AN EXPLORATORY ASSESSMENT OF THE RISK OF LUNG CANCER ASSOCIATED WITH EXPOSURE TO DIESEL EXHAUST BASED ON A STUDY IN RATS

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An Exploratory Assessment of the Risk of Lung Cancer Associated with Exposure to Diesel Exhaust Among Miners Based on a Study in Rats. Randall Smith, M.A., Leslie Stayner, Ph.D., National Institute for Occupational Safety and Health, Cincinnati, Ohio.

ABSTRACT

At the request of the Mine Safety and Health Administration, a quantitative assessment of the risk of lung cancer associated with occupational exposures to diesel exhaust was performed. This assessment was primarily based upon the results from a study of the effects of chronic inhalation exposure to diesel exhaust in Fischer-344 rats (previously reported by Mauderly et al., 1987). An adaptation of the Armitage-Doll multistage model, which allows for an age-dependent effect of exposure, was used to model the tumor response data. This model was fitted to all tumors (benign and malignant), and to malignant neoplasms alone. Estimates of unit risk (potency) were derived based upon a linear approximation to the results from the multistage model. A biologically equivalent dose was developed to scale the results from airborne exposure in rats to humans, which was adjusted for differences in weight, ventilation rate, deposition fraction, and the percentage of time actually exposed. Comparisons are made with risk estimates derived from modeling other rat inhalation bioassays and from applying different models to the study by Mauderly et al. (1987).

We emphasize that our risk estimates are based upon a series of assumptions and carry a great deal of uncertainty. In particular, uncertainties regarding

the effects of exposure on lung clearance mechanisms, the deposition rates in humans, and the relevance of our exposure index limit our confidence in these risk estimates. Because of these uncertainties, this risk assessment would best be viewed as an exploratory effort.

Key words: Diesel, lung cancer, risk assessment

INTRODUCTION

The National Institute for Occupational Safety and Health (NIOSH) estimates that approximately 1.35 million workers are exposed to the combustion products of diesel fuel in the United States (NIOSH 1983). Occupational groups that are likely to be exposed to diesel engine emissions include truck drivers, railroad workers, miners, bridge and tunnel workers, forklift drivers, farm workers, and auto, truck, and bus maintenance garage workers.

Diesel engine emissions are a complex mixture that includes carbon monoxide, aldehydes, oxides of nitrogen and sulfur, and respirable size particles (Cheng et al., 1984). The relative proportion of these substances in diesel exhaust depends on variables such as engine type and condition, fuel composition, and load. As much as 15% to 65% of the mass of the particulate phase from diesel exhaust may be made up of organic compounds adsorbed onto the surfaces of the particles (Travis and Munro 1983; Cuddihy et al., 1984). Among these organic compounds are carcinogenic polycyclic aromatic hydrocarbons (IARC 1983).

As early as 1955, extracts of diesel exhaust were demonstrated to be carcinogenic when applied to mouse skin (Kotin et al., 1955). However, major concern for the potential carcinogenicity of diesel exhaust did not develop until the release of a report demonstrating that extracts of diesel exhaust were mutagenic in bacterial assays (Huisingh et al., 1978).

Some experimental studies involving inhalation exposures to diesel exhaust failed to demonstrate a significant carcinogenic response in animals (Karagianes et al., 1981, Orthoefer et al., 1981, Pepelko and Peirano 1983, White et al., 1983, Lewis et al., 1989). However, other reports have provided convincing evidence that inhalation exposure to diesel exhaust is associated with an excess lung cancer in rodents (Brightwell et al., 1986, Heinrich et al., 1986, Ishinishi et al., 1986, Iwai et al., 1986, and Mauderly et al., 1987). The primary difference between the negative and positive studies is the length of the exposure period, which was up to 30 months in the positive studies and 24 months or less in the negative studies (NIOSH 1988). With the exception of one study (Heinrich et al., 1986), filtered (for particulates) diesel exhaust was not found to be carcinogenic in these studies, suggesting that the carcinogenic activity resides primarily in the particulate fraction of the exhaust.

Epidemiologic studies of occupational groups with potential for exposure to diesel exhaust have produced equivocal results, with some studies reporting negative findings and others reporting small elevations in the relative risk of lung cancer. Many of these studies have suffered from poor documentation of exposure, small sample size, inadequate length of follow-up, and lack of information on potentially confounding and effect-modifying variables such as cigarette smoking and asbestos exposure. The largest and most thorough epidemiologic studies reported to date are a case-control study (Garshick et al., 1987) and a retrospective cohort mortality study (Garshick et al.,

1988) of U.S. railroad workers. Both studies reported a significant association between exposure to diesel exhaust and lung cancer among workers who were young when diesel engines were introduced to the railroads, and who therefore had the highest potential for exposure. The association between lung cancer and diesel exhaust appeared to be independent of asbestos exposure in both studies, and independent of cigarette smoking in the case-control study.

Comprehensive reviews of the toxicologic and epidemiologic literature regarding the carcinogenicity of diesel exhaust have been previously published by NIOSH (1986,1988) and the reader is referred to these reports for additional information regarding the hazards of exposure to diesel exhaust. Based upon these reviews NIOSH (1988) has concluded that diesel exhaust should be regarded as "a potential occupational carcinogen."

