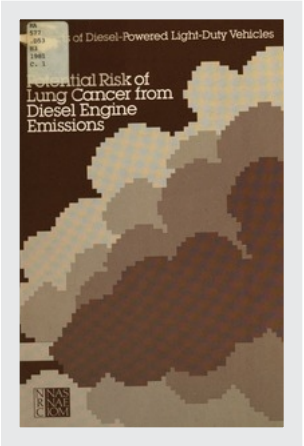

Potential Risk of Lung Cancer From Diesel Engine Emissions: Impacts of Diesel-Powered Light-Duty Vehicles

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Impacts of Diesel-Powered Light-Duty Vehicles

Potential Risk of Lung Cancer from Diesel Engine Emissions

Report to the

Diesel Impacts Study Committee

Assembly of Engineering

National Research Council

by

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PREFACE

In May 1979 the National Research Council began a comprehensive study of the human health effects and public policy issues associated with the prospective increase in the use of diesel-powered light-duty vehicles in the United States. The study was requested and supported by the U.S. Environmental Protection Agency, the U.S. Department of Energy, and the U.S. Department of Transportation.

The purpose of the study is to inform these government bodies, along with the Congress, the automotive industry, and the American public, about the current state of knowledge and understanding of the subject and to provide an authoritative and balanced examination of the risks and implications of the anticipated growth in the number of light-weight diesel vehicles. According to some projections, diesel engines are likely to power some 25 percent of the automobiles, vans and light-duty trucks by the end of the century. All things considered, government organizations responsible for regulating in the health and safety areas and concerned about the technology and economics of diesel engines need the scientific and engineering data and analyses on which to base their policy decisions.

Accordingly, the Research Council organized the Diesel Impacts Study Committee (DISC) in the Assembly of Engineering, which operated in conjunction with the Assembly of Life Sciences for aspects of the study dealing with the possible adverse health effects of diesel engine emissions. The committee consists of 20 members drawn from diverse disciplines and backgrounds--medical research, health care, environmental protection, chemical and mechanical engineering, political science,

economics, banking, and business management. Because the scope of the study involves a complex range of questions and problems, the committee established four panels to examine, respectively, the issues involving technology, environment, human health, and public policy. Each of the four panels is made up of specialists drawn from the relevant subject of concern as well as some members of the committee.

In performing their separate tasks the panels sometimes called on experts to assist in examining special matters and explicating certain problems. Thus, the Analytic Panel, established to assist in the DISC review of public policy issues, asked Jeffrey E. Harris, Associate Professor of Economics at the Massachusetts Institute of Technology, to perform a systematic epidemiological analysis of those few studies of the impacts of particular pollutants on humans exposed to the contaminants in the workplace. The work of Dr. Harris (a member of DISC's Analytic Panel) was used in the preparation of Health Effects of Exposure to Diesel Exhaust, a report of the DISC Health Effects Panel and in the documentation of the Analytic Panel. To provide a wider dissemination of the complete report by Dr. Harris, the Committee requested the National Research Council to publish the document as a Supporting Paper. A majority of committee members have approved its publication.

Although the National Research Council does not customarily submit to review a paper signed by a single author and commissioned as a background or supporting document, this report has been reviewed according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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CONTENTS

TABLES

I. SUMMARY AND CONCLUSIONS

This reports 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. I discuss the value of these estimates for comparing the potential lung cancer risks from exposure to diesel engine emissions with other personal and societal risks. I also consider the limitations of these results in predicting the possible excess incidence of lung cancer from ambient exposure to diesel emissions. This report does not treat comprehensively all 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. It does not examine the broader question of the relation between environmental pollutants in general and human lung cancer.

The report examines the incidence of lung cancer among men, aged 45 to 64, employed by the London Transport Authority during the years 1950-1974. The lung cancer incidence of diesel bus garage workers was not significantly greater than the lung cancer incidence of other employees who were not exposed to excess diesel engine emissions. The reliability of this negative

finding, however, is limited by imprecise measurement of the extent of diesel emission exposure, missing information about the cigarette smoking practices of employees and uncertainty about the exact form of the mathematical relation between the dose of a carcinogenic agent and the incidence of human cancer. I therefore proceed to estimate the possible magnitude of an undetected effect--that is, to calculate an upper limit of statistical confidence in the extent of diesel-related lung cancer. I conclude, with 95 percent confidence, that the undetected incidence of lung cancer among diesel bus garage workers was no greater than 160 percent of the incidence of lung cancer among other unexposed employees.

I then use data on smoke concentrations inside and outside the London Transport Authority's diesel bus garages to convert the estimates of the possible range of occupational risk into estimates of the possible range of lung cancer risk from ambient population exposure to diesel engine emissions. This method of estimation assumes that the proportional increase in lung cancer incidence is a linear function of the cumulative lifetime exposure to diesel engine emissions. It also assumes that the diesel emissions inhaled by workers in bus garages do not undergo significant chemical transformation in the environment prior to inhalation by the general population. Based upon these assumptions, I find that the upper confidence limit of potential risk represents a 0.05 percent proportional increase in lung cancer incidence per unit of exposure to diesel engine emissions, where one unit of exposure is equivalent to inhaling a concentration of 1 microgram of particulates per cubic meter for one year.

I then turn to the comparative analysis of diesel engine emissions and the two related environmental exposures. I use the same mathematical dose-response model of lung cancer incidence to analyze epidemiological data on occupational exposures to 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 coke oven emissions and to roofing tar 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 emissions. However, we can use the results of non-human laboratory bioassays to approximate the relative carcinogenic potencies of the same dosage of diesel engine emissions and the related emissions. Estimates of the human lung cancer risks from exposure to coke oven or roofing tar emissions, based on epidemiological studies, can then be adjusted by the corresponding estimates of their carcinogenic potencies relative to diesel emissions, based on laboratory bioassays. This procedure yields indirect estimates of the human lung cancer risk of diesel emission exposure.

The critical assumption in this procedure is that the relative carcinogenic potencies of diesel engine emissions and the related environmental emissions are preserved across human and non-human biological systems. In view of interspecies and interorgan differences in the distribution of particulates, extractability and clearance of particulate-bound organics, target site of action, metabolism, and genetic repair mechanisms, this assumption needs to be regarded as at best an approximation.

Data from three short-term bioassays of the organic solvent extracts of diesel engine emissions and the two related emissions are used to estimate the relative carcinogenic potencies. The bioassays include tumor initiation in SENCAR mice by skin painting, enhancement of viral transformation in Syrian hamster embryo cells, and mutagenesis with and without metabolic activation in L5178Y mouse lymphoma cells. In each bioassay, the extracts of the emissions of several different diesel engines are analyzed.

