports for which data used to estimate exposure were unavailable, (2) control subjects (and their matched cases) who were discovered not to meet study criteria, and (3) subjects with incomplete information on employment dates and smoking history.

The investigators derived three indices of exposure to diesel exhaust from employment records and records of annual fuel consumption by diesel-powered vehicles, and used them to estimate the exposures of the study subjects. A fuel-per-person index was calculated as the ratio of annual fuel consumption and the number of persons employed in that year. A second index, exposed time, indicated if the fuel-per-person index for a given year exceeded the lower quartile of its distribution in the entire data set. The latter two indices were entered in a calendar time–exposure matrix to derive estimates of cumulative fuel consumption and exposed time for each subject. A third measure, machine time, was calculated as the duration of employment from year of hire or the introduction of diesel-powered vehicles, whichever occurred later. Exposure duration for each case subject and matched control subjects was truncated at two years prior to the date of the case's diagnosis. In the data analysis, each of the three exposure indices was classified as low, medium, or high based on the lower and upper quartiles of their respective cumulative distributions.

Information on past and current smoking was obtained from two sources: questionnaires mailed to either the subjects themselves or their next of kin, and interviews with either foremen or workers who had worked with the subjects. Response to the mailed questionnaire was low for both cases and control subjects (67% and 66%, respectively), but information from interviews was available for 95% of the subjects. Analysis of the concordance of questionnaire and interview data revealed that the interview data misclassified some ex-smokers as "neversmokers," although those who were misclassified had quit many years before. When the data were discordant, the investigators used the questionnaire data to analyze exposure effects. For data analysis, subjects were classified as smokers or nonsmokers; ex-smokers were classified as nonsmokers only if they had quit at least five years prior to diagnosis.

For each of the three exposure indices, the relative risk estimates relative to nonsmokers with low exposure and adjusted for cigarette smoking history using logistic regression for matched case-control data were elevated for medium and high exposure and increased in monotonic fashion; the highest relative risk estimates were observed in analyses based on exposed time, with a relative risk estimate of 6.8 (95% CI 1.3, 34.9) observed for those with high exposure (although measured with considerable imprecision as indicated by the wide confidence interval) (Table 9). The investigators examined the sensitivity of the results to alternative exposure category boundaries and the method of control selection and found nearly identical results. The results displayed more sensitivity to alternative means of classifying smoking. When the investigators excluded the 36% of subjects without a next-of-kin interview (assumed to be the most authoritative source of smoking information), the relative risk estimates for medium- and high-exposure time were reduced to 0.9 and 4.1, respectively.

Emmelin and colleagues also estimated the extent to which cigarette smoking and diesel exhaust exposure acted together to increase the rate of lung cancer. To do so, they calculated relative risks for subjects classified according to smoking and estimated exposure to diesel exhaust relative to a reference group of subjects who never smoked and were exposed to diesel exhaust at the lowest level (Table 9). The investigators observed that cigarette smoking combined with the highest level of diesel exhaust exposure multiplied the rate of lung cancer in the reference group 28-fold, a greater-than-additive increase ($28 > 6.2 + 2.9$, the values for

smokers without exposure and for nonsmokers with exposure, respectively). The authors estimated that diesel exhaust exposure, both independent of and in combination with smoking, accounted for about 50% of the lung cancers in the dockworkers. These analyses are very statistically imprecise, however, because they are based on only six nonsmoking case subjects.

U.S. Heavy Construction Equipment Operators

Wong and colleagues (1985) assembled a cohort of 34,156 members of a heavy construction equipment operators union and compared mortality rates with the national population. Fifty percent of the person-years were contributed by cohort members who, on the basis of partial work histories, were classified as having high diesel exhaust exposure (scraper, dozer, loader, and backhoe operators). Because these equipment operators presumably worked outdoors most of the time, their diesel exhaust exposure levels were probably lower than those in some other occupational groups (e.g., bus garage workers, dockworkers, and certain railroad workers). No adjustments were made for cigarette smoking. Lung cancer mortality was not elevated in the cohort as a whole (SMR = 0.98, 95% CI 0.88, 1.10), nor for the high-exposure group (SMR = 0.94, 95% CI not available). Workers with no available exposure history, however, had excess mortality (SMR = 1.19, 95% CI 1.0, 1.41), as did those with greater than a 20-year duration of union membership (SMR = 1.07, 95% CI 0.91, 1.25), those with greater than 20 years latency (SMR = 1.12, 95% CI 0.97, 1.29), and retirees (SMR = 1.64, 95% CI 1.39, 1.92).

Table 9. Relative Risk Estimates and 90% Confidence Intervals by Categories of Exposure Duration[a] and Cigarette Smoking in Swedish Dockworkers[b]

Low Exposure, Nonsmoker	Medium[c] Exposure	High[c] Exposure	Smoker[d]
(1.0)	2.7 (0.6, 11.3)	6.8 (1.3, 34.9)	6.2 (2.6, 14.6)

	Low	Medium	High
Nonsmokers	(1.0)	1.6 (0.2, 12.5)	2.9 (0.2, 39.0)
Smokers	3.7 (0.9, 14.6)	10.7 (1.5, 78.4)	28.9 (3.5, 240)

[a] Low = 0 yr, medium = 1–5 yr, high = 6–16 yr.

[b] Data are from Emmelin et al. (1993), Tables 3 and 5.

[c] Adjusted for smoking.

[d] Adjusted for diesel exposure.

GENERAL POPULATION STUDIES

Montreal Case-Control Study

Siemiatycki and colleagues (1988) conducted a population-based case-control study in Montreal to evaluate the relation between cancer at several sites and occupational exposure to a wide variety of substances, including diesel exhaust. The complete study was published as a monograph (Siemiatycki 1991), and the results relating various cancers and exposure to 10 types of combustion products, including diesel exhaust, were published separately (Siemiatycki et al. 1988). Investigators interviewed 3,726 male cancer patients, ages 35 to 70 years, in 19 Montreal hospitals (82% response rate) and collected a detailed occupational history. A team of chemists and industrial hygienists then used these histories to estimate exposure to various substances.[21] Siemiatycki (1991) reported that work in occupations considered (in the aggregate) to entail exposure to diesel exhaust was associated with a 10% increase in lung cancer (RR = 1.1, 90% CI 0.9, 1.3), and "substantial exposure" (defined as a cumulative exposure index greater than the median) was associated with a 20% increase (RR = 1.2, 90% CI 0.9, 1.7), after adjustment for age, cigarette smoking, and other factors. The largest overall relative risk was for squamous cell cancer (47% of all lung cancers in this study) (RR = 1.2, 90% CI 1.0, 1.5) (Siemiatycki et al. 1988).

Although Siemiatycki and colleagues coded the occupational histories in detail, jobs were aggregated in ways that make direct comparison with other published studies difficult and may have obscured associations. For example, the occupational category "railway transport workers" comprised only 7% (12 subjects) of the cases and 3% (12 subjects) of the control population considered to have been exposed to diesel exhaust, but the estimated relative risk of lung cancer in this category is 1.4 for any exposure (90% CI 0.6, 3.1) and 1.6 for substantial exposure (90% CI 0.5, 4.6). This value is higher than that for the aggregate and comparable to those from the U.S. RRB and Canadian cohort studies, although far less precise (J. Siemiatycki, personal communication). Some of the railroad jobs considered as exposed in the RRB studies are contained in the category of "railway transport workers," although the more highly exposed shopworkers are not. Similarly, results for truck drivers are subsumed in the category "motor transport workers," of which they compose 32% (Siemiatycki 1991). Whereas no increased risk of lung cancer was observed (RR = 0.9, 90% CI 0.7, 1.1) for the category "motor transport workers,"

drivers of heavy-duty (chiefly diesel) trucks had estimated relative risks of 1.27 (90% CI 0.72, 2.25) for those who drove for 20 or more years, 1.15 (90% CI 0.60, 2.21) for 10 to 19 years of driving, and 1.05 (90% CI 0.65, 1.67) for 1 to 10 years of driving, adjusted for smoking, age, and ethnicity (J. Siemiatycki, personal communication). The relative risk estimates are lower than those from the teamsters study, although the analyses of the teamsters data were more specific, defining exposure as duration of employment after 1959, when diesel trucks had become more prevalent. Siemiatycki (1991) reported a relative risk of 3.1 (90% CI 1.2, 8.0) for dockworkers,[22] a similar result to that reported by Emmelin and colleagues (1993) for Swedish marine dockworkers. Like Sweden, but unlike the United States, diesel equipment had been used for decades in the port of Montreal.

American Cancer Society Cohort Study

Boffetta and colleagues (1988) reviewed the two-year mortality of a cohort of 461,981 male volunteers ages 40 to 79 assembled by the American Cancer Society. Information on occupation and cigarette smoking was also obtained by questionnaire. Cohort members were asked to list their current occupation, last occupation (if retired), and the job held for the longest period of time. Jobs were coded according to an ad hoc classification scheme into broad occupational categories. The investigators queried participants about regular occupational and nonoccupational exposures to diesel exhaust and 11 other substances (e.g., asbestos and gasoline exhaust). Exposure prevalence was low: only 17% of the total person-time was considered exposed, and occupational groups with diesel exposure corroborated by industrial hygiene data (e.g., truckers and railroad workers) contributed only 3.4% and 0.06% of the person-time, respectively.

Detailed smoking histories were obtained and used to classify participants into five strata: neversmokers; ex-cigarette smokers; current smokers using less than 20, or 20 or more cigarettes per day; and pipe and cigar smokers. Preliminary information on vital status was obtained via questionnaire and verified by examining the death certificates.

The age-adjusted relative risk for self-reported diesel exhaust exposure (irrespective of occupation) was 1.41 (95% CI 1.19, 1.66), which fell to 1.31 (95% CI 1.10, 1.54) with control for smoking. Further adjustment for other occupational exposures (e.g., asbestos) reduced the relative risk to 1.18 (95% CI 0.97, 1.44). Lung cancer mortality appeared to increase with duration of diesel exhaust exposure (irrespective of occupation): relative risks of 1.05 (95% CI 0.80, 1.39) and 1.21 (95% CI 0.94, 1.56) were observed for 1 to 15 years and 16 or more years of exposure, respectively.

Misclassification of exposure may have produced considerable underestimates of effect. More than half the occupations classified as exposed were judged to have entailed only possible, as opposed to probable, diesel exhaust exposures (Boffetta et al. 1990). Actual exposures may have been negligible among many persons in several of the most frequently reported occupations in the "possible exposure" category.

Analyses by occupation, adjusted for age and smoking, revealed elevated relative risks for participants who had ever held jobs as railroad workers (RR = 1.59, 95% CI 0.94, 2.69) or truck drivers (RR = 1.24, 95% CI 0.93, 1.66). Truck drivers who reported driving diesel trucks for less than 16 years had a relative risk of 0.87 (95% CI 0.33, 2.25) relative to truckers who reported no exposure, whereas those who reported 16 or more years of exposure had a relative risk of 1.33 (95% CI 0.64, 2.75).

American Health Foundation 1990 Study

Boffetta and colleagues (1990) conducted a case-control study of diesel exhaust exposure and lung cancer in the combined patient populations of 18 hospitals in six U.S. cities. The investigators studied 2,584 male cases of histologically confirmed lung cancer diagnosed between 1977 and 1987, and 5,099 control subjects with admitting diagnoses considered unrelated to tobacco use, who were matched to the cases by age within two years, hospital, and year of interview. Information on cigarette smoking, diet, usual occupation, and other factors was ascertained via questionnaires administered in the hospital at the time of diagnosis. In 1985, the questionnaire was modified to collect additional information on usual occupation and up to five additional jobs, including information on duration. Occupations were classified as entailing probable, possible, or no exposure to diesel exhaust. Participants were also queried about occupational and nonoccupational exposure to 45 groups of chemicals, including diesel exhaust. As in the American Cancer Society cohort study, and for identical reasons, appreciable misclassification of exposure was probable, with its attendant bias to the null. Exposure prevalence was low in this study as well: only 15.6% of control subjects were ever employed in an exposed job, and only 6.4% were employed in a job considered probably exposed; truck drivers constituted only 3.5% of control subjects.

