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Diesel Emissions and Lung Cancer[1]

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This paper uses two different methods to assess the potential risk of human lung cancer from exposure to diesel engine emissions. One method analyzes the best available epidemiological evidence on the lung cancer risks of persons exposed in their occupations to diesel engine emissions. The second conducts a comparative analysis of laboratory and epidemiological data on diesel engine emissions and two chemically related environmental exposures—coke oven emissions and roofing tar emissions. The estimates of potential risk derived from these two distinct methods are compared. The sources of uncertainty in each method are explicitly characterized. The value of these estimates for comparing the potential lung cancer risks from exposure to diesel engine emissions with other personal and societal risks are discussed. Also considered are the limitations of these results in predicting the possible excess incidence of lung cancer from ambient exposure to diesel emissions.

KEY WORDS: lung cancer; diesel emissions; air pollution; occupational carcinogenesis; interspecies comparisons; risk extrapolation.

1. INTRODUCTION

The main purpose of this paper is to estimate quantitatively the potential risk of human cancer from exposure to diesel engine emissions.

In Sec. 2, two different methods of risk estimation are presented. The first method analyzes the preliminary results of 25 years of observation of lung cancer incidence among diesel bus garage workers, bus drivers, and bus conductors in the London Transport Authority.[2-4] The second examines the epidemiological evidence of lung cancer risks from two related environmental exposures—coke oven emissions[5-7] and roofing tar emissions.[8] The estimates of lung cancer risk from exposure to these related emissions are then combined with data on the carcinogenic and mutagenic potency of the emissions relative to diesel emissions, derived from short-term bioassays of their organic extracts.[9-12] The potential risk estimates derived from these two distinct methods are then compared.

In Sec. 3, the risk estimates are critically interpreted. The sources of uncertainty are explicitly characterized. The value of the estimates for comparing the potential lung cancer risks from exposure to diesel emissions with other personal and societal risks are discussed. Also discussed are the limitations of the use of the estimates in the prediction of excess lung cancer incidence and death rates.

This paper does not consider all of the available evidence on the health effects of diesel engine emissions. It does not conduct a benefit-cost analysis of alternative government policies toward diesel automobile emissions, nor does it examine the broader question of the relation between environmental pollutants in general and lung cancer.

2. ESTIMATION OF POTENTIAL LUNG CANCER RISK FROM DIESEL ENGINE EMISSIONS

A robust epidemiological study of the effect of an environmental agent on the risk of human cancer

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should have the following characteristics: Well-defined groups of exposed subjects and comparable control subjects should be identified; the magnitude and duration of individual exposures should be measured; possible significant confounding factors should be evaluated; potential biases caused by the nonrandom selection or follow-up of subjects should be avoided; the duration of the follow-up should be sufficient to observe a significant increase in the incidence of the suspected cancer; and the number of persons or person-years at risk should be sufficient to detect a statistically significant difference in cancer rates between exposed and control subjects. In an ideal study, the presence or absence of cancer should be confirmed pathologically.

No currently completed epidemiological study of the effect of diesel emissions on lung cancer incidence satisfies all of these criteria.[13,14] Of all studies thus far performed, the London Transport Authority study more closely approaches but does not satisfy the ideal.

2.1. The London Transport Study

In 1957, Raffle[2] examined the lung cancer incidence among several categories of London Transport Authority employees in the years 1950–1954. This study has been updated by Waller[3] to cover the period 1950–1974.

The main rationale for this study is the presumption that a specific group of London Transport Authority (LTA) employees—namely, diesel bus garage workers—were exposed to an excess of diesel engine emissions in comparison to other LTA employees or men living in Greater London. The main issue in my analysis of this study is the extent to which observed differences in lung cancer rates among diesel bus garage workers, other LTA workers, and Greater London men can be used to estimate the potential risk of lung cancer from diesel engine emissions.

2.1.1. Data

This study examined the medical records of LTA male workers, aged 45–64. Five job categories were considered:

(1) Engineers, Bus Garages. This group represented all those involved in the maintenance and repair of diesel buses in several dozen garages. Among them were mechanics and workers who refueled buses, refilled radiators, cleaned interiors, and shunted buses in various positions in the garages.

(2) Bus Drivers. Although these men were not continuously exposed to the diesel bus garage environment, they apparently spent some time at the garages during "run-in" and "run-out" of the buses. They might also be exposed to excess diesel emissions from their own buses or other LTA buses in areas of London with a high density of diesel-powered traffic.

(3) Bus Conductors. These men were also not continuously exposed to the diesel bus garage environment. However, as in the case of bus drivers, they could have experienced some degree of excess exposure to diesel engine emissions. During the later part of the study period, many conductors were retrained as drivers. Therefore, the identities of these two groups are not entirely distinct.

(4) Engineers, Central Works. These more skilled blue-collar employees worked on the design and development of new buses and other LTA equipment. They are not expected to have excess exposure to diesel engine emissions.

(5) Motormen and Guards. These men worked in the London Underground (subway system). They are not expected to have excess exposure to diesel engine emissions.

Observed lung cancer cases among these employees included those recorded to have died while still a member of the staff within one of the above job categories; those recorded to have transfered to alternative work within the LTA following the diagnosis of lung cancer; and those recorded on ill-health retirement following a diagnosis of lung cancer. No follow-up of lung cancer incidence is reported for those men not in the service of the LTA.

This study recorded only the incidence of lung cancer among all employees during the 1950–1974 observation period. No specific cohort of employees was identified at the start and followed continuously. Their smoking habits, other aspects of medical history, and socioeconomic characteristics were not recorded. The demographic composition of the work force changed during the course of the period. Thus, some undetermined fractions of LTA workers in the 1950s had their origins in the West Indies and in the 1960s in Asia.

Detailed information on the duration of service of workers or the duration of exposure to diesel emissions is not currently available. Diesel vehicles began to replace trams and electric trolleys in London

in the early 1930s. The use of diesel buses increased markedly after World War II. Since 1952, diesel buses have been used exclusively. The authors of the study indicate that a substantial fraction of subjects in each category were employed by the LTA for their entire lives. Some employees in each group were undoubtedly transient. There is no clear evidence that the extent of turnover differed significantly among job categories.

Table I shows the number of man-years at risk (N) and the number of observed lung cancer cases (O) for each job category during the first 11 years and the last 14 years of the observation period. The age distribution of subjects differed over time among job categories. Direct adjustment for these age differences requires information on the number of person-years at risk and the number of lung cancer cases for specific age categories over calendar time. This detailed information is not currently available. However, the authors do report the results of applying age-specific Greater London male lung cancer death rates to the corresponding numbers of person-years at risk in each age category over successive five-year calendar intervals during the observation period. The "expected" cases resulting from these calculations are given in the final column (E) in Table I.

Table I. Lung Cancer Cases among London Transport Staff and Expected Cases Based Upon Greater London Lung Cancer Death Rates, Males Aged 45–64.[4]

Time period / Job category	Man-years at risk (N)	Observed cases (O)	"Expected" cases[a] (E)
1950–1960			
Engineers, bus garages	49,804	96	106.9
Bus drivers	97,611	125	186.0
Bus conductors	52,194	54	92.5
Engineers, Central Works	16,448	19	31.3
Motormen and guards	17,851	26	33.5
Total	233,908	320	450.2
1961–1974			
Engineers, bus garages	36,250	81	90.2
Bus drivers	78,298	134	160.8
Bus conductors	40,901	76	82.0
Engineers, Central Works	13,583	23	31.8
Motormen and guards	17,759	33	34.2
Total	186,791	347	399.0

[a]Based upon age-specific lung cancer death rates for Greater London males for each five-year interval during the period 1950–74.