In the laboratory bioassays, the mutagenic and carcinogenic potencies of the diesel emission extracts are found to depend on the type of engine tested. The relative potencies of the extracts of diesel engine emissions and related emissions vary considerably. Except in the case of mutagenesis without metabolic activation, the potencies of the diesel extracts are equal to or less than the corresponding potencies of the related emission extracts.

Estimates of the risk of human lung cancer from exposure to diesel engine emissions, based on epidemiological evidence from coke oven emissions and roofing tar emissions, in combination with bioassay

estimates of their potencies relative to diesel emissions, all fall within the statistical confidence interval derived from the analysis of the London Transport Authority data. The approximate upper confidence limit of potential risk derived from this comparative analysis is a 0.03 percent proportional increase in lung cancer incidence per unit of exposure (micrograms of particulates per cubic meter x years).

Despite different sources of data, different analytical assumptions, and different possible types of errors, the estimates of potential risk derived from the two distinct methods are consistent.

This report does not evaluate projections of the increment in ambient concentrations of diesel particulates resulting from alternative levels of market growth in the use of light-duty diesel vehicles. It does not evaluate the impact of alternative particulate emissions standards on ambient concentrations of diesel particulates. Nevertheless, the use of various published estimates of incremental particulate concentrations is helpful in evaluating the significance of the estimated upper confidence limit of human lung cancer risk.

Studies conducted so far suggest that an increase in the market share of light-duty diesel vehicles to 25 percent by the turn of the century could result in a regional average incremental concentration of particulates for a typical area of the nation on the order of 1 microgram per cubic meter over a 20 to 30 year period. Still, for an urban resident living in close proximity to a freeway, such an increase in light-duty diesel vehicle use could result in an average incremental particulate loading on the order of 10 micrograms per cubic meter over the same period. These estimates do not take account of prospective automobile particulate emissions standards or changes in emission control technology for diesel vehicles.

For a male aged 40 to 65 who has been exposed to an average increment of 1 microgram per cubic meter of diesel particulates for 20 years, I calculate the upper confidence limit of risk to be a 1 percent increase in lung cancer incidence. For a male aged 40 to 65 who has been exposed to an average increment of 10 micrograms per cubic meter of diesel particulates for 30 years, I calculate the upper confidence limit of risk to be a 15 percent increase in lung cancer incidence.

The estimates of the upper confidence limit of

increased lung cancer risk do not provide an absolute measure of human health impact. The estimated lower confidence intervals, it must be recognized, include the possibility of no effect or even a reduction in lung cancer risk. These confidence limits do serve, however, as an indicator of the extent of uncertainty regarding the carcinogenic effects of diesel engine emissions in humans. The estimates are useful, in particular, for comparing the potential risks of ambient population exposure to diesel engine emissions with other personal and societal risks. A male nonsmoker aged 40 to 65 who has been occupationally exposed to asbestos for 20 to 30 years incurs a proportional increase in the risk of lung cancer ranging from about 100 to 700 percent. A male, aged 40 to 65, who has smoked cigarettes for a comparable period incurs a proportional increase in the risk of lung cancer ranging from about 1000 to 2000 percent.

Any attempt to predict precisely a range of absolute excess cancer deaths from various magnitudes of increased accumulations of diesel particulates would require the application of the estimated upper confidence limits to durations of exposure and to age and sex groups very different from those observed in the epidemiological studies analyzed in this report. For such an application, our uncertainty about the dependence of cancer incidence on age and duration of exposure would be a critical unknown factor. The additional mathematical complexity and uncertainty inherent in such projections does not appear warranted at this time.

Estimates of the carcinogenic and mutagenic potencies of the emission extracts from a single gasoline-powered automobile engine, run on unleaded fuel and equipped with a catalytic converter, are also reported. The results suggest tentatively that for the particulate phase, tailpipe emissions from such a class of automobile engines have a lower biological activity per vehicle mile travelled than diesel engine emissions. Because of the relatively small data base examined, it is not possible at this time to provide a more precise comparison of the potential lung cancer risks of exhaust emissions from diesel-powered and gasoline-powered engines.

The central analytical issue in this report is the method for quantifying uncertainty about potential health effects. In the analysis of the London Transport Authority data, I express the magnitude of this

uncertainty in the form of statistical confidence limits. In the comparative analysis of diesel engine emissions, I use the observed range of variation of the estimates of diesel-related cancer risk, based on different laboratory bioassays and related emissions, to derive analogous confidence limits. Even so, these methods may not capture all important sources of uncertainty. Possible errors in extrapolation from occupational exposures to ambient population exposures may not be fully incorporated. Potential deviations from the linear dose-response relation may not be completely incorporated. Possible errors in the choice of dosage units or conversions between different dosage units may not be fully reflected. Although the quantitative expressions of uncertainty used in this report are based wherever possible on objective evidence, it ought to be recognized that some subjective judgment is inevitable.

These analytical difficulties need to be viewed in perspective. The problem of quantifying uncertainty about human lung cancer risk from diesel engine emissions applies to the evaluation of environmental hazards generally.

II. INTRODUCTION

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

In Section III, 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 (Raffle, 1957; Waller, 1979; Waller and Raffle, 1980, unpublished). The second examines the epidemiological evidence of lung cancer risks from two related environmental exposures--coke oven emissions (Lloyd, 1971; Mazumdar et al., 1975; U.S. Environmental Protection Agency, 1979) and roofing tar emissions (Hammond et al., 1976). 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 (Huisingh et al., 1979; Nesnow et al., 1980; Mitchell et al., 1979; Casto et al., 1979). The potential risk estimates derived from these two distinct methods are then compared.

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

This report is based on selected published works as

well as unpublished data received by the author prior to August 25, 1980. The report 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.

III. 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 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. 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 (Schenker, 1980; Schenker and Speizer, 1979). Of all studies thus far performed, the London Transport Authority study more closely approaches but does not satisfy the ideal.

A. The London Transport Study

In 1957, Raffle examined the lung cancer incidence among several categories of London Transport Authority employees in the years 1950-54. This study has been updated by Waller (1979) to cover the period 1950-74.

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.

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 refuelled 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 (or subway system). They are not expected to have excess exposure to diesel engine emissions.

Observed lung cancer cases among these employees included those recorded on death while the subject was still a member of the staff within one of the above job categories; those recorded on transfer 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 1950-74 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 workforce changed during the course of the period. Thus, some undetermined fractions of LTA workers in the 1950's had their origins in the West Indies and in the 1960's 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 1930's. 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 1 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 1.