Probable diesel exhaust exposure based on the usual job held and probable exposure based on usual employment as a truck driver were each associated with crude 31% increases in lung cancer mortality. After adjustment for cigarette smoking, age, and other factors, the relative risks decreased to 0.95 (95% CI 0.78, 1.16) and 0.88 (95% CI 0.67, 1.15), respectively. When analyses were conducted using

only the more detailed exposure information collected since 1985 (477 cases, 946 control subjects), self-reported diesel exhaust exposure was associated with a 20% increase in lung cancer (RR = 1.21, 95% CI 0.73, 2.02). Analyses by duration of self-reported exposure suggested an increase in relative risks with duration of exposure, with relative risks of 0.90 (95% CI 0.40, 1.99), 1.04 (95% CI 0.44, 2.48), and 2.39 (95% CI 0.87, 6.57) reported for 1 to 15, 16 to 30, and 31 or more years, respectively, although the individual estimates are very imprecise. An analysis by duration of employment as a truck driver found relative risks of 1.83 (95% CI 0.31, 10.73), 0.94 (95% CI 0.41, 2.15), and 1.17 (95% CI 0.40, 3.41) for 1 to 15, 16 to 30, and 31 or more years, respectively.

The absence of a readily interpretable trend in these data, in contrast to the findings of the teamsters study, may be due to the lack of specificity of the exposure metric. A comparison of truckers who reported diesel exhaust exposure with those who did not yielded a relative risk of 1.25 (95% CI 0.85, 2.76). Relative risks of 1.59 (95% CI 0.81, 3.13), 1.30 (95% CI 0.61, 2.79), and 2.02 (95% CI 0.81, 5.01) can be derived for railroad workers, heavy equipment mechanics, and warehousemen (roughly analogous to dockworkers in the teamsters study), respectively, from the published data, although these estimates are unadjusted for age and smoking.

American Health Foundation 1984 Study

Hall and Wynder (1984) reported the results of a case-control study of 502 histologically confirmed lung cancer cases, ages 20 to 80, at 18 U.S. hospitals. Control subjects matched by age, race, and hospital were selected from patients with diseases considered unrelated to tobacco use. Subjects were interviewed to obtain information on usual lifetime occupation, tobacco smoking history, and demographic factors.

Diesel exhaust exposure for each occupation was estimated as the proportion of exposed workers in each occupation, using information provided by NIOSH and the 1970 U.S. Census. Occupations with at least 20% of their members exposed were classified as high exposure, those with 10% to 19% as moderate exposure, and those with less than 10% as low exposure. In addition, the relative risks for usual employment in certain occupations considered to entail "probably high exposure" were estimated.

The relative risk for diesel exhaust exposure regardless of occupation and adjusted for smoking was 1.4 (95% CI 0.8, 2.4). The unadjusted relative risks for high and moderate exposures were 1.7 (95% CI 0.6, 4.6) and 0.7 (95% CI 0.4, 1.3), respectively. Relative risks for truck drivers and railroad workers, unadjusted for smoking, were 1.4 (95% CI 0.7, 2.6) and 2.6 (95% CI 0.5, 12.8), respectively.

New Mexico Study of Lung Cancer in the General Population

Lerchen and colleagues (1987) conducted a case-control study of lung cancer incidence and occupation in the 1980 to 1982 New Mexico general population. Occupational and smoking histories for 506 cases of lung cancer, identified by the New Mexico Tumor Registry, and 771 control subjects, sampled from residential phone directories and rosters of Medicare subscribers, were obtained from the subject or proxy respondent. Exposure to a variety of substances, including diesel exhaust, was ascertained. Next of kin provided the information on exposure and cigarette smoking for almost half the cases but only 2% of control subjects, and the authors acknowledged the possibility of differential misclassification of exposure.

The investigators examined the relation of occupation, characterized as having ever been employed in a specific occupation, in relation to lung cancer risk, including several occupations considered to entail exposure to diesel exhaust. Underground miners (RR = 2.1, 95% CI 1.1, 3.7, 31 exposed cases), paving equipment operators (RR = 1.6, 95% CI 0.5, 5.0, 7 exposed cases), and people employed in local and suburban passenger transportation (RR = 1.9, 95% CI 0.8, 4.5, 16 exposed cases) appeared to be at increased risk. Diesel engine mechanics, however, appeared to be at decreased risk (RR = 0.6, 95% CI 0.2, 2.0, 5 exposed cases). No results were reported for truck drivers or railroad workers. Given the high prevalence of truck driving in virtually all other general population-based studies, its apparent absence here is remarkable.

The investigators reported a decreased risk for an aggregate of industries and occupations that were determined to entail diesel exhaust exposure (RR = 0.6, 95% CI 0.2, 1.6, 7 exposed cases). Even if one considers the results reported above for underground miners as indicative solely of the effect of radon exposure, it is not clear why so few subjects were considered as exposed to diesel exhaust in this analysis.

Other Studies

Other general population studies—e.g., Williams and coworkers (1977), Damber and Larsson (1985), Hayes and associates (1989), and Burns and Swanson (1991)—report increased relative risks among occupational groups exposed to diesel exhaust (Table 1).

DISCUSSION

The general population studies are consistent with the occupational cohort and nested case-control studies in that they indicate small elevations in lung cancer rates among railroad workers (Figure 1), truckers (Figure 2), mechanics, and dockworkers, although most estimates are based on small numbers of exposed subjects. Those estimates that were controlled for cigarette smoking all gave similar results. Many of the occupation-specific estimates are imprecise and statistically compatible with no effect of exposure, which is to be expected given the low prevalence of employment in the specific occupations in the general population studies.

All the general population studies estimate the relative risk of lung cancer associated with self-reported employment in any occupation considered to entail exposure to diesel exhaust. In general, these analyses are subject to considerable classification errors because they group occupations with documented exposure (e.g., truckers, truck mechanics, and certain railroad workers) with occupations that entail unknown, perhaps minimal, exposure. This was evident even in the carefully designed Montreal case-control study discussed above (Siemiatycki et al. 1988; Siemiatycki 1991). Not surprisingly, the relative risks for such aggregated exposure groups are low, generally about 1.2 (Figure 3).

CONCLUSION

The studies reviewed above suggest that exposure to diesel exhaust in a variety of occupational circumstances is associated with small to moderate relative increases in lung cancer occurrence and/or mortality. These elevations do not appear to be fully explicable by confounding due to cigarette smoking or other sources of bias. Therefore, at present, exposure to diesel exhaust provides the most reasonable explanation for these elevations. The association is most apparent in studies of occupational cohorts, in which assessment of exposure is better and more detailed analyses have been performed. The largest relative risks are often seen in the categories of most probable, most intense, or longest duration of exposure. In general population studies, in which exposure prevalence is low and misclassification of exposure poses a particularly serious potential source of bias in the direction of observing no effect of exposure, most studies indicate increased risk, albeit with considerable imprecision. As noted above, inaccurate methods of exposure assessment and incomplete data analyses make it difficult to quantify precisely the magnitude of effects associated with exposure to diesel exhaust, particularly effects of high or prolonged exposure evaluated after long induction periods.

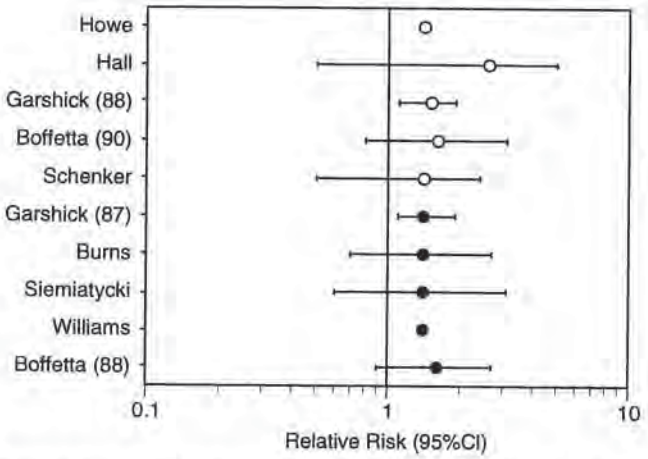

Figure 1. Lung cancer and exposure to diesel exhaust in railroad workers. ● = RR adjusted for cigarette smoking; ○ = RR not adjusted for cigarette smoking. For the two studies by Howe and Williams, CIs were not reported and could not be calculated.

Despite the well-founded concern that confounding by cigarette smoking might explain the apparent exposure-related elevations in lung cancer risk, most studies that controlled for smoking found that the associations with exposure persisted after such control was applied. It could be argued that the control of confounding was inadequate, either due to the use of data from proxy respondents or to insufficiently detailed smoking data. However, proxy respondents (i.e., particularly close relatives) have been found to provide generally accurate assessments of the smoking habits of study subjects (McLaughlin et al. 1987). Studies that used relatively

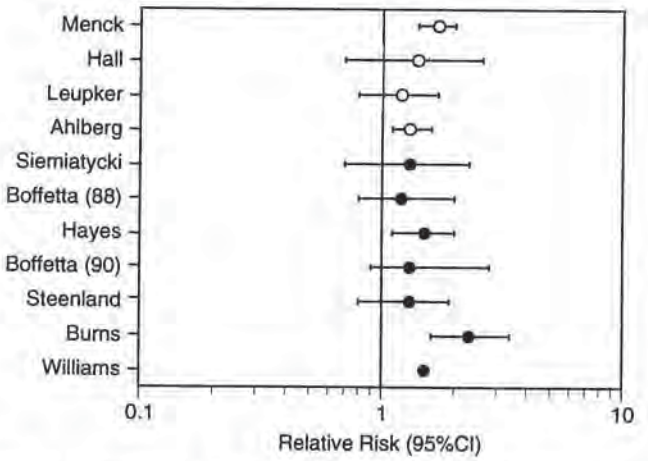

Figure 2. Lung cancer and exposure to diesel exhaust in truck drivers. ● = RR adjusted for cigarette smoking; ○ = RR not adjusted for cigarette smoking. For the study by Williams, CIs were not reported and could not be calculated. For the Steenland study, the data were gathered from union reports of long-haul truckers; for the Boffetta (1988) study, the data were self-reported by diesel truck drivers; and for the Siemiatycki study, they were self-reported by heavy-duty truck drivers (personal communication).

detailed smoking data (e.g., Garshick et al. 1987 and Steenland et al. 1990) found that exposure-related excesses remained. We have argued that confounding by cigarette smoking is not a convincing explanation for the risk elevations observed in two occupational cohort studies (Garshick et al. 1988; Gustafsson et al. 1990) that obtained no information on cigarette smoking. Though our arguments are quantitative and based on plausible patterns of confounding, they are hypothetical and more subject to uncertainty than direct information under some circumstances (Steenland 1986).

It is important to bear in mind that risk elevations of the magnitude observed in the general population studies (i.e., 20% or less) should not be overinterpreted. For example, inaccuracies of exposure measurement, discussed above, could either spuriously elevate risk, or, if measurement error was nondifferential with respect to disease status (as is most likely), could underestimate the true relative risk.

OTHER CANCERS

OCCUPATIONAL COHORTS

Canadian and U.S. Railway Workers

As previously described, Howe and colleagues (1983) and Schenker and colleagues (1984) conducted retrospective cohort studies of the mortality of Canadian and U.S. railroad workers. Both studies compared the cohorts' cancer mortality rates with national rates.

The highest relative risk estimate in each study was for kidney cancer, which was the only cancer elevated in both cohorts (Table 10). The estimates from the Canadian study, which was notably large, are very precise. Only one-fourth of the person-time was contributed by men classified as probably exposed, however, so bias from exposure misclassification could have caused an underestimation of the relative risk. Less potential for exposure misclassification bias existed in the U.S. study, in which 70 percent of the person-time was contributed by men classified as exposed (high plus low exposure).

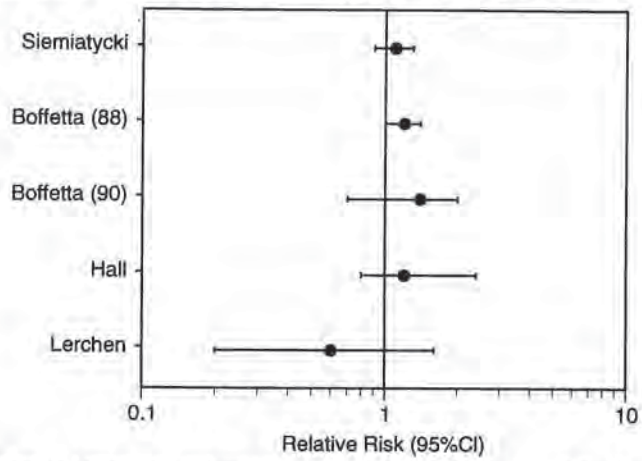

Figure 3. Lung cancer and exposure to diesel exhaust for aggregated diesel-exposed jobs.