The extent of individual exposure to diesel engine emissions was not measured. However, the concentrations of diesel smoke and certain diesel smoke components were measured inside and outside selected garages.[3,15] Figure 1 depicts the frequency distribution of 53 measurements of whole smoke concentration gradients in two bus garages during different seasons and different times of day in 1956 and 1957. These data were obtained by subtracting reported concentrations at several interior sampling sites from contemporaneous measurements outside the garages. In a few cases, especially in the garage office, the absolute particulate concentrations were less than the corresponding outside measurements. The outside measurements varied from 30 to 1460 $\mu g/m^3$, with a mean of 267 $\mu g/m^3$. The outside concentrations recorded during the winter were higher due primarily to coal-burning in the Greater London region. The magnitudes of the ambient concentrations were consistent with those reported for Central London in 1957 (ref. 16, Table 4).

The measured smoke gradients varied according to the time of day. The highest mean gradients were recorded for the main run-out (5 A.M. to 7 A.M.), when buses were started and idled to warm up, and the main run-in, (11 P.M. to 1 A.M.), when buses were refuelled, washed, and shunted into position. The daily mean gradient was 269 $\mu g/m^3$, with standard error 49.7 $\mu g/m^3$. If the distribution of the mean

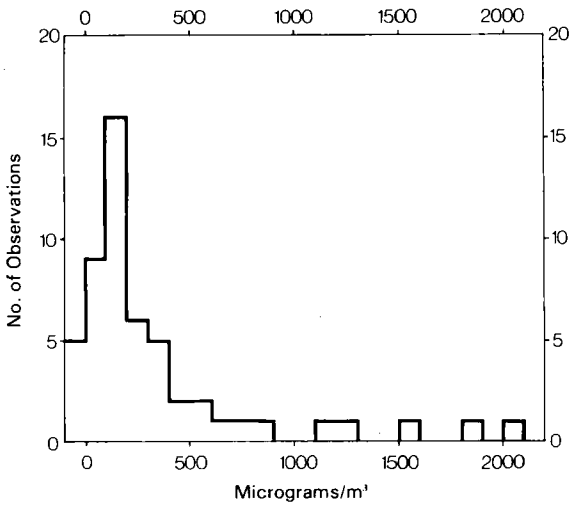

Fig. 1. Frequency distribution of measurements of whole smoke concentration gradients in Dalston and Merton bus garages, London Transport, 1956–1957.[15]

gradient is approximately normal, then the 25% and 75% confidence limits are 235 and 303 $\mu g/m^3$, respectively. The latter estimates will be used in the analysis below.

Commins *et al.*[15] reported gradients in the concentrations of benzo(a)pyrene and other polyaromatic hydrocarbons. Waller[3] has reported the concentration gradient of benzo(a)pyrene in one garage in 1979. Although polyaromatic hydrocarbons are potentially carcinogenic components of diesel emissions, the recorded concentration gradients of these selected components may not correctly reflect the total dose of biologically active material. Therefore, data on whole particulate concentrations are used in the following analysis.

The degree of change over time in the magnitude of smoke gradients in bus garages is not well documented. The average number of diesel buses per garage appears to have declined. Bus washing has been mechanized. However, the type of engine, procedures for maintenance, and bus idling practices have also changed. The concentration gradients for benzo(a)pyrene reported at one site by Waller for 1979 (six measurements) are comparable to those reported in 1957. Data on recent total smoke measurements are not specifically reported. For some measurements, however, 1979 whole smoke concentrations apparently exceeded those recorded in 1957.

2.1.2. Designation of Exposed and Control Groups

The garage engineers (maintenance staff and mechanics) constitute the primary exposed subjects in this study. This group consists of men with varying durations and degrees of exposure to diesel engine emissions. The lung cancer experience of the entire group may therefore represent the diluted effect of a higher level of exposure to diesel emissions among a smaller subset of workers. Only the average dose and the average response can be observed. The bus conductors and bus drivers constitute an intermediate group with uncertain exposure. The engineers in the Central Works and the motormen and guards are admissible control subjects.

Although Waller[3] and Waller and Raffle[4] based their calculations of age-standardized "expected" cases on the lung cancer death rates of Greater London males, the latter is not an appropriate comparison group. The number of observed lung cancer cases in the LTA population (column O, Table I) was substantially lower than the number of "expected" cases based upon Greater London rates (column E, Table I). For the entire study period for all LTA workers, observed cases constitute only 80% of "expected" cases. The overall annual lung cancer rate for the LTA subjects (159 per 100,000) was significantly lower than the corresponding Greater London-based rate (202 per 100,000). (For a two-sided test based on the binomial distribution, $p < 0.0001$. That is, if diesel engine emissions had no effect on lung cancer incidence among LTA workers, and if Greater London men were comparable to LTA workers, then the probability of observing only 667 cases in the LTA population would be less than 1 in 10,000.)

Many factors could account for this discrepancy. Those LTA workers recruited from the West Indies during the 1950s or from Asia during the 1960s might have hereditary and socioeconomic characteristics or smoking habits different from those of Greater London men. On average, men who undertook the type of work required for the LTA jobs might have been more fit than their Greater London counterparts.

Most important, the data for this study included only cases of lung cancer arising during service. There was no follow-up of men after they had left the LTA system. Cases of lung cancer arising at any time after retirement were omitted. Cigarette smokers, in particular, are more likely to leave service prior to age 65 because of smoking-related conditions other than lung cancer. Hence, the lack of follow-up data excluded subjects who were more likely to develop lung cancer. This bias due to a lack of follow-up is relevant even if the full cohort, including those men who left the LTA prematurely, had the same smoking habits as Greater London residents. It does not, however, negate the validity of using LTA motormen and guards as well as Central Works engineers as comparison groups. Any selection bias due to the lack of follow-up is likely to apply equally to each occupational category. It is therefore most appropriate to regard the two comparison groups (engineers in Central Works, and motormen and guards) as the unexposed control subjects.

In Table II, the data of Table I have been combined for these two control job categories and for the two intermediate exposed categories (bus drivers and conductors). The ratio (O/E) of observed cases to the Greater London-based "expected cases" is shown.

Table II. Lung Cancer Cases among Combined London Transport Job Categories and Expected Cases Based upon Greater London Lung Cancer Death Rates, Males Aged 45–64.[4]

Time Period / Combined job category	Main-years at risk (N)	Observed cases (O)	"Expected" cases[a] (E)	Observed/ "expected" (O/E)
1950–1960				
Engineers, bus garages	49,804	96	106.9	0.897
Bus drivers & conductors	149,805	179	278.5	0.643
Engineers in Central Works, motormen & guards	34,299	45	64.8	0.694
Total	233,908	320	450.2	0.711
1961–1974				
Engineers, bus garages	36,250	81	90.2	0.898
Bus drivers & conductors	119,199	210	242.8	0.865
Engineers in Central Works, motormen & guards	31,342	56	66.0	0.848
Total	186,791	347	399.0	0.870
1950–1974				
Engineers, bus garages	86,054	177	197.1	0.898
Bus drivers & conductors	269,004	389	521.3	0.746
Engineers in Central Works, motormen & guards	65,641	101	130.8	0.772
Total	419,699	667	849.2	0.785

[a]Based upon age-specific lung cancer death rates for Greater London males for each five-year interval during the period 1950–1974.

Comparison of age-adjusted lung cancer rates between exposed and unexposed job categories would ordinarily require detailed information on the number of man-years at risk and the number of lung cancers for specific ages. Analysis of the ratios (O/E) of observed cases to Greater London-based, age-standardized "expected" cases, however, offers an indirect method of comparison. This approach requires specific assumptions about the dependence of cancer incidence on age and exposure to diesel emissions.