The extent of individual exposure to diesel engine emissions was not measured. However, the concentrations of diesel smoke and certain diesel smoke components were

TABLE 1. Lung cancer cases among London Transport staff and expected cases based upon Greater London lung cancer death rates. Males aged 45-64.*

Time Period Job Category	Man-years at risk (*N*)	Observed cases (*O*)	"Expected" cases† (*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
1961-74			
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

*Source: Waller and Raffle, 1980, unpublished. Subject to revision.
†Based upon age-specific lung cancer death rates for Greater London males for each five-year interval during the period 1950-74.

measured inside and outside selected garages (Commins et al., 1957; Waller, 1979). 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 (Waller et al., 1961, Table 4).

Table 2 shows the variation in the measured smoke gradients according to the time of day. The highest mean gradients were recorded for the main run-out (period 4), when buses were started and idled to warm up, and the main run-in (period 2), when buses were refuelled, washed, and shunted into position. Table 2 shows that the number of measurements in each period were not proportional to the period's duration. The daily mean gradient, weighted according to the duration of the period, was 269 $\mu g/m^3$. The standard error of the weighted daily mean was 49.7 $\mu g/m^3$. If the distribution of the weighted mean is approximately normal, then the 25 percent and 75 percent confidence limits are 235 and 303 $\mu g/m^3$, respectively. The latter estimates will be used in the analysis below.

Commins et al. (1957) reported gradients in the concentrations of benzo(a)pyrene and other polyaromatic hydrocarbons. Waller (1979) 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 analysis below.

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

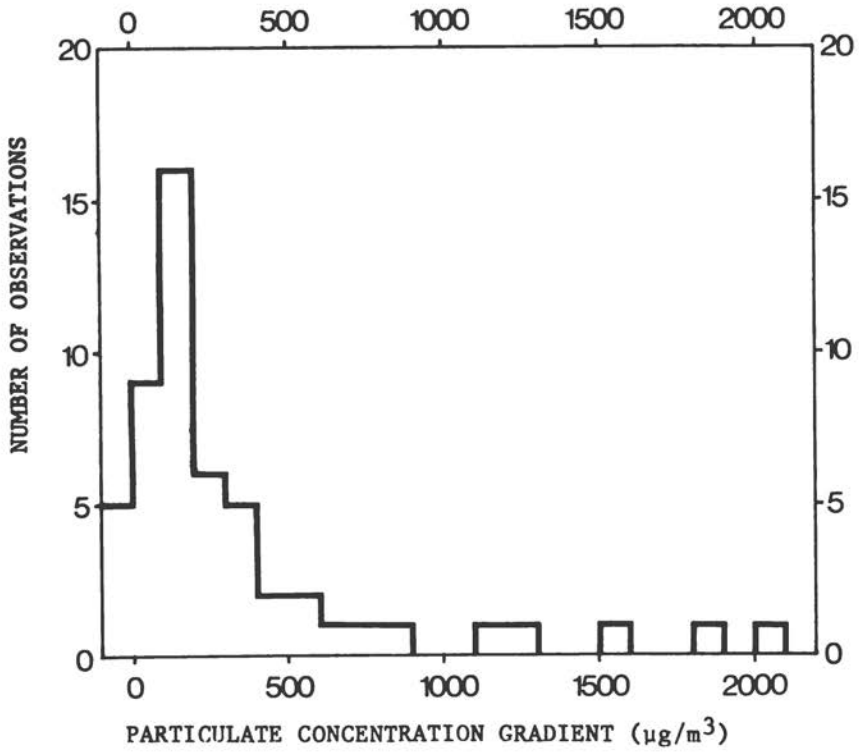

FIGURE 1. Frequency distribution of measurements of whole smoke concentration gradients in Dalston and Merton bus garages, London Transport, 1956-57. Source: Commins et al. (1957).

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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 (6 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.

TABLE 2. Whole smoke concentration gradients at Merton and Dalston bus garages during 1956-1957, London Transport.

Period No.*	Time of Day	Duration (hours)	Number of Measurements	Mean Gradient ($\mu g/m^3$)	Standard Deviation
1	6pm-11pm	5	16	387	455
2	11pm-1am	2	12	545	675
3	1am-5am	4	8	40	41
4	5am-7am	2	9	416	297
5	7am-6pm	11	8	221	184

*1. Buses refuelled and washed at intervals. 2. Main run-in; fueling and washing in progress most of the time. 3. Practically no vehicular activity. 4. Main run-out when buses leave garage at intervals. 5. Day-time.

Source: Calculated from Commins et al. (1957)

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 (1979) and Waller and Raffle (1980, unpublished) 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 1) was substantially lower than the number of "expected" cases based upon Greater London rates (column E, Table 1). For the entire study period for all LTA workers, observed cases constitute only 80 percent 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 1950's or from Asia during the 1960's 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 3, the data of Table 2 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.

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.

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

TABLE 3. Lung cancer cases among combined London Transport job categories and expected cases based upon Greater London lung cancer death rates. Males aged 45-64.*

Time Period Combined Job Category	Man-years at risk (N)	Observed cases (O)	"Expected" cases† (E)	Observed/ "Expected" (O/E)
1950-60				
Engineers, Bus Garages	49,804	96	106.9	.897
Bus Drivers & Conductors	149,805	179	278.5	.643
Engineers in Central Works, Motormen & Guards	34,299	45	64.8	.694
Total	233,908	320	450.2	.711
1961-74				
Engineers, Bus Garages	36,250	81	90.2	.898
Bus Drivers & Conductors	119,199	210	242.8	.865
Engineers in Central Works, Motormen & Guards	31,342	56	66.0	.848
Total	186,791	347	399.0	.870
1950-74				
Engineers, Bus Garages	86,054	177	197.1	.898
Bus Drivers & Conductors	269,004	389	521.3	.746
Engineers in Central Works, Motormen & Guards	65,641	101	130.8	.772
Total	419,699	667	849.2	.785

*Source: Waller and Raffle, 1980, unpublished. Subject to revision.
†Based upon age-specific lung cancer death rates for Greater London males for each five-year interval during the period 1950-74.

ratios $h^*(t)/h(t)$ and $h_{GL}(t)/h(t)$ are independent of t over the age range considered in the study. Equivalently,

$$r^* = h^*(t)/h(t), \text{ and,}$$

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

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

$$O = \Sigma_t\, h(t)N(t) = \frac{1}{r_{GL}} \Sigma_t\, h_{GL}(t)N(t) = \frac{E}{r_{GL}}, \text{ and}$$

$$O^* = \Sigma_t\, h^*(t)N^*(t) = r^* \Sigma_t\, h(t)N^*(t)$$

$$= \frac{r^*}{r_{GL}} \Sigma_t\, h_{GL}(t)N^*(t) = \frac{r^*E^*}{r_{GL}}.$$

and therefore

$$\frac{O^*}{E^*} = r^* \frac{O}{E}.$$

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.