Swedish and English Bus Garage Workers

As noted above, the 695 men in the cohort assembled by Gustavsson and colleagues (1990) worked for at least six months as mechanics, servicemen, and hostlers in Stockholm bus garages. Gustavsson and colleagues compared this cohort's cancer incidence with national cancer rates and to cancer mortality rates for all Stockholm residents. We report only the incidence analyses because they are based on superior diagnostic information and are not influenced by differences in survival.

The 8,684 men in the Rushton and colleagues (1983) cohort study discussed above worked as maintenance men for at least one continuous year at 71 London Transport bus garages and the engineering works at Chiswick. This study included only mortality, with comparisons based on national rates.

No elevated cancer rates were observed in either study (Table 11). Kidney cancer, which was elevated in the two railway workers studies, was not elevated among the Swedish bus garage workers and was not reported in the English study, presumably because the observed number was zero.

These two studies were both small, as indicated by the numbers of observed cancers and the width of the confidence intervals for the relative risk estimates (Table 11). However, all members of the Swedish cohort spent at least six months working indoors while diesel engines were running, and the working conditions for the English cohort were probably comparable. Thus, bias from exposure misclassification should have been minimal. About 40 percent of the person-time of observation in the Swedish study was contributed by men in the intermediate and high categories of a diesel exhaust exposure index, which the authors did not use for analyses of specific cancers other than lung cancer.

U.S. Heavy Construction Equipment Operators

Liver cancer was the only specific cancer that appeared to be elevated in the cohort of heavy equipment operators studied by Wong and colleagues (1985) (Table 12). Analyses by duration of employment and latency did not produce appreciable increases in the relative risk estimates. The four jobs constituting the high-exposure category were analyzed separately, making an informative summary impossible.

Table 10. Observed Deaths, Relative Risks, and 95% Confidence Intervals for Cancers Other Than Lung Cancer Among U.S.[a] and Canadian[b] Railway Workers

	United States (1967–1979)			Canada (1965–1977)		
Cancer	Observed Deaths	Relative Risk	95% CI	Observed Deaths	Relative Risk	95% CI
Stomach	4	0.7	0.2, 1.7	362	0.9	0.8, 1.0
Colorectal	15	0.9	0.5, 1.5	556	1.0	0.9, 1.1
Kidney	6	1.7	0.6, 3.6	58	1.3	1.0, 1.7
Bladder	3	0.8	0.2, 2.2	175	1.0	0.9, 1.2
Brain	5	1.3	0.4, 3.1	38	1.1	0.8, 1.5
Leukemia	7	1.5	0.6, 2.9	97	0.8	0.7, 1.0
Lymphatic	6	1.0	0.4, 2.1	150	1.1	0.9, 1.3

[a] Data are from Schenker et al. (1984).

[b] Data are from Howe et al. (1983).

GENERAL POPULATION STUDIES

American Cancer Society Cohort Study

In the study described earlier, Boffetta and colleagues (1988) compared cancer mortality rates in a cohort of U.S. men that was divided based on judgments about the diesel exhaust exposure in their longest-term occupations. The highest estimated relative risks were for malignant melanoma and pancreatic cancer (Table 13).

Most of the relative risk estimates from this study are moderately precise, and potential confounding by cigarette

Table 11. Observed Deaths, Relative Risks, and 95% Confidence Intervals for Incidence of Cancers Other Than Lung Cancer Among Swedish Bus Garage Workers[a] and for Mortality from Cancers Other Than Lung Cancer Among English Bus Garage Workers[b]

	Sweden (1958–1984)			England (1968–1975)		
Cancer	Observed Cases	Relative Risk	95% CI	Observed Deaths	Relative Risk	95% CI
Stomach	6	0.9	0.3, 2.0	26	1.0	0.7, 1.5
Colon	4	0.6	0.2, 1.6	10	0.8	0.4, 1.4
Rectal	4	0.9	0.2, 2.3	5	0.5	0.2, 1.1
Liver	2	0.9	0.1, 3.2	6	1.5	0.6, 3.0
Pancreatic	2	0.6	0.1, 2.1	9	0.9	0.5, 1.7
Prostate	15	1.0	0.5, 1.6	11	1.2	0.6, 2.1
Kidney	3	0.7	0.1, 2.0	NR[c]	NR	NR
Bladder	4	0.7	0.2, 1.7	12	1.4	0.8, 2.4
Brain	6	1.9	0.7, 4.2	7	1.2	0.5, 2.4
Leukemia	NR	NR	NR	7	1.5	0.7, 3.0
Hematopoietic system	6	0.8	0.3, 1.8	NR	NR	NR

[a] Data are from Gustavsson et al. (1990).

[b] Data are from Rushton et al. (1983).

[c] NR = not reported.

Table 12. Deaths, Relative Risks, and 95% Confidence Intervals for Cancers Other Than Lung Cancer Among U.S. Operators of Heavy Construction Equipment, 1964–1978[a]

Cancer	Deaths	Relative Risk	95% CI
Stomach	44	1.2	0.8, 1.6
Colon	66	0.9	0.7, 1.1
Rectal	12	0.5	0.2, 0.8
Liver	23	1.7	1.0, 2.5
Pancreatic	47	1.0	0.7, 1.3
Prostate	37	0.9	0.6, 1.2
Kidney	17	0.7	0.4, 1.2
Bladder	27	1.2	0.8, 1.7
Leukemia	25	0.8	0.5, 1.1
Lymphoma	28	0.9	0.6, 1.4

[a] Data are from Wong et al. (1985).

smoking was controlled. As noted above, however, exposure misclassification may have produced an appreciable bias toward underestimation of increased risks.

Case-Control Study of Multiple Cancers

As described earlier, Siemiatycki and colleagues (1988) conducted a case-control study of several cancers among Montreal men, using other cancer patients as control subjects. Chemists and industrial hygienists rated job histories, elicited by interview, with respect to diesel exposure. The study was fairly large, so the relative risk estimates were quite precise. The highest estimates in the initial analyses were for cancers of the colon and prostate (Table 14).

In more detailed analyses of these two cancers, high diesel exhaust exposures were defined as being in jobs that scored greater than the median value on an index combining "concentration, frequency, and the chemists' confidence that the exposure occurred" (Siemiatycki et al. 1988). Long exposures were defined as exposure in jobs lasting more than 10 years. For colon cancer and prostate cancer, long exposures—both high and low—were associated with higher relative risks (Table 15).

Case-Control Studies of Bladder Cancer

Thirteen case-control studies of bladder cancer provide at least some information pertinent to diesel exhaust exposure (Howe et al. 1980; Silverman et al. 1983, 1986; Coggon et al. 1984; Hoar and Hoover 1985; Smith et al. 1985; Vineis and Magnani 1985; Wynder et al. 1985; Iscovich et al. 1987; Jensen et al. 1987; Steenland et al. 1987; Risch et al. 1988; Brooks et al. 1992). The methods and study populations are highly diverse (Table 16). Seven studies were conducted in the United States, three in Europe, and the remainder in Canada and South America. Ten studies included incident cases, 10 based exposure assessment on interviews with subjects or proxies, and 11 controlled for cigarette smoking.

Table 13. Deaths, Relative Risks, and 95% Confidence Intervals for Cancers Other Than Lung Cancer Among U.S. Men Exposed to Diesel Exhaust, 1982–1984[a]

Cancer	Deaths	Relative Risk	95% CI
Stomach	16	0.9	0.5, 1.4
Colon	41	1.0	0.7, 1.3
Rectal	10	1.0	0.5, 1.8
Liver	7	1.1	0.5, 2.2
Pancreatic	27	1.4	0.9, 2.0
Prostate	33	0.9	0.6, 1.2
Kidney	14	1.2	0.7, 2.0
Bladder	13	1.0	0.6, 1.7
Brain	12	0.9	0.5, 1.5
Leukemia	17	1.3	0.8, 2.0
Lymphoma	20	0.9	0.6, 1.4
Malignant melanoma	11	1.7	0.8, 3.0

[a] Data are from Boffetta et al. (1988).

Table 14. Cases, Relative Risks, and 95% Confidence Intervals for Cancers Other Than Lung Cancer Among Montreal Men Exposed to Diesel Exhaust, 1979–1985[a]

Cancer	Exposed Cases	Relative Risk	95% CI
Esophagus	12	0.6	0.4, 0.9
Stomach	41	0.9	0.7, 1.1
Colon	68	1.3	1.1, 1.6
Rectosigmoid	39	1.1	0.8, 1.4
Rectal	35	1.1	0.9, 1.5
Pancreatic	15	0.6	0.4, 0.9
Prostate	86	1.2	1.0, 1.5
Kidney	29	0.9	0.7, 1.3
Bladder	82	1.0	0.8, 1.2
Malignant melanoma	17	1.1	0.7, 1.7
Non-Hodgkin's lymphomas	29	0.7	0.5, 1.0

[a] Data are from Siemiatycki et al. (1988).

Table 15. Cases, Relative Risks, and 95% Confidence Intervals for Colon and Prostate Cancers Among Montreal Men by Level of Diesel Exhaust Exposure, 1979–1985[a]

Cancer	Exposure Duration and Level	Cases	Relative Risk	95% CI
Colon	Short, low	6	0.7	0.3, 1.4
	Short, high	5	0.6	0.3, 1.3
	Long, low	27	1.5	1.0, 2.2
	Long, high	30	1.7	1.2, 2.5
	All combined	68	1.3	1.1, 1.6
Prostate	Short, low	8	1.1	0.5, 2.1
	Short, high	11	0.8	0.5, 1.5
	Long, low	21	1.5	0.9, 2.3
	Long, high	46	1.3	0.9, 1.7
	All combined	86	1.2	1.0, 1.5

[a] Data are from Siemiatycki et al. (1988).

Six of the control groups consisted of patients with diagnoses or causes of death other than bladder cancer, five were random samples of the study populations, and two consisted of neighbors of the cases. (One study used a control group composed of hospital patients and neighbors of cases.)

With few exceptions, these studies reported elevated relative risks of bladder cancer among persons who worked in jobs expected to entail exposure to diesel exhaust (Table 17 and Figures 4 and 5). In general, the relative risk estimates increased with greater duration of employment in exposed jobs (Silverman et al. 1983, 1986; Hoar and Hoover 1985; Jensen et al. 1987; Steenland et al. 1987), with more time since employment in exposed jobs (Risch et al. 1988), and when the analysis was based on the usual occupation rather than ever having been employed in an occupation associated with exposure (Silverman et al. 1986).

For the most part, the occupations classified as conferring diesel exhaust exposure in these studies were truck driver, railroad worker, and mechanic. Seldom was the distinction drawn between drivers of diesel- and gasoline-powered vehicles. When it was, the drivers of diesel vehicles did not always show the greatest increase in risk. Silverman and colleagues (1986), for instance, suggest a greater increase in risk among taxi drivers and chauffeurs, who would primarily operate gasoline-powered vehicles, than among drivers of trucks or buses, which are much more often diesel-powered (Table 17). As noted earlier, however,

Table 16. Methodologic Features of General Population Case-Control Studies of Bladder Cancer and Diesel Exhaust

Reference	Occurrence Measurement	Control Subjects[a]	Country	Source of Exposure Information	Smoking Controlled
Howe et al. 1980	Incidence	Neighbors of cases	Canada	Interviews	Yes
Silverman et al. 1983	Incidence	RDD, HCFA	United States	Interviews	Yes
Coggon et al. 1984	Mortality	Other deaths	England, Wales	Death certificates	No
Hoar and Hoover 1985	Mortality	Other deaths	United States	Interviews	Yes
Smith et al. 1985	Incidence	RDD, HCFA	United States	Interviews	Yes
Vineis and Magnani 1985	Incidence	Other patients	Italy	Interviews	Yes
Wynder et al. 1985	Incidence	Other patients	United States	Interviews	Yes
Silverman et al. 1986	Incidence	RDD, HCFA	United States	Interviews	Yes
Iscovich et al. 1987	Incidence	Other patients, cases' neighbors	Argentina	Interviews	Yes
Jensen et al. 1987	Incidence	Census sample	Denmark	Interviews	Yes
Steenland et al. 1987	Mortality	Other deaths	United States	City directories	No
Risch et al. 1988	Incidence	Census sample	Canada	Interviews	Yes
Brooks et al. 1992	Incidence	Other bladder cancer patients[b]	United States	Medical records	Yes

[a] RDD = random-digit dialing; HCFA = Health-Care Financing Administration.