2.1.3. Constant Relative Risk Model

Consider two groups of subjects during a specific calendar time period—an unexposed group and an exposed group. Let $h(t)$ and $h^*(t)$ be the lung cancer rates of the unexposed and exposed subjects, respectively, at age t. Let $h_{GL}(t)$ be the corresponding age-specific lung cancer rate of Greater London males. Let $N(t)$ and $N^*(t)$ be the number of person-years at risk during the specific calendar time period, among the unexposed and exposed subjects, respectively, for age at risk t. Then observed cases are $O = \Sigma_t h(t)N(t)$ and $O^* = \Sigma_t h^*(t)N^*(t)$ for the unexposed and exposed groups, whereas Greater London-based "expected" cases are $E = \Sigma_t h_{GL}(t)N(t)$ and $E^* = \Sigma_t h_{GL}(t)N^*(t)$ for the unexposed and exposed groups.

In this analysis, I shall assume that the incidence of lung cancer conforms to a constant relative risk model (or "proportional hazards" model). That is, the ratios $h^*(t)/h(t)$ and $h_{GL}(t)/h(t)$ are independent of t over the age range considered in the study. Equivalently,

$$r^* = h^*(t)/h(t)$$

and

$$r_{GL} = h_{GL}(t)/h(t)$$

where r^* (the relative risk of lung cancer for exposed subjects in relation to unexposed LTA controls) and r_{GL} (the relative risk of lung cancer among Greater London males in relation to unexposed LTA controls) do not depend on t. The relative risks r^* and r_{GL} could depend on the extent and duration of

exposure to diesel engine emissions, on differences in smoking rates, or on other socioeconomic characteristics. This assumption, in combination with the definitions of O, O^*, E, and E^*, implies

$$O = \Sigma_t h(t) N(t) = (1/r_{GL}) \Sigma_t h_{GL}(t) N(t) = E/r_{GL}$$

and

$$O^* = \Sigma_t h^*(t) N^*(t) = r^* \Sigma_t h(t) N^*(t)$$
$$= (r^*/r_{GL}) \Sigma_t h_{GL}(t) N^*(t) = r^* E^*/r_{GL}$$

and therefore

$$O^*/E^* = r^*(O/E)$$

The relative risk of lung cancer of exposed LTA subjects in relation to unexposed LTA controls can be ascertained by comparing the O/E ratios of exposed and unexposed groups.

2.1.4. Analysis of Data

For the entire study period 1950–1974, the O/E ratio for the garage engineers (0.898) exceeds the corresponding O/E ratios for the other two combined job categories in Table II. For example, the O/E ratio for the garage engineers is about 16% greater than that for the presumed unexposed group, the Central Works engineers, motormen and guards. However, because of the progressive growth in the use of diesel buses from 1930 to 1952, those subjects observed during the earlier part of the study period were not likely to have as much exposure as those observed later during the 1950–1974 period. If the midpoint in the growth of diesel buses occurred at about 1945, then a continuously employed garage engineer observed during the 1950–1960 would experience an average duration of exposure of 10 years, while a continuously employed garage engineer observed during 1961–1974 would experience an average duration of exposure of 23 years. Comparison of O/E ratios among combined job categories for the periods 1950–1960 and 1961–1974 shows that the excess lung cancer incidence among garage engineers was confined primarily to the earlier period. This finding is not consistent with a dose-response relation between duration of exposure to diesel bus emissions and lung cancer incidence.

Moreover, the O/E ratios for the bus drivers and conductors and the Central Works engineers, motormen, and guards increased between 1950–1960 and 1961–1974, while the O/E ratio for the garage engineers remained essentially unchanged. The significance of this observation is weakened by probable changes in the demographic composition of LTA workers over the 1950–1974 period. Nevertheless, the finding that the lung cancer rates of the garage engineers did not increase in proportion to those of other job categories is also inconsistent with a positive relation between duration of exposure to diesel bus emissions and lung cancer incidence.

Finally, for the later period 1961–1974, the O/E ratios for the three combined job categories are ordered in relation to the degree of presumed excess exposure to diesel bus emissions. This finding is consistent with an effect on cancer rates. The O/E ratio for the garage engineers, however, is only about 6% greater than that of the presumed unexposed group, the Central Works engineers, motormen and guards. By itself, this difference in O/E ratios is not statistically significant. (Out of a total of 137 observed cases for the garage engineers and the Central Works engineers, motormen and guards during 1961–1974, the proportion observed for the garage engineers did not differ significantly from that expected under the null hypothesis of equal O/E ratios for the two groups.)

The reliability of these generally negative findings, however, is limited by a number of important sources of uncertainty. The sources of uncertainty are explicitly listed in Table III. Although there is no clear evidence that cigarette smoking rates differed substantially among job categories, small unobserved differences could have a significant effect on lung cancer rates. Smoking was temporarily prohibited in buses and bus garages during the 1950s—although the extent of enforcement of the prohibition is not documented. If workers of Asian or West Indian origin had very different smoking habits, their non-

Table III. Sources of Uncertainty in Analysis of London Transport Data

A.	Differences among job categories in cigarette smoking rates (s_1, s_2, s_3).
B.	Variations in excess diesel emission exposure among garage engineers (x_g).
C.	Uncertain exposure of bus drivers and conductors (f).
D.	Changes in exposure over time (z, d_2).
E.	Stochastic nature of lung cancer incidence (σ).
F.	Uncertainty in the form of the mathematical model relating extent of exposure to lung cancer incidence.

random assignment among job categories could produce significant aggregate differences in smoking rates. While LTA employees were in general blue-collar workers, there could have been important differences in social class or education. According to survey data for the United Kingdom, the proportion of adult male cigarette smokers was about 62% in 1950, and ranged from 53% to 62% among different social classes in 1958 (ref. 17, Fig. 1.3). Although the previously discussed potential bias in smoking rates, resulting from the lack of follow-up, should apply equally to each occupational category, some sedentary workers might be less likely to leave their jobs with smoking-related diseases. It seems likely, in view of these considerations, that absolute differences in smoking prevalence among these job categories could be as much as 10%. In the following, the proportions of cigarette smokers will be denoted by the variables s_1, s_2, and s_3.

There also is uncertainty about the magnitude of exposure of the garage engineers. The concentrations of diesel emissions may have varied among different garages, daily work shifts, and seasons of the year. There may have been sampling errors or other errors of measurement in the reported concentrations of diesel smoke. If the outside measurements used to calculate the concentration gradients in Fig. 1 did not reflect complete mixing with urban air, the measured differences between inside and outside smoke concentrations may understate the true smoke gradient. Below, the average particulate concentration gradient in the garages is denoted by the variable x_g.

Third, there is uncertainty in the degree of exposure, if any, of bus drivers and conductors. The uncertainty is quantified by the fraction f, which represents the ratio of bus driver and conductor exposure to garage engineer exposure. Fourth, there is uncertainty in the extent to which exposure changed over time. Thus uncertain magnitude is quantified by two variables: z, which represents the ratio of 1961–1974 exposure to 1950–1960 exposure; and d_2, which represents the duration of exposure LTA workers observed in 1961–1974. Fifth, even if we could accurately measure exposure and smoking rates, there remain purely random effects arising from the stochastic nature of cancer incidence. Finally, there is uncertainty in the mathematical specification of the model relating the extent of excess exposure to diesel engine emissions to the incidence of lung cancer.

In view of these uncertainties, the main analytical question is: How confident can we be that a carcinogenic effect of diesel exposure has not gone undetected? Can we place some quantitative limits on this possible undetected effect?