Analysis of Data: For the entire study period 1950-74,

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 3. For example, the O/E ratio for the garage engineers is about 16 percent 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 1950-74 period. If the midpoint in the growth of diesel buses occurred at about 1945, then a continuously employed garage engineer observed during 1950-60 would experience an average duration of exposure of 10 years, while a continuously employed garage engineer observed during 1961-74 would experience an average duration of exposure of 23 years. Comparison of O/E ratios among combined job categories for the periods 1950-60 and 1961-74 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 1950-60 and 1961-74, 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 1950-74 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 1961-74, 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 percent 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 1961-74, 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 4. 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 1950's--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 nonrandom 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 percent in 1950, and ranged from 53 to 62 percent among different social classes in 1958 (Royal College of Physicians of London, 1977, Figure 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 percent. Below, the proportions of cigarette smokers will be denoted by the variables δ_1, δ_2, and δ_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 Figure 1 and Table 2 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

TABLE 4 Sources of uncertainty in analysis of London Transport data

A.	Difference among Job Categories in Cigarette Smoking Rates (δ_1, δ_2, δ_3).
B.	Variations in Excess Diesel Emission Exposure among Garage Engineers (x_g).
C.	Uncertain Exposure of Bus Drivers and Conductors (β).
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.

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 β, 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 1961-74 exposure to 1950-60 exposure; and d_2, which represents the duration of exposure of LTA workers observed in 1961-74. 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 specify 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

$$r^* = (1 + \theta X)(1 + mY).$$

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 (Liddell et al., 1977).

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 1950-60 and 1961-74) and job category j = 1,2,3 (indexing the three job categories in Table 3). 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

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

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 δ_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 δ in Table 4 corresponds to X_{i2}/X_{i1} (for $i = 1,2$). The variable z in Table 4 corresponds to X_{2j}/X_{1j} (for $j = 1,2$). If we set $X_{21} = 1$, then any choice of δ and z determines the cumulative dosages X_{ij} relative to the garage engineers in 1961-74. Hence, $1 + \theta$ is the relative risk of lung cancer among the garage engineers in 1961-74.

Figure 2 depicts the maximum likelihood estimates of the upper and lower 95 percent confidence limits of $1 + \theta$, for different preselected values of δ and two extreme values of z . For the calculations in Figure 2, smoking proportions δ_j were assumed to be equal. The maximum likelihood estimates of θ were obtained under the assumption that the data O_{ij} were multinomially distributed across the (ij) cells with mean values $\alpha_i E_{ij}(1 + \theta X_{ij})(1 + m\delta_j)$. Since the maximum likelihood estimates of θ were generally insignificantly different from zero (by the standard likelihood ratio test), they are not depicted in the Figure. However, the goodness of fit of the model was generally acceptable. (A standard likelihood ratio test of observed to expected values, asymptotically distributed as chi-square, showed a significant fit at the 5 percent level.) The upper and lower confidence limits shown in Figure 2 were derived from the estimated asymptotic standard error of θ, assumed to be normally distributed.

As the value of δ increases from zero in Figure 2, the relative exposures among the three job categories become increasingly consistent with the relative O/E values in 1961-74, and increasingly inconsistent with the relative O/E values in 1950-60. The different sensitivities of the estimated confidence bounds for the two values of z reflect the effective weights placed upon

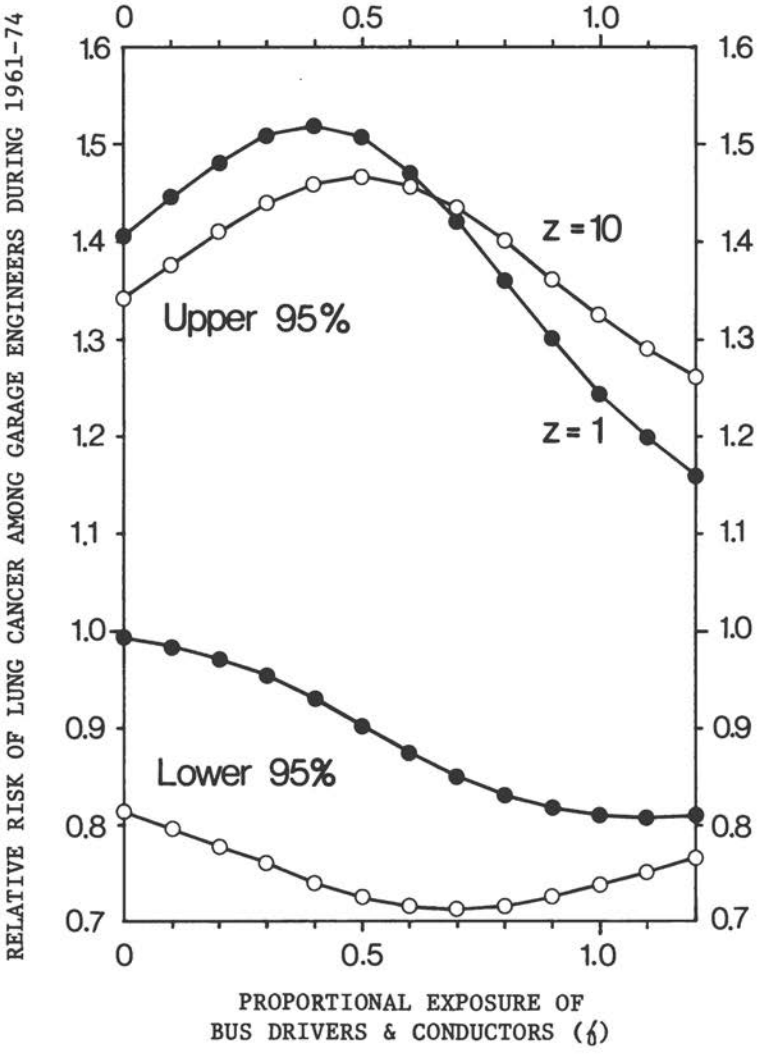

FIGURE 2. Ninety-five percent confidence limits of the relative risk of lung cancer among London Transport garage engineers during 1961-74 for various values of the exposure variables z and δ.

the two periods in the estimation procedure. Nevertheless, if smoking proportions are taken to be identical among the three categories, the upper 95 percent confidence limit on the relative risk of lung cancer among garage engineers in 1961-74 does not generally exceed 1.5 over a wide range of values of γ and z.