[b] Low-grade or early-stage bladder cancer patients were used as control subjects for high-grade or late-stage bladder cancer patients.

trucker exposure to diesel exhaust may have depended both on the type of vehicle driven and the amount of time spent exposed to exhaust in the highway environment (e.g., both on the road and in truckstops).[23]

Zaebst and colleagues (1991) indicated that diesel mechanics have higher exposures to diesel exhausts, especially in colder weather, than do drivers of diesel trucks. The general population case-control studies of bladder cancer (Table 16) have comparatively little information on mechanics. Although vehicle mechanics are usually distinguished from other mechanics, the information is seldom specific enough to identify diesel mechanics separately. One might suspect that automobile mechanics, who predominantly work on gasoline engines, would greatly outnumber diesel mechanics among the vehicle mechanics in any general population case-control study. Thus, one would expect a substantial degree of bias toward underestimation of any effect of diesel exhaust in the results for vehicle mechanics reported in such studies.

DISCUSSION

Aside from lung cancer, only bladder cancer is a serious candidate for a possible causal link to diesel exhaust. When considered together, the cohort studies and the one case-control study of multiple cancers weakly suggest an increased risk of various other cancers. In contrast, the extensive literature of general population case-control studies points quite consistently toward an increased risk of bladder cancer among truck drivers and, less consistently and in fewer studies, among railroad workers and vehicle mechanics. The much smaller group of studies on diesel-exposed cohorts, however, suggests that such exposures create little or no increase in bladder cancer risk.

The cohort study of Swedish bus garage workers (Gustavsson et al. 1990) did not suggest an increased risk of bladder cancer; however, the mortality data from the English cohort study was more consistent with an increased risk. For the two cohorts combined, the bladder cancer relative risk was 1.1 (95% CI 0.7, 1.8). Thus, in the aggregate, the two studies do not indicate a pronounced increase in risk. The working conditions in bus garages arguably gave these cohorts a greater average degree of diesel exhaust exposure than in any group classified as exposed in the general population case-control studies.

The cohort studies of Canadian and U.S. railway workers (Howe et al. 1983; Schenker et al. 1984) and the cohort study of U.S. operators of heavy construction equipment (Wong et al. 1985) showed no elevation in bladder cancer risk. Arguably each of these cohorts contained relatively high proportions of men whose diesel exhaust exposures were probably low. Nevertheless, every member of that cohort would have been classified as a railroad worker in each case-control study that reported an elevated bladder cancer relative risk for that occupational category. In addition, the average exposure of the railway workers cohort may have been higher than in the groups of railroad workers identified in the case-control studies because all the Canadian cohort members worked in a relatively cold climate, which has been associated with higher diesel exhaust exposures (Woskie et al. 1988a,b), and worked long enough to earn pensions. Moreover, the Canadian railway worker study in particular is notably large and its relative risk estimate of 1.0 for bladder cancer is extremely precise, with an upper 95 percent confidence limit of only 1.2.

The apparent conflict between the case-control and cohort study results could be explained by attributing the

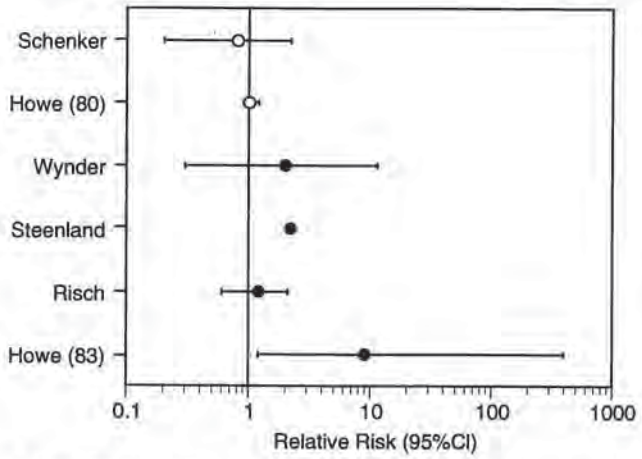

Figure 4. Bladder cancer and exposure to diesel exhaust in railroad workers. ● = Case control study; ○ = Cohort study. For the study by Steenland, CIs were not reported and could not be calculated.

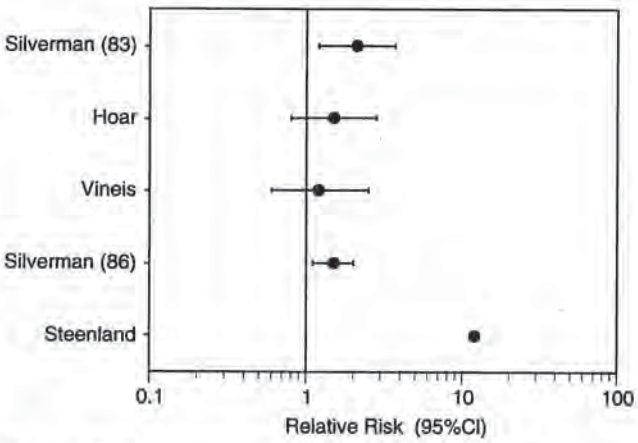

Figure 5. Bladder cancer and exposure to diesel exhaust in truck drivers. For the study by Steenland, CIs were not reported and could not be calculated.

absence of an increased risk in the cohort study of bus garage workers to statistical imprecision and the absence of increased bladder cancer risk in the cohort study of railway workers to bias from exposure misclassification. At least as tenable, however, is the hypothesis that some aspect of truck driving other than diesel exhaust exposure is associated with increased risk of bladder cancer. Silverman and colleagues (1986) raised the alternative hypothesis of urinary stasis brought on by delay of micturition, which could be common among professional highway drivers. The authors cited two previous studies in which persons with medical conditions that can cause urinary stasis were associated

Table 17. Cases, Relative Risks, and 95% Confidence Intervals for Measures of Occupational Diesel Exhaust Exposure from General Population Bladder Cancer Case-Control Studies

Reference	Occupation or Exposure	Cases	Relative Risk (95% CI)
Howe et al. 1980	Railroad worker	9	9.0 (1.2, 394.5)
	Diesel and traffic "fumes"	11	2.8 (0.8, 11.8)
Silverman et al. 1983	Truck driver	42	2.1 (1.2, 3.7)
	Deliveryman	41	1.8 (1.1, 3.3)
	Operated vehicle with diesel engine	13	11.9 (2.3, 61.1)
Coggon et al. 1984	Any exposure to diesel "fumes"	68	1.0 (0.7, 1.3)
	High exposure to diesel "fumes"	19	1.7 (0.9, 3.3)
Hoar and Hoover 1985	Truck driver	35	1.5 (0.9, 2.6)
	Diesel exposure in truck-driving job	26	1.5 (0.8, 2.8)
	Diesel fuel or engine exposure	14	1.8 (0.5, 7.0)
Smith et al. 1985	Auto or truck mechanic, smoker	NR[a]	1.2 (0.9, 1.6)
	Auto or truck mechanic, nonsmoker	NR	1.3 (0.8, 2.3)
Vineis and Magnani 1985	Truck driver ≥6 months	16	1.2 (0.6, 2.5)
Wynder et al. 1985	More than minimal diesel exhaust exposure	NR	0.9 (0.5, 1.6)
	Warehouseman, materials handler	2	0.8 (0.2, 4.1)
	Bus or truck driver	10	0.9 (0.4, 1.9)
	Railroad worker	2	2.0 (0.3, 11.6)
	Heavy equipment operator or mechanic	2	0.8 (0.2, 3.5)
Silverman et al. 1986	Truck driver or deliveryman (usual occupation)	99	1.5 (1.1, 2.0)
	Bus driver (usual occupation)	9	1.5 (0.6, 3.9)
	Taxi driver or chauffeur (usual occupation)	10	6.3 (1.6, 29.3)
Iscovich et al. 1987	Truck or railway driver	20	4.3 (NR)
Jensen et al. 1987	Bus, taxi, or truck driver	42	1.3 (1.0, 1.6)
Steenland et al. 1987	Truck driver (≥20 years)	6	12.0 (NR)
	Railroad worker (≥20 years)	22	2.2 (NR)
Risch et al. 1988	Railway occupations (8-28 years ago)	NR	1.2 (0.6, 2.1)
	Mechanic (8-28 years ago)	NR	1.0 (0.6, 1.5)
	Diesel or traffic "fumes" (8-28 years ago)	NR	1.7 (1.2, 2.3)
Brooks et al. 1992			
High-grade vs. low-grade tumors	Vehicle mechanic	5	1.2 (NR)
	Truck driver	14	2.7 (NR)
Late-stage vs. early-stage tumors	Vehicle mechanic	10	2.4 (NR)
	Truck driver	9	0.8 (NR)

[a] NR = not reported.

with increased bladder cancer risk. Another explanation might be potential biases in the selection of control subjects for the case-control studies. Control subject selection can pose subtle difficulties and has yet to be examined in great detail for these particular studies. Given the inconsistency between the case-control and cohort study results, and the lack of persuasive explanations for the absence of increased risks in the cohort studies, it would be best to characterize the present state of the epidemiologic evidence on diesel exhaust and bladder cancer as still in need of further development.

NONMALIGNANT RESPIRATORY DISEASE

Diesel exhaust exposure produces chronic changes in the lungs of laboratory animals (see background paper by Watson and Green, this report). It is plausible, therefore, that exposure to diesel exhaust might cause chronic nonmalignant respiratory disease. Several studies, described below, have examined the association of occupational exposure to diesel exhaust with respiratory morbidity and mortality.

Study of the epidemiology of chronic nonmalignant respiratory disease in relation to occupational exposure to diesel exhaust has suffered from methodologic problems that have plagued the field of respiratory epidemiology in general. Not the least of these has been the lack of precise and consistent definitions of disease. For example, the nonspecific term chronic obstructive pulmonary disease (COPD) is frequently used to refer to diseases characterized by persistent slowing of expiratory flow, but the term is also used to refer collectively to emphysema, chronic bronchitis, and associated conditions. Asthma may or may not be included under the COPD rubric, depending on whether it can be distinguished from other conditions, a distinction that is often impossible to make from mortality statistics or other commonly available data. An additional source of inconsistency is that estimates of morbidity and mortality are derived from diverse sources, such as death certificates, medical records, and subject self-reporting using standardized questionnaires. This latter problem has been minimized in epidemiologic studies by the use of standardized definitions proposed by the American College of Chest Physicians–American Thoracic Society in 1975 (Higgins and Thom 1989); however, current definitions still are not in good agreement with physicians' diagnoses. In general, this situation has probably led to the underascertainment of chronic respiratory diseases in national data bases and in epidemiologic studies using similar methods, such as review of death certificates.

STUDIES OF RESPIRATORY MORBIDITY

Short-Term Exposure

Six studies measured the effects of exposure to diesel exhaust on changes in pulmonary function during a single work shift (Table 18). All but one found little evidence of changes in pulmonary function related to diesel exhaust exposure. Jörgensen and Svensson (1970) studied a cohort of 240 male Swedish iron ore miners and found little evidence of exposure-related differences in any spirometric index. Gamble and colleagues (1978) studied a cohort of male U.S. salt miners and observed small decreases in pulmonary function over an eight-hour shift. Pulmonary function appeared to deteriorate during a work shift in relation to the level of nitrogen dioxide (NO_2), but all estimates were imprecise.[24] Ames and colleagues (1982) found little evidence of diesel exhaust–related changes in pulmonary function among male U.S. coal miners, but noted small, rather consistent diminutions in lung volumes and flows in relation to diesel exposure, among non- and ex-smokers. Gamble and colleagues (1987a) found that U.S. bus garage workers tested before and after work showed no readily interpretable changes in spirometric measurements adjusted for smoking in relation to either NO_2 or particles.