To answer such questions, we must satisfy a quantitative relation between the relative risk of lung cancer and the extent of exposure to diesel emissions and smoking rates. The simplest and most tractable model for this purpose is the combined linear form

$$r^* = (1 + \theta X)(1 + mY) \tag{1}$$

Here, X is the excess cumulative lifetime exposure to diesel engine emissions, and θ is the potency of diesel emissions, a parameter to be estimated from the data. Moreover, Y is an indicator variable measuring smoking status, which takes on the value 1 for smokers and 0 otherwise, and m is a coefficient representing the incremental relative risk of lung cancer for cigarette smokers. This model implies that, for a given smoking status, the proportional increase in lung cancer incidence is a linear function of cumulative lifetime exposure to excess diesel engine emissions. Moreover, the joint effects of diesel exposure and cigarette smoking are multiplicative. Uncertainty about cigarette smoking practices will have a larger effect on the possible risk from diesel emissions in this multiplicative specification than in a purely additive interaction between smoking and excess diesel exposure. A similar mathematical model has been applied to epidemiological data on smoking habits and cumulative lifetime exposure to chrysotile asbestos.[18]

Using a more general notation, we let O_{ij} be the observed lung cancer cases in calendar time period $i = 1,2$ (indexing the two periods 1950–1960 and 1961–1974) and job category $j = 1,2,3$ (indexing the three job categories in Table II). Let E_{ij} be the corresponding Greater London-based "expected cases" and let X_{ij} be the corresponding excess cumulative exposures. The statistical specification corresponding to the above linear constant relative risk model is

$$O_{ij} = \alpha_i E_{ij}(1 + \theta X_{ij})(1 + ms_j) \quad \text{for all } i, j$$

The dependence of the proportionality parameter α_i on the index i reflects the possibility that the demographic composition of LTA subjects, and therefore their risk of lung cancer in relation to Greater London males could have changed over time. For any given choice of X_{ij}, m, and s_j, we can then estimate a

statistical confidence interval on the parameter θ from the data on O_{ij} and E_{ij} by maximum likelihood methods.

Let us first estimate a statistical confidence interval for the relative risk of lung cancer among the garage engineers. The assumption that the Central Works engineers, motormen and guards (group $j = 3$) constitute the unexposed control subjects implies $X_{i3} = 0$ (for $i = 1,2$). The variable f in Table III corresponds to X_{i2}/X_{i1} (for $i = 1,2$). The variable z in Table III corresponds to X_{2j}/X_{1j} (for $j = 1,2$). If we set $X_{21} = 1$, then any choice of f and z determines the cumulative dosages X_{ij} relative to the garage engineers in 1961–1974. Hence $1 + \theta$ is the relative risk of lung cancer among the garage engineers in 1961–1974.

Figure 2 depicts the maximum-likelihood estimates for the upper and lower 95% confidence limits of $1 + \theta$ for different values of the smoking proportion s_1, for fixed values of the other variables $f = 0.5$, $z = 2.3$, $s_2 = s_3 = 0.55$. The variable m, the increment

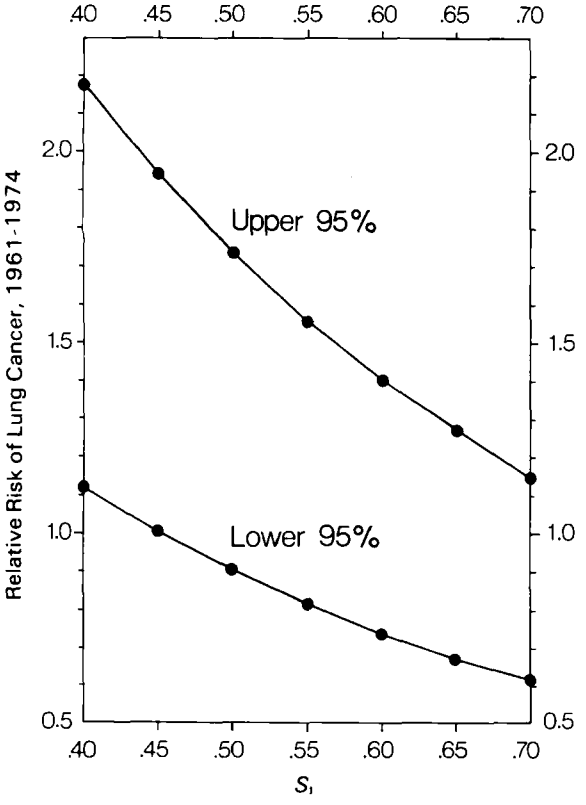

Fig. 2. Ninety-five percent confidence limits of the relative risk of lung cancer among London Transport garage engineers during 1961–1974 for various values of the smoking proportion variable s_1.

in relative risk of lung cancer for cigarette smokers, was taken to be 10.[19,20] At values of s_1 below 50%, the maximum-likelihood estimate of θ was significantly different from zero, but the linear constant relative risk model fit poorly. At higher values of s_1, the maximum-likelihood estimates of θ was insignificantly different from zero, but the goodness of fit of the model improved. Despite a wide range of variation in smoking habits illustrated in Fig. 2, the upper 95% confidence limit of the relative risk of lung cancer among garage engineers does not exceed 2.1.

To calculate an overall estimate of the range of uncertainty in the relative risk of lung cancer, I have proceeded as follows. Each of the variables z, f, s_1, s_2, s_3, can be regarded as having some probability density. (The value of m was taken to be 10 hereafter.) It is simplest to approximate each density by an independent two-point distribution, where the upper and lower points can be regarded as the 75% and 25% fractiles of the underlying continuous distribution. In that case, the joint density of the variables $\{z, f, s_1, s_2, s_3\}$ takes on $2^5 = 32$ equally likely values. Each value of $\{z, f, s_1, s_2, s_3\}$ corresponds to an equally likely estimate of θ. Let $\hat{\theta}_k$ and $\hat{\sigma}_k^2$ ($k = 1,\ldots,32$) denote these maximum-likelihood estimates and asymptotic variances. Then the overall estimate is $\tilde{\theta} = (1/32)\Sigma_k \hat{\theta}_k$ and the variance of $\tilde{\theta}$ is

$$V(\tilde{\theta}) = (1/32)\Sigma_k \hat{\sigma}_k^2 + (1/32)\Sigma_k (\hat{\theta}_k - \tilde{\theta})^2 \quad (2)$$

The first term on the right-hand side is the variance in $\tilde{\theta}$ due to the stochastic error components in the relative risk model (source E in Table III). The second term reflects the additional variance due to uncertainty about the values of the exposure and smoking variables.

For this procedure, I have selected possible values of the variables as follows: $z = 2.0$ or 2.6; $f = 0.2$ or 0.8; each $s_j = 0.5$ or 0.6. These values were chosen to reflect the wide range of uncertainties discussed previously. The overall estimate resulting from these choices was $\tilde{\theta} = 0.16$ with a standard error of 0.23. The variance of $\tilde{\theta}$ due to uncertainty in the dosage and smoking variables was 51% of the total variance of $\tilde{\theta}$. The overall 95% upper and lower confidence limits of the relative risk of lung cancer among the garage engineers in 1961–74 were 1.61 and 0.70, respectively.

In order to obtain an estimate of θ applicable to other populations, we must measure X in actual units of cumulative lifetime exposure. If x_g is the mean

daily concentration gradient of diesel engine particulates in the bus garages, and p is the proportion of an average day spent at work, and d_2 is the average duration of exposure to diesel engine emissions among garage engineers in 1961–1974, then $X_{21} = px_g d_2$ is their mean cumulative lifetime dose. Any given choice of p, x_g, d_2, f, and z therefore completely specifies the dosages X_{ij}. If x_g is measured in $\mu g/m^3$ particulates and d_2 is measured in years, then the estimate of θ will be in units of relative risk per $\mu g/m^3$ particulates × years.