Figure 3 depicts the corresponding maximum likelihood estimates of the upper and lower 95 percent confidence limits of $1 + \theta$ for different values of the smoking proportion δ_1, for fixed values of the other variables $\gamma = 0.5$, $z = 2.3$, $\delta_2 = \delta_3 = 0.55$. The variable m, the increment in relative risk of lung cancer for cigarette smokers, was taken to be 10 (Doll and Peto, 1976; U.S. Department of Health, Education, and Welfare, 1979). Figure 3 shows a substantially greater sensitivity to variations in the smoking proportion of the garage engineers. At values of δ_1 below 50 percent, the maximum likelihood estimate of θ was significantly different from zero, but the linear constant relative risk model fit poorly. At higher values of δ_1, the maximum likelihood estimate 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 Figure 5, the upper 95 percent 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, γ, δ_1, δ_2, δ_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 percent and 25 percent fractiles of the underlying continuous distribution. In that case, the joint density of the variables $\{z, \gamma, \delta_1, \delta_2, \delta_3\}$ takes on $2^5 = 32$ equally likely values. Each value of $\{z, \gamma, \delta_1, \delta_2, \delta_3\}$ 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 $\tilde{\theta} = \frac{1}{32} \Sigma_k \hat{\theta}_k$ and the variance of $\tilde{\theta}$ is

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

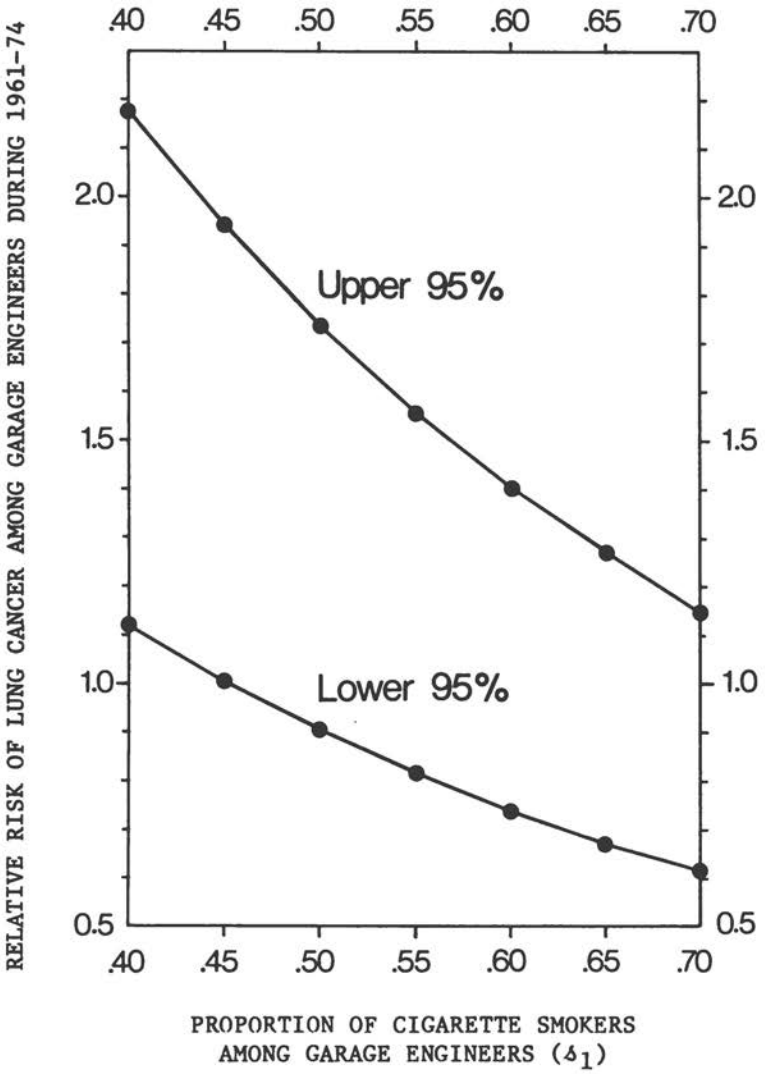

FIGURE 3. Ninety-five percent confidence limits of the relative risk of lung cancer among London Transport garage engineers during 1961-74 for various values of the smoking proportion variable δ_1.

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 4). 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; $\delta = 0.2$ or 0.8; each $\delta_j = 0.5$ or 0.6. These values were chosen to reflect the wide range of uncertainties discussed above. 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 percent of the total variance of $\tilde{\theta}$. The overall 95 percent 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.

These statistical confidence limits were obtained from the data of Table 3. When I repeated the analysis on the disaggregated data of Table 1, the maximum likelihood estimate remained unchanged, but the statistical confidence limits were narrowed slightly due to the increased degrees of freedom. The use of the combined job categories therefore represents an unbiased, conservative procedure for assessing the range of potential risk.

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 1961-74, then $X_{21} = px_g d_2$ is their mean cumulative lifetime dose. Any given choice of p, x_g, d_2, δ, 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 estimates of θ will be in units of relative risk per $\mu g/m^3$ particulates x years.

Table 5 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 5, it is assumed to take on the previously specified independent two-point density. When a variable

TABLE 5. Effects of various sources of uncertainty on the estimated 95 percent confidence limits of the parameter θ for the London Transport study

Source of Uncertainty§	Maximum Likelihood Estimate* ($\times 10^{-4}$)	95 Percent Lower Limit* ($\times 10^{-4}$)	95 Percent Upper Limit* ($\times 10^{-4}$)	Percent of Variance Due to Uncertainty
$z\ \delta$	1.12	-1.48	+3.73	12
$z\ \delta\ x_g\ d_2$	1.15	-1.56	+3.85	13
$z\ \delta\ \delta$	1.21	-2.30	+4.72	49
$z\ \delta\ \delta\ x_g\ d_2$	1.23	-2.41	+4.87	50

§
z = Ratio of diesel exposure among exposed employees observed in 1961-74 to diesel exposure among exposed employees observed in 1950-60. Assumed values: 2.0 and 2.6.

δ = Ratio of Bus Driver and Conductor diesel exposure to Garage Engineer diesel exposure. Assumed values: 0.2 and 0.8.

*Estimates of θ measured in $(\mu g/m^3$ particulates x years$)^{-1}$.

TABLE 5. (Con't) Effects of various sources of uncertainty on the estimate 95 percent confidence limits of the parameter θ for the London Transport study

δ	= 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 expsoure among exposed employees during 1961-74. Assumed values: 20 and 26.

*Estimates of θ measured in ($\mu g/m^3$ particulates x years)$^{-1}$.

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 percent 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 5, uncertainty in the exposure parameters alone contributed about 12 percent to the total variance of $\tilde{\theta}$. Inclusion of uncertainty in smoking practices raises the proportion of the contributed variance to 50 percent. 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 percent 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 percent proportional increase in lung cancer incidence per unit of cumulative lifetime exposure, where one unit of exposure is equivalent to inhaling a concentration of 1 microgram of particulates per cubic meter for one year.