Ulfvarson and colleagues (1987) studied changes in pulmonary function occurring over a work shift among several groups of workers exposed to motor vehicle exhausts, including 47 stevedores exposed chiefly to diesel exhaust. Over an eight-hour shift the subjects experienced decreases in forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), but not percentage of forced expiratory volume (FEV%), maximal mid-expiratory flow rate (MMEF), or nitrogen washout curves. Pulmonary function recovered after three days without occupational exposure. The authors noted that changes in pulmonary function were not correlated with measured levels of oxides of nitrogen (NO_x) or formaldehyde, leading them to speculate that some aspect of exposure to the particulate fraction of diesel exhaust might be responsible.

To test the hypothesis that reducing exposure to the particle component of diesel emissions would decrease the acute pulmonary effects of exposure, Ulfvarson and Alexandersson (1990) studied stevedores before and following a work shift after the stevedores had been unexposed for three days: 24 subjects worked with standard diesel-powered vehicles, whereas 18 subjects worked with vehicles equipped with particle filters. Workers exposed to unfiltered exhaust experienced a 5% reduction in FVC and a 2% increase in FEV%, whereas workers exposed to filtered exhaust experienced a 2% decrease in FVC and a 0.7%

Table 18. Studies of Short-Term Respiratory Effects of Occupational Exposure to Diesel Exhaust[a]

Reference	Population (Males Only)	Exposure	Results
Jörgensen and Svensson 1970	Iron ore miners	NO_2: 0.5–1.5 ppm Particles: 3–9 mg/m^3 Duration: unknown	Underground vs. surface:[b] ΔFVC (L): 0.05 vs. 0.01 ΔFEV$_1$ (L): 0.03 vs. −0.02 ΔFEV%: −1.0 vs. 0.0
Gamble et al. 1978	Salt miners	NO_2: 1.5 ppm Particles: 0.7 mg/m^3 Duration: 8 hr	ΔFVC (mL/ppm NO_2): −6 (NA)[c] ΔFEV$_1$ (mL/ppm NO_2): −14 (−32, 3) ΔFEF$_{25}$ (mL/sec/ppm NO_2): −117 (−239, 5) ΔFEF$_{50}$ (mL/sec/ppm NO_2): −99 (−183, −15) ΔFEF$_{75}$ (mL/sec/ppm NO_2): −45 (−94, 6)
Ames et al. 1982	Coal miners	NO_2: 0.2 ppm Particles: 2.0 mg/m^3 CO: 12 ppm Formaldehyde: 0.3 ppm Duration: 8 hr	Ex- and nonsmokers:[d] ΔFVC (mL): −57 (p = 0.08) ΔFEV$_1$ (mL): −35 (p = 0.30) ΔVmax $_{50}$ (mL/sec): −107 (p = 0.47) Current smokers: ΔFVC (mL): −73 (NA) ΔFEV$_1$ (mL): −8 (NA) ΔVmax $_{50}$ (mL/sec): 10 (NA)
Gamble et al. 1987b	Bus garage workers	NO_2: <1.5 ppm Particles: 0.24 mg/m^3 Duration: 8 hr	Δ/mg/m^3 respirable particles:[e] ΔFEV$_1$ (mL): 124 (−66, 316) ΔFEF$_{50}$ (mL/sec): 158 (−597, 913) ΔFEF$_{75}$ (mL/sec): 371 (−56, 798) Δ/ppm NO_2: ΔFEV$_1$ (mL): 12 (−172, 196) ΔFEF$_{50}$ (mL/sec): 47 (−680, 774) ΔFEF$_{75}$ (mL/sec): −236 (−648, 176)
Ulfvarson et al. 1987	Bus garage workers, ferry boat crewmen, and stevedores	NO_2: 0.03–1.2 ppm NO: 0.06–2.3 mg/m^3 Particles: 0.13–1.0 mg/m^3 CO: 0.96–4.45 ppm Formaldehyde: 0.4 ppm Duration: 8 hr	ΔFVC (L): −0.44 ($p \leq 0.01$)[f] ΔFEV$_1$ (L): −0.30 ($p \leq 0.001$) ΔFEV%: 1.0 (NA) ΔMMEF (L/sec): −0.33 (NA)
Ulfvarson and Alexandersson 1990	Stevedores	NO_x: 1.12 ppm Respirable dust: 0.12 mg/m^3 CO: 2.14 ppm Formaldehyde: 0.27 ppm Duration: 8 hr	Unfiltered vs. filtered vs. control:[g] ΔFVC: 0.95 (0.93, 0.97) vs. 0.98 (0.96, 1.00) vs. 1.01 (0.97, 1.05) ΔFEV$_1$: 0.98 (0.94, 1.02) vs. 0.99 (0.95, 1.03) vs. 0.99 (0.97, 1.01) ΔFEV%: 1.03 (1.01, 1.05) vs. 1.01 (0.97, 1.05) vs. 0.98 (0.94, 1.02)

[a] CO = carbon monoxide; Δ = change in; Vmax$_{50}$ = maximal flow at 50% of vital capacity.

[b] Average differences in pre- vs. postshift values for younger workers (ages 22–39 yr and 23–35 yr for underground and surface miners, respectively) calculated from data in Table III of the reference. Standard errors could not be derived from the data presented. Data were not adjusted for smoking.

[c] Coefficient (95% CI) for change in pulmonary function test/ppm NO_2. Confidence intervals calculated as ± (1.96 × standard error [SE]). Data are from the text of Gamble et al. (1978), p. 120.

[d] Differences in means of workshift changes in diesel vs. control miners adjusted for age, height, dust levels, and years underground. Calculated from data in Table 4 of the reference.

[e] Mean changes (95% CI) over a workshift from a linear regression analysis controlling for cigarette smoking. Confidence intervals calculated from standard errors. Data are from Table 4 of the reference.

[f] Changes pre- vs. postworkshift following 10 days of no exposure. Data are from Table 4 of the reference.

[g] Results presented as mean quotients (± 2 SE) of before and after workshift values. A quotient of <1.0 indicates decreased value after a workshift. Data are from Table III of the reference.

increase in FEV%. A group of 17 nonsmoking control subjects unexposed to diesel exhaust experienced no changes in pulmonary function over the work shift.

Summary. It is not clear to what extent acute responses to diesel exhaust exposure may indicate an increased risk of chronic respiratory disease. It is certainly plausible, however, that repeated exposure to particles, known pulmonary irritants, and other substances in diesel exhaust could elicit an inflammatory response in the lung that would progress to structural and functional changes and eventual clinical disease. Thus, acute symptoms and changes in pulmonary function could be relevant to chronic disease risk to the extent that they indicate chronic inflammatory processes.

Long-Term Exposure

Nine studies provide data on the effect of long-term exposure to diesel exhaust on respiratory symptoms and pulmonary function (Table 19). Six studies addressed effects in miners. The remaining three studies examined

Table 19. Studies of Chronic Respiratory Effects of Occupational Exposure to Diesel Exhaust

Reference	Population (Males Only)	Exposure	Smoking Adjustment	Results[a]	
				Respiratory Symptoms[b]	Pulmonary Function
Battigelli et al. 1964[c]	364 U.S. railroad workers	Exposed jobs vs. unexposed jobs	No	Dyspnea: 7.6 vs. 16.9 Cough: 7.6 vs. 15.4 Phlegm: 9.0 vs. 18.2	FVC (L): 4.3 vs. 4.3 FEV_1 (L): 2.9 vs. 2.9
Jörgensen and Svensson 1970[d]	240 Swedish iron ore miners	Surface vs. underground miners	Yes	Productive cough Smokers: 28 vs. 8 Nonsmokers: 10 vs. 2	NA
Attfield et al. 1982[e]	630 U.S. potash miners	Miners vs. other blue-collar workers	Yes	Nonsmokers Dyspnea: 4 vs. 1 Cough: 12 vs. 6 Phlegm: 21 vs. 8 Smokers Dyspnea: 11 vs. 9 Cough: 37 vs. 20 Phlegm: 38 vs. 23	Nonsmokers FVC (L): 5.10 vs. 4.88 FEV_1 (L): 4.02 vs. 3.98 Smokers FVC (L): 4.93 vs. 4.80 FEV_1 (L): 3.70 vs. 3.69
Reger et al. 1982[f]	1,646 U.S. coal miners	Diesel mines vs. nondiesel mines	Yes	Dyspnea: 9.3 vs. 23.8 Cough: 23.6 vs. 16.5 Phlegm: 26.5 vs. 22.8	FVC (L): −0.2 (−0.12, −0.3) FEV_1 (L): −0.1 (−0.02, −0.07) FEF_{50} (L/sec): −0.01 (−0.2, 0.08) FEF_{75} (L/sec): −0.12 (−0.03, −0.2)
Gamble et al. 1983[g]	259 U.S. salt miners	Cumulative exposure to respirable particles and NO_2	Yes	Dyspnea: 12.1 vs. 12.3 Cough: 34.6 vs. 30.7 Phlegm: 42.3 vs. 37.4	FVC (mL/mg[RP]/m^3): 0 (−2, 2) FEV_1 (mL/mg[RP]/m^3) : 0 (−2, 2) FEF_{50} (L/sec/mg[RP]/m^3): 1 (−7, 7) FEF_{75} (L/sec/mg[RP]/m^3): (−4 (−18, 10)

(Table continues next page).

Table 19. Studies of Chronic Respiratory Effects of Occupational Exposure to Diesel Exhaust *(continued)*

Reference	Population (Males Only)	Exposure	Smoking Adjustment	Results[a]	
				Respiratory Symptoms[b]	Pulmonary Function
Ames et al. 1984[h]	1,118 U.S. coal miners	Diesel mines vs. nondiesel mines	Yes	Dyspnea: 9.3 vs. 13.1 Cough: 14.7 vs. 22.4 Phlegm: 20.7 vs. 24.8	FVC (mL): −99 vs. −218 FEV_1 (mL): −122 vs. −153 FEF_{50} (L/sec): −290 v. 211
Gamble et al. 1987b[i]	283 U.S. bus garage workers	Bus garage vs. reference population	Yes	Dyspnea: 1.20 (0.71, 1.89) Cough: 2.31 (1.82, 2.92) Phlegm: 1.88 (1.49, 2.36)	FVC (% pred.): 103.9 (75, 133) FEV_1 (% pred.): 102.7 (69, 136) FEF_{50} (% pred.): 102.9 (37, 169) FEF_{75} (% pred.): 105.9 (−35, 247)
Purdham et al. 1987[j]	17 Australian longshoremen	Exposed longshoremen vs. unexposed office workers	Yes	Dyspnea: 6 vs. 6 Cough: 18 vs. 27 Phlegm: 35 vs. 16	FVC (% pred.): 95.6 vs. 99.6 ($p = 0.514$) FEV_1 (% pred.): 84.9 vs. 97.3 ($p = 0.021$) FEF_{50} (% pred.): 75.5 vs. 115.5 ($p = 0.001$) FEF_{75} (% pred.): 44.3 vs. 71.0 ($p = 0.008$)
Jacobsen et al. 1988	19,901 British coal miners	Exposed job categories vs. nonexposed	Yes	Respiratory infection: 1.7 (0.9, 2.5)[k]	NA

[a] NA = not available.

[b] Values are given in percentage of prevalence, except for the Jacobsen et al. 1988 and Gamble et al. 1987b studies. For these two studies, values given are relative risks (95% CI).

[c] Results from Figures 2 and 4. The authors reported neither p values nor standard errors.

[d] Results from Figure 4. The authors reported neither p values nor standard errors.

[e] Symptom prevalence and pulmonary function results of potash miners vs. normal nonmining workers (data are from Table 6 in reference). Data were insufficient to calculate confidence intervals; no p values or standard errors were reported.

[f] Symptom results for underground miners vs. matched control subjects (data are from Figures 1a–1c in reference). Data were insufficient to calculate confidence intervals, but the authors reported that the prevalences of cough and phlegm were elevated in underground miners at diesel mines ($p < 0.05$) and dyspnea was elevated in miners at control mines ($p < 0.05$). Pulmonary function results are mean differences (95% CI) for underground miners at diesel mines vs. matched control subjects (data are from Figure 3a in reference).

[g] Observed vs. expected symptom prevalence results for high cumulative respirable particles (>75 mg/m^3) (data are from Tables I through III in reference). Data were insufficient to calculate confidence intervals for observed vs. expected prevalence, but p values were reported as < 0.05. Pulmonary function results are linear regression coefficients in units as shown ± 2 SE (data are from Table IV in reference).