Table IV shows the effects of introducing uncertainty in various combinations of the underlying set of exposure variables. (The value of p, considered to be subject to much less uncertainty, was fixed at 0.22.) When a particular variable is denoted as a source of uncertainty in Table IV, it is assumed to take on the previously specified independent two-point density. When a variable is not listed as a source of uncertainty, it is assumed to take on a fixed value corresponding to the mean of the density. For example, x_g was assumed to take on the values of 235 and 303 $\mu g/m^3$, which correspond to its estimated 25% and 75% fractiles, when it is included in the list of uncertain variables. Otherwise, it takes on its estimated mean value of 269 $\mu g/m^3$.

As indicated in Table IV, uncertainty in the exposure parameters alone contributed about 12% to the total variance of $\tilde{\theta}$. Inclusion of uncertainty in smoking practices raises the proportion of the contributed variance to 50%. That is, the additional uncertainty concerning the extent, duration, and time course of dosage, and smoking practices was equal to the uncertainty due to the purely stochastic error component of the model. The 95% upper confidence limit for θ, in that case, is in the order of 5×10^{-4}. Thus, we have derived a statistical upper confidence limit of potential risk equal to a 0.05% proportional increase in lung cancer incidence per unit of cumulative lifetime exposure, where one unit of exposure is equivalent to inhaling a concentration of one microgram of particulates per cubic meter for one year.

2.2. Comparative Analysis of Coke Oven Emissions, Roofing Tar Emissions, and Diesel Engine Emissions

So far I have used a linear, constant relative risk model to estimate an upper confidence limit on the potential effect of diesel engine emissions in the data of the London Transport Authority. I now apply the same model to two related environmental exposures —coke oven emissions and roofing tar emissions. This procedure yields analogous estimates of the proportional increase in lung cancer incidence per unit of cumulative lifetime exposure to the respective emissions.

Although diesel engine emissions, coke oven emissions, and roofing tar emissions are known to have related chemical compositions, the effect in man of a given exposure to diesel engine emissions is not necessarily equal to the effect in man of the same exposure to coke oven emissions or to roofing tar

Table IV. Effects of Various Sources of Uncertainty on the Estimated 95% Confidence Limits of the Parameter θ for the London Transport Study

Source of uncertainty[a]	Maximum likelihood estimate[b] ($\times 10^{-4}$)	95% lower limit[b] ($\times 10^{-4}$)	95% upper limit[b] ($\times 10^{-4}$)	Percent of variance due to uncertainty
zf	1.12	−1.48	+3.73	12
$zfx_g d_2$	1.15	−1.56	+3.85	13
zfs	1.21	−2.30	+4.72	49
$zfsx_g d_2$	1.23	−2.41	+4.87	50

[a] z = ratio of diesel exposure among exposed employees observed in 1961–1974 to diesel exposure among exposed employees observed in 1950–1960. Assumed values: 2.0 and 2.6; f = ratio of bus driver and conductor diesel exposure to garage engineer diesel exposure. Assumed values: 0.2 and 0.8; s = proportions of cigarette smokers in each of three job categories. Assumed values: 0.5 and 0.6; x_g = mean concentration gradient in London Transport diesel bus garages in $\mu g/m^3$ particulates. Assumed values: 235 and 303; d_2 = mean lifetime duration (in years) of diesel exposure among exposed employees observed during 1961–1974. Assumed values: 20 and 26.

[b] Estimates of θ measured in $(\mu g/m^3 \text{ particulates} \times \text{years})^{-1}$.

emissions. However, the results of nonhuman laboratory bioassays can be used to approximate the relative carcinogenic potencies of a given dosage of diesel engine emissions and the related emissions. Estimates of human lung cancer risks from exposure to coke oven or roofing tar emissions, based upon the laboratory bioassays, can then be adjusted by the corresponding estimates of their carcinogenic potencies relative to diesel emissions, based upon the laboratory bioassays. This procedure yields indirect estimates of the human lung cancer risk of diesel emissions exposure. The critical assumption in this procedure is that the relative carcinogenic potencies of diesel emissions and the related environmental emissions are preserved across human and nonhuman biological systems. In view of interspecies and interogan differences in distribution of particulates, extractability of particulate-bound organics, target site of action, metabolism, and genetic repair mechanisms, this assumption must be regarded as, at best, an approximation.

Let $\hat{\theta}_e$ be an estimate of the potency in man of related environmental exposure e. Let $\hat{\beta}_e$ and $\hat{\beta}_d$ be estimates of the potencies in a nonhuman bioassay system of related environmental exposure e and diesel emission d, respectively. Then our indirect estimate of θ_d, the effect of diesel in man, is

$$\hat{\theta}_d = \hat{\theta}_e(\hat{\beta}_d/\hat{\beta}_e) \tag{3}$$

2.2.1. *Epidemiological Studies*

Table V shows the estimates of the parameter θ for three epidemiological studies of lung cancer. In each case, a linear, constant relative risk model has been assumed. The first row of the table summarizes my analysis of the LTA data. The estimate in the second row is based on observed respiratory cancer deaths and person-years at risk among nonwhite steel workers during 1951–1966, according to lifetime exposure to coke oven emissions. The data, compiled by the U.S. Environmental Protection Agency (ref. 7, Table 1), are derived from a study of mortality among steel workers in Allegheny County, Pennsylvania.[5,6] Cumulative lifetime dosage is measured in $\mu g/m^3$ benzene-soluble organics × years.

The estimate of θ in the third row of the table is based on observed lung cancer deaths among members of the United Slate, Tile and Composition Roofers, Damp and Waterproof Workers Association during 1960–1971, derived from Hammond *et al.* (ref. 8, Table 8). The authors also reported expected deaths based on lung cancer rates among all U.S. males during the period. Although the data were organized according to the duration of occupational exposure to roofing tar emissions, the authors provided independent measurements of the mean quantity of benzo(a)pyrene inhaled per day. The raw data for both the coke oven and roofing tar studies, as well as the details of estimating θ, are given in Harris.[1]

2.2.2. *Short-Term Bioassays*

In this report, the quantitative analysis of relative potencies of diesel and related environmental emissions is confined to experiments conducted as part of the U.S. Environmental Protection Agency's Diesel Emission Research Program.[9] This choice of

Table V. Estimates of the Parameter θ for Three Epidemiological Studies of Lung Cancer

Occupational exposure (years of observation)	Source of data	Total number of lung cancers observed	Unit of cumulative exposure	Maximum likelihood estimate (standard error)
Diesel bus garage workers, drivers, and conductors, London Transport (1950–1974)	Waller and Raffle[4]	667 lung cancer cases	$\mu g/m^3$ particulates × years	1.23×10^{-4} (1.86×10^{-4})
Coke plant workers in Allegheny County, Pennsylvania (1951–1966)	U.S. EPA[7]	79 respiratory cancer deaths	$\mu g/m^3$ benzene-soluble organics × years	4.40×10^{-4} (1.50×10^{-4})
United Slate, Tile and Composition Roofers, Damp and Waterproof Workers Association (1960–1971)	Hammond et al.[8]	121 lung cancer deaths	ng/m^3 BaP × years	1.46×10^{-4} (2.06×10^{-4})

experiments was constrained by the limited availability of published data comparing diesel emissions to other related environmental emissions in the same bioassay under identical experimental conditions. Three assays were selected for analysis: (i) skin tumor initiation by in vivo skin painting in SENCAR mice[10]; (ii) enhancement of viral oncogenic transformation in vitro in Syrian hamster embryo (SHE) cells[12]; and (iii) mutagenesis in vitro in L5178Y mouse lymphoma cells.[11] These specific assays were chosen for the following reasons. Each experiment was considered to have been performed reliably and reproducibly. The experimental results were displayed in a manner susceptible to statistical analysis. Each assay was considered a valuable, quantitative measure of carcinogenicity [assays (i) and (ii)] or mutagenicity [assay (iii)] in mammalian systems. These three assays were performed on organic solvent extracts of collected particulates. No reproducible, quantitative test of the comparative bioavailability of whole particulates or whole emissions could be obtained.