B. 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 emissions. However, the results of non-human 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 emission 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 non-human biological systems. In view of interspecies and interorgan 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 non-human bioassay system of related environmental exposure e and diesel emission d, respectively. Then our indirect estimate of θ_d, the effect of diesel emissions in man, is

$$\hat{\theta}_d = \hat{\theta}_e \cdot \hat{\beta}_d / \hat{\beta}_e$$

Epidemiological Studies: Table 6 presents data on observed respiratory cancer deaths (O) and person-years at risk (N) among non-white steel workers during 1951-66, according to lifetime exposure to coke oven emissions. These data, compiled by the U.S. Environmental Protection Agency (1979, Table 1), are derived from a study of mortality among steel workers in Allegheny County, Pennsylvania (Lloyd, 1971; Mazumdar et al., 1975). Cumulative lifetime dosage (X) is measured in $\mu g/m^3$ benzene-soluble organics x years.

Table 7 presents data on observed lung cancer deaths (O) among members of the United Slate, Tile and Composition Roofers, Damp and Waterproof Workers Association during 1960-71, derived from Hammond et al., (1976, Table 8). Also presented are expected deaths (E) based on lung cancer rates among all U.S. males during the period. Although these data are organized according to the duration of occupational exposure to roofing tar emissions, the authors have provided independent measurements of the mean quantity of benzo(a)pyrene inhaled per day.

Both Table 6 and Table 7 provide sufficient information to estimate the parameters of the linear relative risk model described in Section III.A. In the case of coke oven workers (Table 6), the number of observed cancers (O) and the number of person-years at risk (N) are provided for each age and dosage group. Hence, without resorting to the assumption of age independent relative risk, we can estimate the linear relative risk model of the form

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

where X_{ij} is the excess cumulative lifetime exposure of subjects in age group $i = 1,\ldots,4$, and dosage group $j = 1,\ldots,5$. The parameters α_i then represent the estimated absolute respiratory cancer death rates at zero dose at each age. In the case of the roofers (Table 7), only the total number of observed cancers (O) and the number of expected cancers based on lung cancer death rates for U.S. males (E) are reported. Hence, as in the analysis of the LTA data, we must make the constant relative risk assumption. The statistical specification is

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

TABLE 6. Respiratory cancer deaths and person-years at risk among non-white steel workers according to lifetime exposure to coke oven emissions. Males Aged 25 to 69 at Entry.*

Age at Entry into Study	Dosage Group**	Mean Excess Lifetime Exposure in $\mu g/m^3$ Benzene-Soluble Organics x Years (X)	Observed deaths (O)	Person-Years at Risk (N)	Respiratory Cancer Death Rate/year per 10^5 (O/N)
25-34	1	152.9	3	22,405	13.4
	2	719.6	1	3,202	31.2
	3	2419.2	0	2,658	0
	4	3960.3	3	3,030	99.0
	5	6050.9	4	3,062	130.6
35-44	1	194.5	4	16,277	24.7
	2	1283.7	0	2,388	0
	3	3794.0	2	2,976	67.2
	4	5997.6	3	2,727	110.2
	5	9551.1	5	2,027	246.7

*Source: U.S. Environmental Protection Agency (1979, Table 1).
**Subjects divided into broad dosage ranges based upon mg/m^3 BSO x months. Mid points of dosage intervals converted into $\mu g/m^3$ BSO x years.

TABLE 6. (Con't) Respiratory cancer deaths and person-years at risk among non-white steel workers according to lifetime exposure to coke oven emissions. Males aged 25 to 69 at Entry.*

Age at Entry into Study	Dosage Group**	Mean Excess Lifetime Exposure in $\mu g/m^3$ Benzene-Soluble Organics x Years (X)	Observed Deaths (O)	Person-Years at Risk (N)	Respiratory Cancer Death Rate/year per 10^5 (O/N)
45-54	1	234.4	17	11,306	150.4
	2	3127.9	1	1,527	65.5
	3	6003.7	4	1,706	234.5
	4	9486.4	4	1,545	258.9
	5	14797.5	8	1,330	601.5
55-69	1	272.6	4	5,713	70.0
	2	2866.7	1	491	203.7
	3	5828.0	1	596	167.8
	4	10352.3	4	716	558.7
	5	44924.0	10	450	2,222.2

*Source: U.S. Environmental Protection Agency (1979, Table 1).
**Subjects divided into broad dosage ranges based upon mg/m^3 BSO x months. Mid points of dosage intervals converted into $\mu g/m^3$ BSO x years.

TABLE 7. Lung cancer deaths among roofers according to attained time since joining union and expected deaths based upon U.S. male lung cancer death rates. Males aged 39 and over.*

Time Period	Attained Time Since Joining Union	Observed Deaths (O)	Expected Deaths† (E)	Observed/ Expected (O/E)
1960-1965	9-19 years	16	17.82	0.90
	20-29 years	23	15.22	1.51
	30-39 years	4	3.49	1.15
	40 + years	3	1.47	2.04
1966-1971	9-19 years	6	6.11	0.98
	20-29 years	43	28.23	1.52
	30-39 years	17	10.53	1.61
	40 + years	9	3.38	2.66
1960-1971	9-19 years	22	23.93	0.92
	20-29 years	66	43.45	1.52
	30-39 years	21	14.02	1.50
	40 + years	12	4.85	2.47

*Source: Hammond et al. (1976, Table 8)
†Based on U.S. male lung cancer death rates for 1960-1971.

where X_{ij} is the cumulative dose in time period $i = 1,2$ (corresponding to 1960-65 and 1966-71) and duration of service group $j = 1,\ldots,4$ (corresponding to the ranges 9-19, 20-29, 30-39, and 40+ years). The parameters α_i then represent the estimated risk of lung cancer among unexposed workers relative to U.S males for each time period.

In both of these epidemiological studies, the cigarette smoking practices of the subjects are not recorded. Although there is no clear evidence that the smoking proportions differed among dosage groups, the absence of smoking information necessarily increases the variance of the parameter estimates. As in the analysis of the LTA data, assessment of the magnitude of this additional uncertainty requires data on the possible variation of cigarette smoking rates across dosage groups. In order to avoid this additional subjective element in estimating the parameter θ for occupational exposure to coke oven and roof tar emissions, I have assumed that the smoking proportions were identical in each dosage group. Accordingly, therefore, the precision of the estimate of θ_e for the related emissions may be overstated.

Table 8 compares the estimates of θ for the studies of related environmental emissions to the estimate of θ for diesel engine emissions (last row, Table 5). Also indicated are the asymptotic standard errors of the estimates. In the analysis of exposure to roofing tar emissions, the maximum likelihood estimate was $\hat{\theta} = 0.0927$ per year exposed (asymptotic standard error 0.1297). The authors report that the mean dose of benzo(a)pyrene among the subjects was 16.7 µg per working day (calculated standard error 2.2) (Hammond et al., 1976, Table 2). The estimate of $\hat{\theta}$ in Table 8 has therefore been converted into units of relative risk per equivalent ng/m^3 benzo(a) pyrene x years under the assumption that subjects spend 250 days per year at work and have a total ventilation per working day of 18±2m^3 (estimated from Task Group on Lung Dynamics, 1966; Henderson and Haggard, 1943).