[h] Five-year symptom incidence and pulmonary function changes for Western miners with >1 yr of underground work, age-adjusted (data are from Tables 3 and 4 in reference). Data were insufficient to calculate confidence intervals and neither p values nor standard errors were reported.

[i] Respiratory symptom results are prevalence ratios (95% CI) for bus garage workers vs. a reference population (data are from Table 7 in reference). Pulmonary function results are the percentage of predicted values (95% CI) for bus garage vs. blue-collar workers. CIs were calculated as ± [1.96 × SD] (data are from Table 8 in reference).

[j] Prevalence results for exposed longshoremen vs. unexposed control subjects (data are from Table II in reference). Data were insufficient to allow calculation of confidence intervals; neither p values nor standard errors were reported. Pulmonary function results are percentage of predicted values, corrected for age, height, and pack-years of smoking for exposed longshoremen vs. unexposed control subjects (data are from Table III in reference).

[k] Relative risk (95% CI) of reporting a respiratory infection among drivers of diesel-powered vehicles vs. surface workers (data are from Figure 13 in reference).

railroad workers, bus garage workers, and longshoremen. Three of the six studies of miners (Reger et al. 1982; Ames et al. 1984; Jacobsen et al. 1988) examined coal miners in mines that used diesel equipment (referred to below as "diesel mines"). Seven of the nine studies are discussed below.

Reger and Colleagues (1982). Reger and colleagues measured the prevalence of respiratory symptoms and the level of pulmonary function among 1,646 underground and surface miners at diesel and nondiesel mines. The prevalence of cough and phlegm, but not dyspnea, was elevated among underground miners in diesel mines relative to control subjects from nondiesel mines matched by age, height, and years worked underground. Lung volumes and forced expiratory flow at 75% of FVC (FEF_{75}) were also reduced. The same general pattern was observed for surface miners, who were presumably less exposed to diesel exhaust. The prevalence of obstructive disease (characterized by $FEV_1/FVC < 0.70$) was the same in diesel and nondiesel miners (both underground and surface), but the prevalence of mild restrictive defects (percentage of forced vital capacity [FVC%] predicted 0.66 to 0.80) was greater among both underground and surface miners in diesel mines (4.1% versus 1.8% and 5.8% versus 3.1%, respectively). Average levels of respirable dust among underground and surface miners were low at both diesel and nondiesel mines, but were higher among underground miners in diesel mines (1.16 versus 1.02 mg/m^3). On average, miners in the diesel mines had worked underground for only a short time (less than 5 years).

Ames and Colleagues (1984). Ames and colleagues followed 1,118 coal miners who had worked underground for more than one year and who had been examined in 1977 and reexamined in 1982; no data are provided on loss to follow-up. The unadjusted baseline symptom and pulmonary function status of each diesel coal miner was generally superior to that of nondiesel miners, but symptom prevalence rates were high among all miners, regardless of diesel exposure.[25] No measurements of diesel exhaust constituents were provided, but the authors note that levels of diesel exhaust–related contaminants were low. The investigators observed higher symptom rates and greater decline in most indices of pulmonary function among miners in nondiesel mines in both the Eastern and Western United States, controlling for age, smoking, and years worked underground. For most indices, analyses of the relation of pulmonary function decline and cumulative exposure in terms of years worked in diesel mines showed declines in all cumulative exposure strata, although these were nonmonotonic, with the exception of FVC.[26]

The authors cautioned against overinterpretation of their apparently negative results because ". . . diesel and nondiesel comparisons reflect a host of social discrepancies such as union status, age at time of entry into mining, educational background, prior work experience . . . in addition to differences based on mining methods." An additional and arguably more important problem is that the authors failed to account for the effects that baseline differences in lung function and symptom prevalence may have had on the rates over five years. Nondiesel miners had both poorer function and higher symptom rates and may have continued to experience accelerated rates of decline relative to diesel miners, independent of exposure.[27]

Jacobsen and Colleagues (1988). Jacobsen and colleagues examined the rate of absence from work due to self-reported chest illnesses in a cohort of 19,901 British coal miners over a five-year period. Slightly over half the cohort (52.1%) were occupationally exposed to diesel exhaust. Measurements of recent levels of NO_2, nitric oxide (NO), and respirable dust were available, and the investigators estimated past exposure levels for periods when no measurements were made. Underground miners who worked with diesel-powered vehicles had a higher rate of absences due to chest illnesses than aboveground workers, but no consistent relationship between levels of NO or respirable dust and illness rates was observed. In general, underground miners reported higher illness rates than surface workers regardless of their estimated exposures to NO.

Gamble and Colleagues (1983). Gamble and colleagues conducted a prevalence survey of 259 salt miners in five salt mines. Analysis revealed small elevations in the prevalence of cough, phlegm, and dyspnea when exposure was characterized either as cumulative exposure to NO_2 or RP, or in terms of which mine a subject had worked in (ranked according to average levels of diesel exhaust surrogates, NO_2 and RP). Cumulative exposure to either NO_2 or RP had no effect on either FVC or FEV_1. In all analyses of the effects of cumulative exposure to NO_2 and RP, the investigators adjusted for the mine in which a subject worked. This may have had the effect of adjusting for exposure to diesel exhaust itself, since the individual mines varied widely in the extent to which diesel equipment was used and in prevalent levels of diesel exhaust surrogates. Consequently, this approach may have produced a bias toward observing no effect of exposure.

Attfield and Colleagues (1982). Attfield and colleagues conducted a prevalence survey of 630 miners at six potash mines that differed in the extent to which diesel equipment had been used. They compared miners at the most heavily dieselized mine to workers at a mine with considerably less diesel equipment and observed no exposure-related differ-

ences either in symptoms or level of pulmonary function in analyses of cumulative NO_2 exposure. The prevalence of cough, phlegm, and dyspnea was elevated when potash miners were compared to nonmining workers, with nonsmokers showing more pronounced relative increases (Table 19).

Gamble and Colleagues (1987b). Gamble and colleagues conducted a prevalence study of 283 U.S. bus garage workers. Symptom prevalence and pulmonary function levels were compared among bus garage workers with different durations of employment and between bus garage workers and a reference worker population. Both analyses showed small elevations in symptom prevalence. An apparently monotonic relationship regarding employment duration was found for cough and wheeze but not for phlegm or dyspnea. Employment duration was associated with declines in pulmonary function for FVC, FEV_1, peak flow, and forced expiratory flow at 50% FVC (FEF_{50}). The values for FEF_{75} were reduced at all durations, but not monotonically. Direct comparisons of predicted levels of pulmonary function revealed no important differences between bus garage workers and the reference control population.

Purdham and Colleagues (1987). Purdham and colleagues studied symptom prevalence and baseline pulmonary function in 17 Australian dockworkers and 11 control subjects. Prevalence of cough, phlegm, and dyspnea were not elevated, and baseline pulmonary function was slightly lower among dockworkers.

Summary. The studies reviewed above do not provide strong or consistent evidence for chronic, nonmalignant respiratory effects associated with occupational exposure to diesel exhaust. Several studies are suggestive of such effects, however, particularly when viewed in the context of possible biases in study design and analysis.

As noted above, all the current studies of chronic respiratory morbidity and exposure to diesel exhaust are prevalence surveys, except the prospective cohort study of coal miners by Ames and colleagues. Prevalence surveys, or cross-sectional studies, are subject to biases due to selective participation and the healthy worker effect. For example, those workers most sensitive or responsive to the effects of exposure may have left employment or may have been absent more frequently. Small positive associations, or the apparent absence of associations, must be interpreted in this light. For this reason, the results of prospective cohort studies are considered to provide a firmer basis for inferring the relation of exposure to disease development, although selective participation (e.g., due to loss to follow-up) can produce biased results in this design as well.

Unfortunately, it is not clear whether any loss to follow-up occurred in the Ames and colleagues study. The authors report only that the subjects participated in both surveys, but do not say how many were included in the first survey. Selection bias could account for the apparent absence of strong and consistent effects of exposure if exposed miners with symptoms or decreased levels of lung function, or both, did not participate in the second survey.

Studies of miners present an additional problem in that miners, particularly coal miners, are exposed to high levels of dust. Chronic respiratory impairment is common among coal miners, and it is difficult to measure what may be a small additional effect of diesel exhaust exposure against a high background rate of respiratory impairment.

Finally, as noted below, it is not clear what form of chronic respiratory disease exposure to diesel exhaust might produce. The experimental evidence, as reviewed by Watson and Green (this report), suggests that exposure, albeit at concentrations greater than those in occupational settings, produces chronic changes that could correspond to a variety of chronic human respiratory diseases. Clearly the epidemiologic data are not adequate to address these issues, and the most fruitful speculation should be based on a more thorough consideration of mechanisms of lung injury than is possible in this paper. We can certainly draw the obvious conclusion that, given the lack of both sensitivity and specificity in the epidemiologic definitions of disease outcome, a relatively rare chronic restrictive disease, such as pulmonary fibrosis, would be hard to detect.

MORTALITY STUDIES

Several studies provide information on mortality from nonmalignant respiratory disease among workers known or presumed to be exposed to diesel exhaust (Table 20). With one exception (Garshick 1987), these are cohort studies that examined multiple causes of death in relation to occupational exposure to diesel exhaust.

Railroad Workers

Two studies described earlier (Howe et al. 1983; Schenker et al. 1984) examined the mortality of Canadian and U.S. railroad workers, respectively, and reported apparently discrepant findings. Howe and colleagues reported apparent excess mortality from emphysema among those with probable occupational exposure, whereas Schenker observed an apparently protective effect of exposure on mortality from all nonmalignant respiratory diseases combined. Neither study controlled for cigarette smoking. Comparisons with national rates may have obscured small elevations in mortality associated with exposure. It is worth noting that Schenker reported an SMR for lung cancer of 0.82 (95% CI 0.59, 1.11) relative to U.S. rates, but found an apparent excess (RR = 1.42, 95% CI 0.45, 2.39) when he compared exposed and unexposed workers.

Table 20. Studies of Mortality from Nonmalignant Respiratory Disease

Reference	Population	Source of Exposure Classification	Smoking Adjustment	Cause of Death (ICD Code): Number of Deaths	Relative Risk Estimate (95% CI)
Howe et al. 1983	Canadian male railroad workers	Job titles from records: last job held (not, possibly, probably exposed)	No	Emphysema: NA[a]	(1.00), 1.35, 1.44[b] (NA)
				Chronic bronchitis: NA	(1.00), 0.81, 1.04[b] (NA)
Rushton et al. 1983	British male bus garage maintenance workers	Job titles from records: last job held	No	Pneumonia: 28	0.87 (0.58, 1.26)[c]
				Bronchitis: 50	0.77 (0.57, 1.02)
Schenker et al. 1984	U.S. male railroad workers	Job titles from records: low, high (exposure considered uniform for this analysis)	No	All respiratory diseases (ICD 8 460-469): 21	0.54 (0.33, 0.82)[d]
Wong et al. 1985	U.S. male heavy-equipment operators	Union work histories	No	All nonmalignant diseases (ICD 7 470-527): 196	0.84 (0.73, 0.97)[e]
				Emphysema (ICD 7 527): 116	1.65 (1.37, 1.98)
				Pneumonia (ICD 7 490-493): 41	0.54 (0.39, 0.73)
Garshick et al. 1987	U.S. male railroad workers	Job titles from records; ≥5 yr in exposed job	Yes	Chronic diseases (ICD 8 490–493, 515–519): 575	1.23 (1.01, 1.49)[f]
Boffetta et al. 1988	U.S. male volunteers	Self-reported regular exposure via questionnaire	Yes	Emphysema (ICD 9 492): 10	1.21 (NA)[g]
				COPD (ICD 9 496): 23	1.18 (NA)
				Pneumonia/influenza (ICD 9 480-489): 14	1.97 (NA)
				Other (ICD 9 460-479, 490-491, 493-495, 500-519): 5	0.43 (NA)
Gustavsson et al. 1990	Swedish male bus garage workers	Exposed jobs from work records	No	All respiratory diseases (ICD 8 460-519): 10	1.43 (0.68, 2.62)[h]
				Asthma, bronchitis, emphysema (ICD 8 490-493): 4	0.75 (0.20, 1.92)[i]
Ahlman et al. 1991	Finnish sulfide ore miners	Occupational histories via questionnaire	No	Respiratory diseases (ICD 8): 3	0.88 (0.22, 2.40)[j]
Michaels and Zoloth 1991	U.S. male bus drivers	Employment from union records	No	Nonmalignant respiratory diseases (ICD 9 460-519): 16	0.61 (0.35, 1.00)[k]

[a] NA = not available.