Table VI presents a summary of the emission extracts tested in each assay, including sampling conditions, emission rates for mobile sources, extractable fraction, and benzo(a)pyrene concentration. One

Table VI. Characterization of Emission Extracts[9]

Emission sample	Sampling conditions	Emission rates (mobile sources only)	Percent dichloro-methane extractable	ng B(a)P per mg extract
Coke oven	Atop coke oven battery, Republic Steel, Gadsden, Alabama, 2100 hours	—	5–10	478
Roofing tar	Tar pot with pitch-based tar at 360°–380°F, 8 hr	—	> 99	889
Caterpillar 3304 diesel engine	Diesel Fuel No. 2, Mode II driving cycle, 2200 rpm, 85-lb load, 12.75 min, 10.24 miles	0.72 g/hp/hr	26–27	2
Datsun Nissan 220-C diesel engine	Diesel Fuel No. 2, Highway Fuel Economy Test (HWFET) Cycle; average 48 mph, 12.75 min, 10.24 miles	0.33 g/mile	4–8	1173
Oldsmobile 350 diesel engine	Diesel Fuel No. 2, Highway Fuel Economy Test (HWFET) cycle; average 48 mph, 12.75 min, 10.24 miles	0.52 g/mile	12–17	2
Volkswagen turbo-charged Rabbit diesel engine	Diesel Fuel No. 2, Highway Fuel Economy Test (HWFET) Cycle; average 48 mph, 12.75 min, 10.24 miles	0.18 g/mile	18	26
1978 Mustang II-302 engine	Unleaded gasoline; V-8, equipped with catalytic converter with exhaust gas re-circulation HWFET cycle; average 48 mph, 12.75 min, 10.24 miles	0.0053 g/mile	39–43	103

heavy-duty diesel engine (Caterpillar) and three light-duty diesel engines (Datsun, Oldsmobile, and Volkswagen) were sampled. Also included is an emission sample from a spark-ignition engine (Mustang), run on unleaded fuel with a catalytic converter at a rich stoichiometry.

For the purpose of risk quantification, it is desirable that the results of different bioassays be analyzed in the same manner. In this report, therefore, all short-term bioassay data were analyzed in terms of a linear dose-response model analogous to that used in the epidemiological studies of Table V. Alternative measures of relative potency based, for example, upon lowest effective concentrations tested or maximum response without toxicity, do not necessarily conform to such a linear model and may therefore produce results that are misleading for risk quantification.

Let n_j be the number of positive responses (skin papillomas, transformed cells, mutant colonies) and N_j the number of surviving experimental sites (surviving mice, surviving SHE cells in culture, surviving L5178Y cells in culture) at dose X_j. The results of these bioassays were analyzed under the assumption that n_j are independent Poisson distributed with means

$$N_j(\alpha + \beta X_j)$$

The parameters α and β were estimated by maximum-likelihood techniques from data on n_j, N_j, and X_j. The slope parameters β measure the effect of a unit change in dose on mean positive response per site (papillomas/mouse, transformations/surviving cell, mutant colonies/surviving cell).

This simple statistical model is necessarily an approximation of the more complicated dose-response processes that actually generated the data in each experiment. It is likely that the mean positive response rate varies among different sites at any

Table VII. Estimates of the Potency of Organic Extracts of Diesel Exhaust and Related Environmental Emissions in Two Short-Term Bioassays[a]

Emissions extract	Tumor initiation in SENCAR mice[b] (papillomas/mouse per mg extract at 27 weeks)	Enhancement of SA7 viral transformation in Syrian hamster embryo cells[c] (transformations/2×10^6 cells per μg extract/ml)
Coke oven	2.10	.86
	(.09)	(.09)
Roofing tar	0.54	2.07
	(.02)	(.36)
Caterpillar 3304 diesel engine	.01	.04
	(.01)	(.02)
Nissan Datsun 220-C diesel engine	.53	.65
	(.02)	(.10)
Oldsmobile 350 diesel engine	.16	.07
	(.03)	(.02)
Volkswagen turbocharged Rabbit diesel engine	—	.13
	—	(.02)
1978 Mustang II-302 V-8 catalyst engine	.03	.20
	(.007)	(.03)
Benzo(a)pyrene positive control	85.3	540
	(2.7)	(22)

[a] Maximum-likelihood estimates of slope of linear dose response model based upon Poisson distribution of positive responses. Asymptotic standard errors in parentheses.
[b] Data from Nesnow *et al.*[10]
[c] Data from Casto *et al.*[12]

given dosage. (For example, mice may vary in their susceptibility to tumorigenesis.) If this heterogeneity is substantial, the variances of the observed response rates will be incorrectly estimated by the simple Poisson model. To overcome this difficulty, we could specify a compound Poisson model (for example, a negative binomial). To apply such a model, however, we would have to specify how the variability of response rates depends upon dose. The use of the simpler Poisson specification in this report therefore should be regarded as an initial attempt to apply a uniform statistical model to diverse experimental data.

Table VII shows the resulting estimates of β for tumor initiation in SENCAR mice and enhancement of viral transformation. Table VIII shows the resulting estimates of β for mutagenesis in mouse lymphoma cells with (+) and without (−) metabolic activation by S-9. In all experiments, the potencies of the diesel extracts depended upon the type of engine tested. In Table VII, the estimated potencies of roofing tar and coke oven emission extracts exceeded those of the diesel emission extracts. In Table VIII, the estimated potencies of coke oven and roofing tar extracts exceeded those of the diesel extracts only in the presence of metabolic activator.

On a pure weight basis, the potencies of the diesel emission extracts range from approximately 20 times that of the spark-ignition engine emission extract to one-third that of the spark-ignition engine emission extract. When these relative potencies are combined with the extractable fraction and emission rate data in Table VI, the spark-ignition engine emissions consistently had a lower biological activity per mile traveled than the diesel engine emissions. For example, the average dichloromethane extractable fraction of the Oldsmobile diesel engine sample was 14.5%. This engine therefore emitted 0.52 g/mile × 14.5% = 0.075 g/mile of extractable material. This emission rate of extractable material is about 35 times the corresponding rate of emission of extractable material for the spark-ignition engine. By contrast, the potency of the spark-ignition extract was at most about three times that of the Oldsmobile sample (see the viral transformation data in Table VII).