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 (Huisingh et al., 1979). This choice of experiments was constrained

TABLE 8. Estimates of the parameter θ for three epidemiological studies of lung cancer

OCCUPATIONAL EXPOSURE (YEARS OF OBSERVATION)	TOTAL NUMBER OF LUNG CANCERS OBSERVED	UNIT OF CUMULATIVE EXPOSURE	MAXIMUM LIKELIHOOD ESTIMATE (STAND. ERROR)
Diesel bus garage workers, drivers, and conductors, London Transport (1950-74)	667 lung cancer cases	$\mu g/m^3$ Particulates x years	1.23×10^{-4} (1.86×10^{-4})
Coke plant workers in Allegheny County, Pennsylvania (1951-66)	79 repiratory cancer deaths	$\mu g/m^3$ Benzene-Soluble Organics x Years	4.40×10^{-4} (1.50×10^{-4})
United Slate, Tile and Composition Roofers, Damp and Waterproof Workers Association (1960-71)	121 lung cancer deaths	ng/m^3 BaP x years	1.46×10^{-4} (2.06×10^{-4})

Source: Waller and Raffle (1980); U.S. E.P.A. (1979); and Hammond et al. (1976).

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: (1) skin tumor initiation by *in vivo* skin painting in SENCAR mice (Nesnow *et al.*, 1980); (2) enhancement of viral oncogenic transformation *in vitro* in Syrian hamster embryo (SHE) cells (Casto *et al.*, 1979); and (3) mutagenesis *in vitro* in L5178Y mouse lymphoma cells (Mitchell *et al.*, 1979). 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 1 and 2) or mutagenicity (assay 3) 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 9 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 heavy-duty diesel engine (Caterpillar) and three light-duty diesel engines (Datson, 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. Data on cigarette smoke condensate, provided in these studies, were not analyzed.

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 8. 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

TABLE 9. Characterization of emission extracts

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 hours	-	> 99	889
Caterpillar 3304 diesel engine	Diesel Fuel No. 2, Mode II driving cycle, 2200 rpm, 85-pound load, 12.75 minutes 10.24 miles	0.72g/hp/hr	26-27	2

Source: Huisingh et al. (1979)

TABLE 9. (Con't) Characterization of emission extracts

Emission Sample	Sampling Conditions	Emission Rates (mobile sources only)	Percent Dichloro-methane Extractable	ng B(a)P per mg extract
Datsun Nissan	Diesel Fuel No. 2, Highway Fuel Economy Test (HWFET) Cycle; ave. 48mph, 12.75 minutes, 10.24 miles	0.33g/mi	4-8	1173
Oldsmobile 350 diesel engine	Diesel fuel No. 2, Highway Fuel Economy Test (HWFET) Cycle; ave. 48mph, 12.75 min., 10.24 miles	0.52g/mi	12-17	2

Source: Huisingh et al. (1979)

TABLE 9. (Con't) Characterization of emission extracts

Emission Sample	Sampling Conditions	Emission Rates (mobile sources only)	Percent Dichloro-methane Extractable	ng B(a)P per mg extract
Volkswagen turbo-charged Rabbit diesel engine	Diesel Fuel No. 2 Highway Fuel Economy Test (HWFET) Cycle; ave., 48mph, 12.75 minutes, 10.24 miles	0.18g/mi	18	26
1978 Mustang II 302 engine	Unleaded gasoline; V-8, equipped with catalytic converter with exhaust gas re-circulation, HWFET cycle; ave. 48mph, 12.75 minutes, 10.24 miles	0.0053g/mi	39-43	103

Source: Huisingh et al. (1979)

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 to 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 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 10 shows the resulting estimates of β for tumor initation in SENCAR mice and enhancement of viral transformation. Table 11 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 10, the estimated potencies of roofing tar and coke oven emission extracts exceeded those of the diesel emission extracts. In Table 11, 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

TABLE 10. Estimates of the potency of organic extracts of diesel exhaust and related environmental emissions in two short-term bioassays*

Emissions Extract	Tumor Initiation in SENCAR Mice§ (papillomas/mouse per mg extract at 27 weeks)	Enhancement of SA7 Viral Transformation in Syrian Hamster Embryo Cells¶ (transformations/$2x10^6$ cells per µg extract/ml)
Coke oven	2.101 (0.090)	0.859 (0.089)
Roofing Tar	0.535 (0.024)	2.066 (0.363)
Caterpillar 3304 diesel engine	0.011 (0.009)	0.039 (0.023)

*Maximum likelihood estimates of slope of linear dose response model based upon Poisson distribution of positive responses. Asymptotic standard errors in parentheses.

§Data from Nesnow et al. (1980).

¶Data from Casto et al. (1979).

TABLE 10. (Con't) Estimates of the potency of organic extracts of diesel exhaust and related environmental emissions in two short-term bioassays*

Emissions Extract	Tumor Initiation in SENCAR Mice§ (papillomas/mouse per mg extract at 27 weeks)	Enhancement of SA7 Viral Transformation in Syrian Hamster Embryo Cells¶ (transformations/$2x10^6$ cells per µg extract/ml)
Nissan Datsun 220-C diesel engine	0.528 (0.023)	0.645 (0.095)
Oldsmobile 350 diesel engine	0.156 (0.034)	0.067 (0.023)
Volkswagen turbocharged Rabbit diesel engine	- -	0.128 (0.023)

*Maximum likelihood estimates of slope of linear dose response model based upon Poisson distribution of positive responses. Asymptotic standard errors in parentheses.

§Data from Nesnow et al. (1980).

¶Data from Casto et al. (1979).

TABLE 10. (Con't) Estimates of the potency of organic extracts of diesel exhaust and related environmental emissions in two short-term bioassays*

Emissions Extract	Tumor Initiation in SENCAR Mice§ (papillomas/mouse per mg extract at 27 weeks)	Enhancement of SA7 Viral Transformation in Syrian Hamster Embryo Cells¶ (transformations/$2x10^6$ cells per µg extract/ml)
1978 Mustang II-302 V-8 Catalyst engine	0.027 (0.007)	0.204 (0.025)
Benzo(a)pyrene positive control	85.28 (2.71)	540. (21.9)

*Maximum likelihood estimates of slope of linear dose response model based upon Poisson distribution of positive responses. Asymptotic standard errors in parentheses.

§Data from Nesnow et al. (1980).
¶Data from Casto et al. (1979).