[b] Relative risk estimates were calculated as the ratio of SMRs in the middle and high categories to the SMR in the low category (data are from reference text, p. 1,019).

[c] SMRs for entire cohort relative to British national rates (data are from reference Table 4). Exact confidence intervals calculated from observed and expected counts using mid-P method (Program 14, Rothman and Boice 1982).

[d] SMR for entire cohort relative to U.S. male rates (data are from reference Table 4).

[e] SMRs for entire cohort relative to U.S. national rates (data are from reference Table 3).

[f] Odds ratio estimate of incidence relative risk from conditional logistic regression.

[g] Relative risks standardized to distribution of age, smoking, and other occupational exposures among unexposed (data are from reference Table IX).

[h] SMR for entire cohort relative to occupationally active population of Stockholm (data are from reference Table 1).

[i] SMR relative to general population of Stockholm (data are from reference Table 1).

[j] SMR for entire cohort relative to local rates (data are from reference Table IV). Exact confidence interval computed from observed and expected counts by mid-P method (Program 14, Rothman and Boice 1982).

[k] Standardized proportionate mortality ratio for entire cohort relative to U.S. population (data are from reference Table 1).

Garshick (1987) reported the results of a case-control study of diesel exhaust exposure and mortality from respiratory disease among U.S. railroad workers exposed for at least five years. They observed a 20% increase in mortality from chronic respiratory disease after controlling for cigarette smoking. Garshick apparently used the same methods that Garshick and colleagues (1987) used in the case-control study of lung cancer discussed earlier; however, the results appeared only in abstract form, precluding detailed review. If valid, Garshick's results are consistent with a small relative increase in mortality from chronic obstructive pulmonary disease.

Bus Garage Workers

Rushton and colleagues (1983) and Gustavsson and colleagues (1990) studied British and Swedish bus garage workers, respectively, and found little evidence of increased mortality due to respiratory disease. Neither study controlled for cigarette smoking. Gustavsson, however, computed SMRs relative to both the general and occupationally active populations; thus, comparison is less likely to have been confounded by cigarette smoking and is less susceptible to downward bias from the healthy worker effect. The SMR for all nonmalignant respiratory disease relative to the occupationally active population was higher than the SMR relative to the general population (1.43 versus 0.87), the result of a 60% reduction in expected deaths, due perhaps to a healthy worker effect or confounding, or both. The SMR for COPD mortality alone relative to the general population was 0.75 (4 observed versus 5.3 expected, 95% CI 0.20, 1.92); no parallel results were reported relative to the occupationally active population.[28]

Heavy Equipment Operators

Wong and colleagues (1985) observed an overall deficit in deaths from all types of nonmalignant respiratory disease in the cohort of heavy equipment operators described earlier. Deaths from emphysema, however, were increased overall, and the SMRs increased with duration of union membership.[29] As noted above, diesel exhaust exposure may have been low, but total dust levels may have been high, introducing a possible source of positive confounding in addition to cigarette smoking.

General Population Study

In a prospective cohort study of a general population, Boffetta and colleagues (1988) reported small elevations in mortality from emphysema and other chronic obstructive diseases and from pneumonia and influenza among those reporting occupational exposure to diesel exhaust. The relative risks were adjusted for age, smoking, and other occupational exposures. No estimates of the statistical precision of the relative risks are available.

Summary

The studies to date do not provide consistent evidence of an effect of occupational exposure on mortality from nonmalignant respiratory disease. Nonetheless, they do not provide a basis to conclude that occupational exposure is not associated with mortality.

The use of mortality data to estimate the incidence of nonmalignant respiratory disease is fraught with problems. First, death certificates frequently fail to list nonmalignant respiratory disease (Higgins and Thom 1989; U.S. Department of Health and Human Services 1985). The estimated relative risk will not be biased if such omissions occur equally for all exposed and unexposed subjects; however, effects may be missed and absolute risk underestimated. A potentially important problem is that the investigators frequently aggregate all deaths from nonmalignant respiratory disease, perhaps to increase statistical precision. If exposure to diesel exhaust causes only certain types of disease, however, aggregation may obscure this association. Fashions in labeling these conditions have varied over time and ascertainment of COPD during a lifetime has increased. Nevertheless, measurement of pulmonary function in physicians' offices is a rare event, and leading causes of death, especially heart disease, may be recorded preferentially when diagnosis is uncertain. These problems could be particularly severe for restrictive diseases plausibly related to exposure (see paper by Watson and Green, this report), such as interstitial fibrosis, which are relatively rare and frequently do not appear on the death certificates of those affected (Hammond 1966).

Lack of information on cigarette smoking makes it difficult to interpret the results of many of the cohort studies. The two studies in which smoking was accounted for (Garshick 1987; Boffetta et al. 1988) found small relative increases in COPD mortality of the same magnitude (about 20%), although both estimates were quite imprecise.

DISCUSSION

Doll and Peto (1981) offer advice on interpreting apparently negative epidemiologic results: Unless epidemiologists have studied reasonably large, well-defined groups of people who have been heavily exposed to a particular substance for two or three decades without apparent effect, they can offer no guarantee that continued exposure to moderate levels will, in the long run, be without material risk.

Though they offered this advice with regard to cancer, it applies equally well to chronic nonmalignant respiratory diseases such as emphysema or pulmonary fibrosis. It would be premature to conclude that occupational exposure to diesel exhaust does not cause nonmalignant respiratory disease, given that few of the studies reviewed above meet the standards suggested by Doll and Peto and several studies have other deficiencies, as noted above.

Only additional longitudinal studies of the relationship of chronic respiratory disease to occupational exposure to diesel exhaust can resolve the ambiguities in the largely cross-sectional results reviewed above. These studies will need to follow exposed cohorts long enough to accumulate sufficient experience in the 20- to 30-year induction time categories with minimal loss to follow-up. Potentially confounding exposures, such as exist among coal miners, are probably best addressed by choosing study populations without such exposures.

PAPER SUMMARY

We have reviewed the epidemiologic evidence for the health effects of exposure to diesel exhaust as it pertains to lung cancer, other cancers, and nonmalignant respiratory disease. The strength of the evidence varies for these diverse outcomes.

Epidemiologic data are strongest for lung cancer. More studies have been conducted for lung cancer than for other diseases, and more detailed information has been collected on exposure, particularly in several recent studies of specific occupational groups. The available evidence suggests that occupational exposure to diesel exhaust from diverse sources increases the rate of lung cancer by 20% to 40% in exposed workers generally and to a greater extent among workers with prolonged or intense exposure, or both. These results are not readily explicable by confounding due to cigarette smoking or other known sources of bias. In a general sense, the elevated rates of lung cancer among exposed workers are consistent with experimental data reviewed elsewhere in this report. These data indicate that whole diesel exhaust and selected constituents are mutagenic and produce cancer in several rodent species.

People are exposed to diesel exhaust in the ambient environment in addition to exposures they may sustain in the occupational settings that have been the focus of epidemiologic research. The current data do not readily allow a comparison of occupational exposure with urban exposures experienced by the general population. However, several recent studies (Mills et al. 1991; Dockery et al. 1993; Pope et al. 1995) and a body of earlier research summarized by Speizer and Samet (1994) suggests that exposure to air pollution from fossil fuel combustion, to which diesel exhaust is a contributor (see background paper by Cass, this report), is associated with increased lung cancer rates independent of smoking and occupation. We should, therefore, be wary of concluding that the increased risk of lung cancer due to diesel exhaust exposure is a problem confined to occupationally exposed people.

As noted above, cigarette smoking accounts for the majority of lung cancer in the United States and most other industrialized nations, and smoking is certainly the most readily avoidable cause of lung cancer. Many smokers, however, live and work in environments polluted with diesel exhaust. A thorough accounting of lung cancer attributable to diesel exhaust exposure would require estimating the independent contributions of smoking and diesel exhaust to disease occurrence among the population exposed to diesel. It would also require estimating the amount of disease attributable to the joint effect of smoking and diesel exhaust. The current occupational studies generally provide the former estimates but not the latter. A notable exception is the recent study by Emmelin and colleagues (1993), which suggests that smoking and diesel exhaust exposure have a greater-than-additive effect on lung cancer occurrence.

Compared to the evidence for lung cancer, the evidence for an effect of diesel exhaust on other cancers, including bladder cancer, is less consistent. It is certainly plausible that diesel exhaust might produce cancer at the same sites as cigarette smoking (e.g., the lung, bladder, and upper airways), given that diesel exhaust contains constituents similar to those in cigarette smoke. However, until larger and more detailed studies are conducted that include more information on the amount and timing of exposure and that address potential confounding factors (e.g., urinary stasis among truckers), the epidemiologic evidence will remain weak.

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ENDNOTES

[1] Recently, Garshick reanalyzed these data and found that when the effect of age was allowed to vary within birth cohorts, the apparent upward trend in the relative risk for cumulative exposure disappeared and the relative risk associated with greater than 15 years of exposure decreased from 1.7 to 1.4 (Garshick 1991).

[2] A survey of 517 railroad employees actively employed in 1982 reportedly found no differences in smoking habits between those with and without potential exposure to diesel exhaust, though the published report presents no data (Garshick 1987). In any case, this survey of surviving cohort members may have underestimated the true prevalence of smoking in the cohort because of the well-known effect of smoking on mortality.

[3] For example, 67% of U.S. males in the 1911 to 1920 birth cohort (which includes those aged 40 to 44 in 1959) were smokers in 1950, whereas only 57% of those in the 1901 to 1910 birth cohort (roughly those 50 to 59 in 1959) smoked in 1950 (data from 1978 to 1980 National Center for Health Studies Health Interview Surveys, cited in U.S. Department of Health and Human Services 1985). There is also some evidence that exposure to cigarette smoking within each birth cohort may have been greater for the exposed workers than for the unexposed. An American Cancer Society survey indicates that in the 1914 to 1923 birth cohort, 27% and 48% of railroad workers were current and former smokers, respectively, in contrast to 22% and 43% of office workers. In the 1904 to 1913 birth cohort, similar disparities were observed: 22% and 45% of railroad workers were current and former smokers, respectively, in contrast to 12% and 48% of office workers. Even if one assumes, however, that current smokers and former smokers face 20- and 10-fold increases in lung cancer mortality, respectively, then the differences in cigarette smoking prevalence notes above would produce only a 13% excess of lung cancer mortality in the younger cohort and a 3% excess in the older cohort.

[4] If, indeed, diesel exhaust exposure causes increased mortality from nonmalignant respiratory disease, the relative risk is probably small. For example, a case-control study by Garshick and associates (1988) observed a relative risk of 1.2 for nonmalignant respiratory disease among railroad workers (see this background paper for additional discussion). This, combined with the relatively small proportion of control subjects who died from nonmalignant respiratory disease, suggests that the degree of underestimation of the lung cancer relative risk would be negligible.

[5] Investigators assigned the additional jobs a dichotomous diesel exhaust exposure value based on (1) the similarity of the job in question to jobs for which contemporary levels had been measured, and (2) the extent of contact with operating diesel equipment that the job entailed.

[6] Garshick notes that analyses that used alternative characterizations of smoking found evidence of negative confounding. Analyses that used finer gradations of pack-years, years of smoking, average numbers of cigarettes smoked, and age at starting smoking produced relative risk estimates for 20 or more years of diesel exhaust exposure between 1.46 and 1.55 (Garshick 1987, p. 1245). In this regard, it is interesting to note that in the industrial hygiene study (Woskie 1988a,b), the unexposed clerks and station agents were observed to be exposed to more tobacco smoke in their work environment than the more heavily diesel-exposed workers. Based on these considerations and the general similarity of the study populations in the case-control and cohort studies, it is reasonable to assume that the cohort study results cannot be explained in their entirety by cigarette smoking, though without smoking data for cohort members this issue cannot be addressed directly.

[7] The use of such a broad middle category of exposure may have concealed actual effects among those with 10 to 19 years of exposure who were observed in the cohort study to have experienced increased lung mortality (Table 4).