2.2.3. *Estimates of Diesel-Related Risk*

The estimates of the effects of coke oven emissions and roofing tar emissions in man (Table V) can now be combined with estimates of the relative

Table VIII. Estimates of the Potency of Organic Extracts of Diesel Exhaust and Related Environmental Emissions in the L5178Y Mouse Lymphoma Mutagenesis Assay[a]

Emissions extract	Average mutant colonies/10^6 survivors per μg extract/ml	
	− Metabolic activation	+ Metabolic activation
Coke oven	.73 (.15)	9.96 (.73)
Roofing tar	.31 (.12)	.56 (1.55)
Caterpillar 3304 diesel engine	.16 (.04)	.05 (.02)
Nissan Datsun 220-C diesel engine	1.66 (.51)	1.87 (.49)
Oldsmobile 350 diesel engine	.27 (.12)	.76 (.11)
Volkswagen turbocharged Rabbit diesel engine	2.55 (.40)	1.01 (.20)
1978 Mustang II-302 V-8 catalyst engine	.35 (.04)	.99 (.10)

[a]Maximum-likelihood estimates of slope of linear dose response model based upon Poisson distribution of positive responses. Asymptotic standard errors in parentheses. Data from Mitchell *et al.*[11]

potencies of the extracts of diesel emissions and the related emissions (Tables VII and VIII). Consider, for example, the potency of the Nissan Datsun extract relative to the coke oven extract in the skin tumor initiation experiments. From Table VII

$$\hat{\beta}_d = \underset{(.02)}{0.53} \text{ papillomas/mouse per mg extract}$$

and

$$\hat{\beta}_e = \underset{(.09)}{2.10} \text{ papillomas/mouse per mg extract}$$

and, therefore

$$\hat{\beta}_d/\hat{\beta}_e = \underset{(.02)}{.25} \qquad (4)$$

where the standard error of the ratio was calculated from the conventional first-order approximation. The potency of coke oven emissions in man, from Table V, is

$$\hat{\theta}_e = \underset{(1.5)}{4.4} \times 10^{-4} \text{ per } \mu g/m^3$$

benzene-soluble organics × years.

The resulting estimate of $\hat{\theta}_d = \hat{\theta}_e(\hat{\beta}_d/\hat{\beta}_e)$ [Eq. (3)] is therefore 1.1×10^{-4} per $\mu g/m^3$ benzene-soluble organics × years (standard error 3.8×10^{-5}). To convert this estimate into particulate exposure units, we multiply it by the 6% extractable fraction of diesel particulates for the Nissan Datsun sample (Table VI).

Table IX. Range of Estimated Values of the Parameter θ Derived from Comparative Analysis of Diesel Engine Emissions, Coke Oven Emissions, and Roofing Tar Emissions

	Range of estimates (in units of relative risk of lung cancer per $\mu g/m^3$ particulates × yr)	
Diesel emission extracts	Tumor initiation and viral enhancement only ($\times 10^{-4}$)	All bioassays ($\times 10^{-4}$)
Nissan Datsun 220-C	0.03–0.20	0.02–0.60
Oldsmobile 350	0.01–0.07	0.01–0.24
Volkswagen Rabbit[a]	0.02–0.12	0.02–2.78
Caterpillar 3304	0.01–0.05	0.01–0.25

[a] No data for tumor initiation.

This yields $.07 \times 10^{-4}$ per $\mu g/m^3$ particulates × years (standard error $.02 \times 10^{-4}$).

For each diesel emission extract, we have up to eight different estimates of θ_d. The range of these estimates for different diesel emission extracts and different types of experiments is summarized in Table IX. Because skin tumor initiation and viral enhancement experiments may be considered by some scientists to be more reliable assays of relative carcinogenic potency than mutagenesis experiments, the range of estimates from the former two assays is displayed separately. The estimates in Table IX fall within the 95% confidence interval derived from the LTA study (upper confidence limit 5×10^{-4} per $\mu g/m^3$ particulates × years; see Tables IV and V). The highest value of $\hat{\theta}_d$ represents the case in which the relative potencies of the Volkswagen Rabbit turbocharged diesel extract and coke oven extract are derived from the mutagenesis assay in the absence of metabolic activator. In that case, the diesel extract is a more potent indirect mutagen (Table VIII).

It is not obvious how to combine the indirect estimates into an overall measure of the range of uncertainty in human cancer risk. Each indirect estimate $\hat{\theta}_d$ has its own statistical confidence interval, determined by the statistical variations in the underlying epidemiological and bioassay data. But there are also variations among the different estimates which, roughly speaking, gauge the uncertainty arising from our approximation of relative potencies in humans by means of nonhuman bioassay data. If I regard each estimate $\hat{\theta}_d$ as an equally likely measure of the true value of the parameter θ_d, then I can proceed in a manner similar to Eq. (2) to calculate an overall mean estimate and an overall variance. For the three light-duty diesel engine extracts, the overall mean estimate for the lung cancer risk in man was 0.35×10^{-4}, with a standard error of 1.11×10^{-4}, a 95% lower confidence limit of -1.82×10^{-4}, and a 95% upper confidence limit of 2.52×10^{-4} (all estimates in units of relative risk per $\mu g/m^3$ particulates × years). Thus, 45% of the variance of the overall mean reflected variation between the estimates $\hat{\theta}_d$. Inclusion of the indirect estimates from the heavy-duty diesel engine extract (Caterpillar) reduced the 95% upper confidence interval slightly to 2.15×10^{-4} per $\mu g/m^3$ particulates × years.

It needs to be clear that this method of expressing the overall uncertainty in human cancer risk is at best approximate. Because the indirect estimates $\hat{\theta}_d$ are derived from common experiments, they are not stat-

istically independent. Moreover, they are not necessarily equally probable estimates of the true value of θ_d. A weighted average of the indirect estimates, rather than the simple arithmetic mean, would be more appropriate. The assignment of these weights, however, would depend upon a precise statistical model of the deviations from the underlying hypothesis of constant relative potencies across species. The formulation of such a model, however, is beyond the scope of this report.[21]

3. INTERPRETATION OF THE RESULTS

Despite different sources of data, different analytical assumptions, and different possible sources of error, both methods of analysis yielded a statistical upper confidence limit for lung cancer risk in humans in the order of a 0.05% increase in lung cancer incidence per unit of lifetime cumulative exposure, where one unit is equivalent to inhaling a concentration of one microgram of particulates per cubic meter for one year.

This paper does not evaluate projections of the increment in ambient diesel particulate concentrations resulting from alternative periods in the market growth of light-duty diesel vehicles. It does not evaluate the impact of alternative particulate emissions standards on ambient diesel particulate concentrations. Nevertheless, the use of various published estimates of incremental particulate concentrations is helpful in evaluating the magnitude of the estimated range of risk.

Williams and Chock (ref. 22, Table XIV) have projected an increase in the concentration of particulates in the atmosphere if 25% of the light-duty automobile fleet in the year 2000 were diesel powered. The estimates of the annual mean for "worst cases in the downtown areas" ranged from 2.0 $\mu g/m^3$ particulates for Cincinnati, Denver, and Philadelphia to 10.5 $\mu g/m^3$ particulates in the region of the Los Angeles freeways. Forrest *et al.* (ref. 23, Table 6) have estimated under a similar market scenario that the diesel contribution to particulate concentrations 300 feet from the edge of urban freeways was in the range of 9–12 $\mu g/m^3$ by the turn of the century. Briggs *et al.* (ref. 24, Table 5–11) have estimated the average regional contribution of diesel emissions to be 0.96 $\mu g/m^3$ (best case) up to 1.73 $\mu g/m^3$ (maximum) by the year 1990. Calculations performed by the U.S. Environmental Protection Agency (ref. 25, Table V-10) indicate an incremental regional contribution of light-duty diesel vehicles by 1990 ranging from 1.2 to 1.7 $\mu g/m^3$ in cities with under 100,000 population and up to 3.6–6.2 $\mu g/m^3$ in cities with more than 1 million. The estimates do not appear to take into account possible future automobile particulate emissions standards or future changes in diesel automobile emission control technology.

The potential risk estimates in this report were based primarily on occupational exposures of men aged 40–65. The use of these estimates to evaluate the potential risk from ambient population exposure to diesel emissions is most reliable for the same age and sex group. For a male aged 40–65, who has been exposed to an average incremental particulate loading of 1 $\mu g/m^3$ for 20 years, I calculate the upper confidence limit of risk to be a 1% increase in lung cancer incidence. For a male aged 40–65, who has been exposed to an average increment of 10 $\mu g/m^3$ of diesel particulates for 30 years, I calculate the upper confidence limit of risk to be a 15% increase in lung cancer incidence.