TABLE 11. Estimates of potency of organic extracts of diesel exhaust and related environmental emissions in L5178Y mouse lymphoma mutagenesis assay*

Emissions Extract	Average mutant colonies/10^6 survivors per µg extract/ml	
	- Metabolic Activation	+ Metabolic Activation
Coke Oven	0.726 (0.152)	9.963 (0.734)
Roofing Tar	0.311 (0.121)	9.556 (1.547)
Caterpillar 3304 diesel engine	0.156 (0.038)	0.049 (0.021)
Nissan Datsun 220-C diesel engine	1.662 (0.509)	1.869 (0.485)

*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. (1979).

TABLE 11. (Con't) Estimates of the potency of organic extracts of diesel exhaust and related environmental emissions in the L5178Y mouse lymphoma mutagenesis assay*

Emissions Extract	Average mutant colonies/10^6 survivors per µg extract/ml	
	- Metabolic Activation	+ Metabolic Activation
Oldsmobile 350 diesel engine	0.270 (0.117)	0.764 (0.109)
Volkswagen turbocharged Rabbit diesel engine	2.545 (0.402)	1.012 (0.200)
1978 Mustang II-302 V-8 Catalyst engine	0.348 (0.039)	0.990 (0.101)

*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. (1979).

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 9, the spark-ignition engine emissions consistently had a lower biological activity per mile travelled than the deisel engine emissions. For example, the average dichloromethane extractable fraction of the Oldsmobile diesel engine sample was 14.5 percent. This engine therefore emitted 0.52g/mile x 14.5% = 0.075g/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 3 times that of the Oldsmobile sample (see the viral transformation data in Table 10).

Estimates of Diesel-Related Risk: The estimates of the effects of coke oven emissions and roofing tar emissions in man (Table 8) can now be combined with estimates of the relative potencies of the extracts of diesel emissions and the related emissions (Table 10 and 11). Consider, for example, the potency of the Nissan Datsun extract relative to the roofing tar extract in the skin tumor initiation experiments. From Table 10

$\hat{\beta}_d$ = 0.528 papillomas/mouse per mg extract, and
(0.023)

$\hat{\beta}_e$ = 0.535 papillomas/mouse per mg extract, and therefore
(0.024)

$\hat{\beta}_d/\hat{\beta}_e$ = 0.987
(0.062)

where the standard error of the ratio was calculated from the conventional first-order approximation. The potency of roofing tar in man, from Table 8, is

$\hat{\theta}_e$ = 1.46×10^{-4} per ng/m^3 BaP x years
(2.06)

= 1.64×10^{-4} per µg/m^3 dichloromethane-extractable organics x years,
(2.32)

where the conversion of units is based on the benzo(a)pyrene concentration in roofing tar extract in Table 9. The resulting estimate of $\hat{\theta}_d = \hat{\theta}_e(\hat{\beta}_d/\hat{\beta}_e)$ is therefore 1.62×10^{-4} per $\mu g/m^3$ dichloromethane-extractable organics x years (standard error 2.29×10^{-4}). To convert this estimate into particulate exposure units, we multiply it by the 6 percent extractable fraction of diesel particulates for the Nissan Datsun sample (Table 9). This yields 0.10×10^{-4} per $\mu g/m^3$ particulates x years (standard error 0.14×10^{-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 12. 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 12 fall within the 95 percent confidence interval derived from the LTA study (upper confidence limit 5×10^{-4} per $\mu g/m^3$ particulates x years; see Tables 5 and 8). 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 11).

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 non-human 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 that of Section III.A 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

TABLE 12. Range of estimated values of the parameter θ derived from comparative analysis of diesel engine emissions, coke oven emissions, and roofing tar emissions.

Diesel Emission Extracts	Range of Estimates (in units of relative risk of lung cancer per $\mu g/m^3$ particulates x years.)	
	Tumor Initiation and Viral Enhancement Only	All Bioassays
	x 10^{-4}	x 10^{-4}
Nissan Datsun 220-C	0.03 to 0.20	0.02 to 0.60
Oldsmobile 350	0.01 to 0.07	0.01 to 0.24
Volkswagen Rabbit*	0.02 to 0.12	0.02 to 2.78
Caterpillar 3304	0.01 to 0.05	0.01 to 0.25

*No data for tumor initiation.

a standard error of 1.11 x 10^{-4}, a 95 percent lower confidence limit of -1.82 x 10^{-4}, and a 95 percent upper confidence limit of 2.52 x 10^{-4} (all estimates in units of relative risk per $\mu g/m^3$ particulates x years). Thus, 45 percent 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 percent upper confidence interval slightly to 2.15 x 10^{-4} per $\mu g/m^3$ particulates x 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 statistically 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.

IV. 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 percent increase in lung cancer incidence per unit of lifetime cumulative exposure, measured in micrograms of particulates per cubic meter x years.

This report 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 (1979, Table XIV) have projected an increase in the concentration of particulates in the atmosphere if 25 percent 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.* (1979, 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 to 12 $\mu g/m^3$ by the turn of the century. Briggs *et al.* (1978, 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 (1980, 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 to 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 to 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 to 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 percent increase in lung cancer incidence. For a male, aged 40 to 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 percent 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 to 30 years suffers a proportional increase in lung cancer risk ranging from 100 to 700 percent (Selikoff *et al.*, 1979; Liddell *et al.*, 1977). A male, aged 40 to 65, who has smoked cigarettes for a comparable period suffers a proportional increase in lung cancer incidence ranging from about 1000 to 2000 percent (Doll and Peto, 1976; U.S. Department of Health, Education, and Welfare, 1979).

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 percent increase in lung cancer mortality would diminish his probability of surviving to age 65 by about 1 in 4500. A 15 percent increase in lung cancer mortality would diminish his probability of surviving to age 65 by about 1 in 300. A 1000 percent 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 to 65 in the United States and therefore reflect the average effect among different birth cohorts.

The comparative analysis of Section III.B 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 travelled than diesel engine emissions. Lofroth (1979) and Misfeld (1979) 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.

A. 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 percent to the total variance in the parameter estimate. 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 9). The standard errors of these relative potencies, as illustrated in the calculations in Section III.B, 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 $\hat{\theta}_d$, 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 non-human 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 National Research Council, 1975; Meselson and Russell, 1977; Crouch and Wilson, 1979).

B. 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 to 30 year duration of exposure typically observed in the underlying occupational studies, the approximations may no long be valid. It is possible, as suggested in multistage theories of cancer etiology (Peto, 1977; Whittemore, 1977), 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 (Schneiderman *et al.*, 1979). In view of these uncertainties about the relation between 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. This multiplicative effect was introduced explicitly in Section III.A to assess the effect of uncertainty in smoking rates among the LTA job categories. 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 (Peto, 1977). The effect of discontinuation of exposure to diesel emissions, however, may be quite different.

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