[8] Crump's report is available from the U.S. EPA, who sponsored the reanalysis, but has not to our knowledge been submitted for publication in a peer-reviewed journal. It has only recently been made more widely available to the scientific community, having been included as an appendix in recent drafts of the EPA's (1994) Health Assessment Document for Diesel Emissions.

[9] For example, Garshick (1991) notes that shopworkers may have worked in either diesel or nondiesel shops, that

exposure to diesel exhaust may have occurred prior to 1959, and that shopworkers may have had more job instability than other railroad workers. He explains that he did not pursue the job-specific analyses in his 1988 paper because of these potential sources of error.

[10] For example, Crump reported that exposed railroad workers ages 40 through 44 in 1959 had a relative risk of 1.6 (95% CI 1.2, 2.3) when follow-up was restricted to 1959 through 1976 and a relative risk of 1.5 (95% CI 1.1, 1.9) for the years 1959 through 1980 (Crump 1991, Table 6). Garshick (1991) acknowledged the underascertainment and corroborated these results in his own reanalysis.

[11] Crump noted that the estimated levels of diesel exhaust were subject to considerable error from several sources, and may not have been representative of actual historical levels. In addition, as noted by both Crump and Garshick (1991) the shopworker job category included both workers with high likely diesel exhaust exposure and those with little exposure, contributing an unknown, but possibly large, measurement error that could bias downward the slope of the relation between exposure and risk.

Garshick (1991) also notes that the exposure metrics used by Crump and associates entail assumptions that are unlikely to be true and might serve to understate the differences in exposure among job categories. For example, a clerk would be assigned a value of zero for diesel exhaust exposure in an analysis based on years of exposure (as in the original analyses by Garshick et al. 1988); whereas in an analysis using the industrial hygiene measurements of adjusted respirable particles, the clerk would be assigned a value of 33 $\mu g/m^3$. In contrast, according to industrial hygiene measurements, a freight conductor would be assigned a value of 65 $\mu g/m^3$. This would make 20 years of work as a clerk equivalent to 10 years of work as a freight conductor, with respect to diesel exhaust exposure; the validity of this equivalence is questionable.

[12] Steenland (personal communication) reports that in a preliminary mortality analysis the proportionate mortality ratio for emphysema among teamsters was 1.2 and that nonmalignant respiratory disease deaths accounted for only 7% to 8% of control subjects.

[13] Over 90% of the men identified by their next of kin as diesel truck drivers were listed as long-haul drivers in the Teamsters Union records, but only 82% of mechanics identified by their next of kin were listed as such in the same records.

[14] To examine the pattern of effect with increasing duration of employment as a long-haul driver since 1959, we performed a weighted regression analysis (Rothman 1986; Maclure and Greenland 1992) of the data in Table 3 of the report by Steenland and colleagues (1990). This analysis takes advantage of the ordering of the exposure categories and provides point estimates that are comparable to Steenland's but are more precise (Table 7). The analysis produced the following RR and CI values: 0 yr: (1.0), 1 to 11 yr: 1.18 (1.03, 1.36), 12 to 17 yr: 1.51 (1.46, 1.99), 18+ yr: 1.66 (1.23, 1.99). The weighted regression coefficient was 0.02766, nearly identical to that reported by Steenland from his logistic regression analysis (0.027).

[15] If a monotonic increase in risk of lung cancer with duration of employment does exist for mechanics, it may have been obscured by nondifferential misclassification because no information was available concerning the types of trucks on which mechanics worked.

[16] The average organic carbon levels (measured in nonsmokers) for each job category demonstrate the same relation to the epidemiologic results as the elemental carbon levels (Tables III and IV in Zaebst et al. 1991). Although diesel exhaust itself is the most likely contributor to the organic carbon levels, other sources of polycyclic aromatic hydrocarbons, primarily environmental tobacco smoke, may also contribute. Given a summary relative risk for lung cancer and passive smoking of 1.34 (95% CI 1.18, 1.53) reported by the National Research Council (1986), uncontrolled confounding by passive smoke exposure is probably not a tenable explanation for the results of the case-control study.

[17] Studies of friction-products production workers who manufacture brake linings have not found excess lung cancer, perhaps because the fibers are not of the right size to cause lung cancer (Dement 1991). Gustavsson and colleagues (1990) did not find increased lung cancer among Swedish bus garage workers exposed to asbestos during repair operations, but it is not clear whether the types of asbestos fibers used in Swedish brake pads are comparable to those in the United States.

[18] Gustavsson and colleagues interpreted the cohort mortality results as inconsistent with a monotonic increase in incidence over increasing levels of exposure. On reanalysis, the investigators' conclusion appears to be in error, the result of comparing SMRs standardized to different age distributions (Rothman 1986). When Dr. Gusstavsson kindly provided a number of person-years for each exposure category, we calculated both the expected incidence rates and the SMDs, a measure of the absolute, rather than the relative, effect (Table 8). The largest SMD is found in the highest category of exposure, in contrast to the pattern observed for the SMR. This is due to the fact that the SMD is less affected than the SMR by the marked increase in expected rates over categories

of exposure that occurs due to the relation of age with cumulative exposure (Bell and Coleman 1983; Poole 1986).

[19] Damber and Larsson (1985) present data on cigarette-smoking prevalence and smoking-associated lung cancer risk among males in northern Sweden. Using these data and the methods described by Axelson (1978), it is possible to estimate, albeit crudely, the extent to which uncontrolled confounding by cigarette smoking could explain the results reported by Gustavsson. Damber and Larsson (1985) present data for 885 male control subjects, both living and deceased. Information on smoking was obtained by questionnaire from close relatives. A total of 301 (34%) were nonsmokers, 351 (39.7%) smoked less than 20 cigarettes/day, and 232 (26.3%) smoked 20 or more cigarettes/day. Estimated risks relative to nonsmokers were 5.9 for smokers using less than 20 cigarettes/day, and 9.0 for smokers using 20 or more cigarettes/day. Under the assumption that the unexposed bus garage workers have similar smoking habits and disease rates as the control subjects in Damber and Larsson's study, the incidence for the unexposed workers, I_u, can be expressed as:

$$I_u = 0.34\ I_o + 0.397(5.9)I_o + 0.263(9.0)I_o = 5.040$$

where I_o is the rate for nonsmokers.

The hypothetical incidence in the exposed population under various distributions of smoking prevalence, I_e, can be similarly estimated, and the ratio I_e/I_u calculated as an estimate of the lung cancer relative risk due to smoking. Relative risks of 1.28 to 1.44 were calculated by varying the hypothetical prevalence of nonsmokers among the exposed population from 0.10 to 0.20 and the hypothetical prevalence of smokers using 20 or more cigarettes/day from 0.50 to 0.60. Only when the hypothetical prevalance of nonsmokers among the exposed population was reduced to 0.05 and the prevalence of smokers using 20 or more cigarettes/day to 0.80 did the relative risk exceed 2.0.

[20] The cohort studied by Rushton and colleagues (1983) included a wider range of jobs than the cohort studied by Gustavsson and associates, which was formed to include the most exposed population. When Rushton and colleagues examined risk by job title, however, they found a 33% increase (95% CI 1.03, 1.69) in lung cancer mortality among "general hands."

[21] The team estimated the probability ("possible," "probable," "definite"), frequency (less than 5%, 5% to 30%, and 30% of working time), intensity (low, medium, high), and duration of exposure based on team members' knowledge of the industries and occupations involved.

[22] Only 16 of 48 Montreal dockworkers were considered exposed to diesel exhaust by the industrial hygienists (J. Siemiatycki, personal communication).

[23] In earlier years, when vehicles with exhaust systems that vented under the cab predominated, the type of vehicle driven may have been a more important factor (Ziskind et al. 1977). Only the lung cancer case-control study by Steenland and colleagues (1990) analyzed risk since the early 1960s, when diesel-powered vehicles were widely introduced into the trucking industry. They reported that lung cancer risk increased with duration of truck driving since that time. No similar analyses have been conducted for other cancers.

[24] The authors interpreted the data as not showing an effect of respirable particles on lung function, but the coefficient for the change in FEV_1, –18 mL/mg, was comparable to that observed for NO_2, –14 mL/ppm. NO_2 from diesel exhaust could not be distinguished from that due to use of explosives.

[25] For example, in Western mines, prevalence of cough (greater than or equal to 3 mo/yr) was 15.5% and 26.3% for diesel and nondiesel miners, respectively, and 27.1% and 33.0%, respectively, in Eastern mines. Comparable figures for phlegm (greater than or equal to 3 mo/yr) were 18.5%, 27.2%, 23.8%, and 36.6%. Baseline levels of dyspnea were 4.3%, 14.6%, 8.5%, and 28.6%, suggesting that nondiesel miners were, on average, initially in poorer respiratory health. (Data are from Table 2 in Ames et al. 1984.)

[26] FVC: <6 yr at +46 mL, 6 to 7 yr at –8 mL, ≥ 8 yr at –38 mL.
FEV_1: <6 yr at –107 mL, 6 to 7 yr at –114 mL, ≥ 8 yr at –57 mL.
FEF_{50}: <6 yr at –480 mL, 6 to 7 yr at –483 mL, ≥ 8 yr at +2 mL.
(Data for Western diesel miners are from Table 5 in Ames et al. 1994.)

[27] Fletcher and colleagues (1976) referred to this phenomenon as the "horse racing effect."

[28] If one assumes a 60% reduction in expected COPD mortality for the occupationally active population, however, then the SMR for COPD would be 1.9.

[29] Less then 5 yr, SMR = 0.99 (4 observed, 95% CI 0.32, 2.39); 5-9 yr, SMR = 1.07 (7 observed, 95% CI 0.47, 2.12); 10-14 yr, SMR = 1.59 (16 observed, 95% CI 0.94, 2.52); 15-19 yr, SMR = 1.95 (24 observed, 95% CI 1.28, 2.86); ≥ 20 yr, SMR = 1.75 (65 observed, 95% CI 1.35, 2.23). (Data

from Table 4 in Wang et al. 1985.) Exact confidence intervals were computed by the mid-P method (Program 14, Rothman and Boice 1982).

ABBREVIATIONS

ARP	adjusted respirable particles
CI	confidence interval
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
FEF_{75}	forced expiratory flow at 75% of FVC
FEV_1	forced expiratory volume in one second
FEV%	percentage of forced expiratory volume (FEV_1/FVC)
FVC	forced vital capacity
FVC%	percentage of forced vital capacity
ICC	Interstate Commerce Commission
ICD #	International Classification of Diseases (World Health Organization) (# is 7, 8, or 9 indicating edition)
MMEF	maximal mid-exploratory flow rate
NIOSH	National Institute of Occupational Safety and Health
NO	nitric oxide
NO_x	oxides of nitrogen
NO_2	nitrogen dioxide
RP	respirable particles
RR	relative risk
RRB	Railroad Retirement Board
SIR	standardized incidence ratio
SMD	standardized mortality difference
SMR	standardized mortality ratio
$Vmax_{50}$	maximal flow at 50% of vital capacity

Related HEI Publications: Diesel Exhaust

Report No.	Title	Principal Investigator	Publication Date
Constituents of Diesel Exhaust: Metabolism, Biomarkers, and Carcinogenicity			
2	Disposition and Metabolism of Free and Particle-Associated Nitropyrenes After Inhalation	J. Bond	1986
4	The Metabolic Activation and DNA Adducts of Dinitropyrenes	F. Beland	1986
7	DNA Adducts of Nitropyrene Detected by Specific Antibodies	J.D. Groopman	1987
16	Metabolism and Biological Effects of Nitropyrene and Related Compounds	C.M. King	1988
17	Studies on the Metabolism and Biological Effects of Nitropyrene and Related Nitro-Polycyclic Aromatic Compounds in Diploid Human Fibroblasts	V.M. Maher	1988
19	Factors Affecting Possible Carcinogenicity of Inhaled Nitropyrene Aerosols	R.K. Wolff	1988
26	Investigation of a Potential Cotumorigenic Effect of the Dioxides of Nitrogen and Sulfur, and of Diesel-Engine Exhaust on the Respiratory Tract of Syrian Golden Hamsters	U. Heinrich	1989
31	DNA Binding by 1-Nitropyrene and Dinitropyrenes in Vitro and in Vivo: Effects of Nitroreductase Induction	F.A. Beland	1989
32	Respiratory Carcinogenesis of Nitroaromatics	R.C. Moon	1990
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Health Effects Institute

141 Portland Street
Suite 7300
Cambridge, MA 02139