These estimates of the upper confidence limit of increased lung cancer risk should not be construed as absolute measures of human health impact. The estimated lower confidence limits, I emphasize, include the possibility of no effect or even in a reduction in lung cancer risk. The confidence limits do serve, however, as an indicator of the extent of uncertainty regarding the carcinogenic effects of diesel engine emissions for man.

The estimated confidence limits are valuable, in particular, for comparing the potential risks of ambient population exposure to diesel engine emissions with other personal and societal risks. A male nonsmoker who has been occupationally exposed to asbestos for 20–30 years suffers a proportional increase in lung cancer risk ranging from 100%–700%.[18,26] A male, aged 40–65, who has smoked cigarettes for a comparable period suffers a proportional increase in lung cancer incidence ranging from about 1000%–2000%.[19,20]

Based upon 1977 age-specific death rates for both lung cancer and for all causes among men aged 40–64 years (provided by U.S. National Center for Health Statistics), I computed the effect of a given proportional increase in the lung cancer death rate on the overall force of mortality. For a white male aged 40, a 1% increase in lung cancer mortality would diminish his probability of surviving to age 65 by about 1 in 4500. A 15% increase in lung cancer

mortality would diminish his probability of surviving to age 65 by about 1 in 300. A 1000% increase in lung cancer mortality would diminish his probability of surviving to age 65 by about 1 in 5. These calculations are based on the current cross section of men aged 40–65 in the United States and therefore reflect the average effect among different birth cohorts.

The comparative analysis of Sect. 2.2 also includes extracts from a single-spark-ignition engine run on unleaded fuel and equipped with a catalytic converter. The results suggest that for the particulate phase of emissions, catalyst-equipped spark-ignition engine emissions have less biological activity per mile traveled than diesel engine emissions. Lofroth[27] and Misfeld[28] have also compared diesel engine condensates with those of gasoline-powered automobiles. But these investigators did not analyze condensates from spark-ignition engines run on unleaded fuel with catalytic converters. Accordingly, the comparative analysis of spark-ignition automobiles and diesel-powered automobiles requires further investigation.

3.1. Quantifying Sources of Uncertainty

The main analytical issue in this report is the method of quantifying the extent of uncertainty about potential health effects. In the analysis of the London Transport Authority data, I have expressed the magnitude of this uncertainty in the form of statistical confidence limits on a parameter of a specific mathematical model relating exposure to an environmental agent with the incidence of lung cancer. In the comparative analysis of diesel engine emissions, I have used the observed range of variation of the estimates of diesel-related cancer risk, based on different laboratory bioassays and related epidemiological studies, to derive analogous confidence limits.

These methods, however, may not capture all the important sources of uncertainty. In the analysis of the LTA study, an attempt was made to introduce explicitly the effect of uncertainty in the magnitude, duration, and time period of occupational exposure to diesel engine emissions, as well as the possible variations in cigarette smoking rates across occupational categories. These sources of uncertainty contributed together about 50% to the total variance in the parameter estimate [Eq. (2) and Table III]. But possible errors in extrapolation from occupational exposures to ambient population exposures may not be fully incorporated in the final estimates. Potential errors in the choice of dosage units or conversions between dosage units may not be fully reflected. Possible deviations from the linear dose-response model may not be fully incorporated. Moreover, the linearity of dose-response models for cancer incidence, especially at low doses, is a well-known object of debate. A linear specification was assumed here because it is more conservative for purposes of risk characterization than a threshold dose-response model.

In the comparative analysis of diesel and related environmental emissions, there are additional sources of uncertainty not necessarily captured in the reported confidence limits. For each estimated relative potency $\hat{\beta}_d/\hat{\beta}_e$, a critical source of uncertainty is the condition under which each emission test sample has been obtained. The estimates of the potency of a particular diesel engine emission extract relative to coke oven emission extracts, for example, were based on environmental samples from one coke oven battery and one engine under one set of operating conditions (Table VI). The standard errors of these relative potencies, as illustrated in the calculations in Eq. (4), were estimated conditional upon these selections. The unconditional potency of all diesel engine emissions relative to all coke oven emissions is likely to have a greater variance. Finally, for each indirect estimate $\hat{\theta}_d$ [from Eq. (3)], the main source of uncertainty was the validity of the underlying hypothesis that the relative potencies of diesel and related emissions in man could be approximated from nonhuman bioassay data. Because humans and other species (in this case mice and hamsters) may differ in the distribution of exposed particulates, extractability of particulate-bound organics, target site of action, metabolism, and genetic repair mechanisms, the hypothesis of constant relative carcinogenic potencies across species cannot be maintained exactly. On the other hand, information about the relative potencies of different environmental emissions in mammalian systems is not completely irrelevant to man.

The main issue is to characterize precisely how relevant the comparisons are. Although this report takes some steps in that direction, the problem of quantifying our degree of confidence in interspecies comparisons remains poorly understood (see refs. 21, 29–32).

3.2. The Calculus of Lives Lost

The parameter estimates derived in this report are most applicable to age and sex groups and for durations of exposure comparable to those observed

in the underlying epidemiological studies. For substantially different age and sex groups and durations of exposure, uncertainty about the specific mathematical form of the dose response relation becomes critical.

The linear, constant relative risk model used in this analysis measured dosage in terms of cumulative lifetime exposure. A cancer latency period was not specifically incorporated. The relative risk of lung cancer was assumed to be proportional to the duration of exposure. If cancer incidence were to be projected outside the 20–30 year duration of exposure typically observed in the underlying occupational studies, the approximations may no longer be valid. It is possible, as suggested in multistage theories of cancer etiology,[33,34] for the incidence of cancer to increase as a power of the duration of exposure. If such a model were a more accurate representation, then the proportional relation assumed in this report would overstate the potential lung cancer risk for very short durations of exposure and understate the potential lung cancer risk for very long durations of exposure. It remains unclear, however, how to distinguish the pure effect of duration of exposure from the effect of age on susceptibility to cancer.[35] In view of these uncertainties about the relation among age, duration of exposure, and cancer incidence, projections of potential health effects to very old or very young persons are considerably more uncertain.

The proportional hazards assumption used in this report implies that the effect of diesel emissions enter multiplicatively into the determination of the lung cancer incidence [Eq. (1)]. This multiplicative effect was introduced explicitly in Sec. 2.1 to assess the effect of uncertainty in smoking rates among the LTA job categories (Fig. 2). Although this implied synergy is not ruled out by the available evidence, and may be a useful conservative assumption for quantifying uncertainty, it complicates the application of the relative risk model for future population exposures. The results of any prediction about the range of lung cancer risk in the entire population will depend on the background lung cancer rate and, therefore, on the status of other carcinogenic exposures—in particular future smoking habits. Although lung cancer mortality rates for women in the United States are now approximately one-fourth of those for men, this relationship is rapidly changing. These considerations introduce further difficulties in devising quantitative estimates of potential risk applicable to both sexes.

Finally, realistic scenarios of the market growth of diesel vehicles do not correspond to the instantaneous realization of a steady-state increment in particulate concentrations. More complex patterns of exposure are involved. For policy decisions, in particular, it is critical to assess the potential course of cancer rates over time after a possible end to diesel emission exposure. For cigarette smoking, which is far and away the most extensively studied and most important cause of lung cancer, the quantitative effect of cessation of smoking has been characterized.[33] The effect of discontinuation of exposure to diesel emissions, however, may be quite different.

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