At the request of the Mine Safety and Health Administration (MSHA), we have modeled the relationship between exposure to diesel exhaust and the risk to rodents of lung tumors, and used the results of this modeling to produce quantitative estimates of human lung cancer risk. A number of assumptions were made in order to produce our estimates. Many of the assumptions were evaluated in our analysis, but uncertainties related to other factors could not be fully evaluated at this time. Because of the unresolved uncertainties, we view this as an exploratory analysis.

METHODS

Data Source

We have primarily based our risk estimates on the findings of the toxicologic study by Mauderly et al. (1987). This study was chosen because it had a long period of follow-up, several well-characterized exposure concentrations, and a large number of animals per exposure group. A detailed summary of these data and the associated experimental protocol were previously described by Mauderly et al. (1987). Briefly, groups of 364 to 367 Fischer-344 rats were exposed to unfiltered diesel exhaust diluted to measured average particulate concentrations of 0.35, 3.47, or 7.08 mg/m^3. A control group was exposed to filtered air. All exposures began when the rats were 17 weeks old and continued for up to 30 months. Sacrifices were performed at approximately 6-month intervals. Some tests performed using lung tissues from these interim sacrifices precluded histopathologic evaluation. All other rats were histopathologically evaluated for lung tumors.

The Inhalation Toxicology Research Institute of the Lovelace Biomedical and Environmental Research Institute, Inc., provided NIOSH with data on age at death or sacrifice and lung tumor observations for the rats examined histopathologically. Table I summarizes the lung tumor responses for each sex and exposure group.

Lung tumor response data from several other positive rat diesel exhaust inhalation studies (Brightwell et al., 1986, Heinrich et al., 1986, Ishinishi et al., 1986, Iwai et al., 1986) were also examined in this analysis in order to evaluate the degree to which our risk estimates were dependent on our choice of the study by Mauderly et al. (1987). An analysis was also performed in which the results from all of the positive rat bioassay studies were pooled together.

Model Fitting

The risk of developing lung tumors was estimated using a method based on the Armitage-Doll multistage model (Armitage and Doll, 1961). This model is based on the theory that carcinogenesis is the result of at least one cell passing through a fixed number of irreversible and heritable stages. The model is consistent with the observation that the incidence of most human cancers increases with age raised to a constant power. A mathematical form of this model that allows for an age-dependent exposure acting linearly on one of the stages was adopted (Crump and Howe, 1984). This time-to-tumor implementation of the Armitage-Doll model provides a way to incorporate data on the age of animals when examined for tumors and is distinct from a quantal approach that ignores the age at which tumor status is determined.

The model specifies that the probability (P) of a tumor at age t is approximately

$$P(t) = 1 - \exp\{ -q_0 t^k - q_r Z_{rk}(t) \}$$

where $Z_{rk}(t)$ is an exposure function that depends on age (t), the age-dependent exposure pattern before t, the total number of stages (k), and the stage that is affected by exposure (r) (Crump and Howe, 1984). The effects of exposure on this probability are represented by the $q_r Z_{rk}(t)$ term and background effects by the $q_0 t^k$ term.

The average concentrations of airborne particulates measured by Mauderly et al. (1987) were used in determining the exposure function (i.e., the dose-rate). Thus, the exposure function was assumed to be zero before exposure began, and equal to the air concentration during exposure. Expressions for the resulting exposure function $Z_{rk}(t)$ and the likelihood function are presented in the Appendix.

Maximum likelihood estimates for the unknown parameters (q_0 and q_r) were obtained using Newton-Raphson interactive techniques programmed in the SAS/IML matrix language (SAS Institute 1985 and 1987). This process was repeatedly performed for values of k between 2 and 6 and for all possible affected stages between 1 and k. The asymptotic normal distribution of the maximum likelihood estimators of q_0 and q_r, and the variance matrix given by the inverse of the

observed information were used to derive standard errors and approximate confidence intervals for the excess risks.

The age of the rat (years) and the airborne concentration (mg/m^3) were used in the computations. The likelihood function reflected treatment of the rat lung tumor data as incidental (i.e., nonfatal) findings at necropsy. This form is consistent with the observation that lung tumor incidence appeared to be unrelated to survival in both the study by Mauderly et al. (1987) and in the historical control data for Fischer-344 rats from the National Toxicology Program (Portier et al., 1986). Data on rats that were not histopathologically examined for lung tumors do not contribute any information relevant to the tumor occurrence parameters when tumors are incidental, and thus these observations were excluded from this analysis.

The adequacy of the model was tested by comparing its likelihood with those produced by two hierarchical models with additional parameters governing exposure and sex. The test statistic was based on twice the negative of the log-likelihood ratio statistic (-2lnLR), which has an approximate chi-square distribution with degrees of freedom equal to the difference in the number of parameters included in the models being compared. The resulting two tests are (1) a test for sex effects found by maximizing the likelihood over separate q_0's and q_r's for each sex, and (2) a test for homogeneity of the dose-response formed by fitting separate q_r's for each of the three exposure groups. Each test had 2 degrees of freedom. The total number of stages and

the stage affected by exposure were restricted to be equal in the two models being compared.

To evaluate the degree to which our risk estimates were model dependent, quantal forms of the multistage, one-stage, Weibull, probit and Mantel-Bryan models were also fitted to the results from the study by Mauderly et al. (1987) using TOXRISK Version 1.0 (Crump et al., 1989). The multistage and one-stage formulae are motivated by the same mechanistic assumptions about carcinogenesis as the Armitage-Doll model. The Weibull model resulted when the assumptions of the gamma-multihit model derived by Rai and Van Ryzin (1981) for malignant transformation of a single cell were extended to a tissue by Crump (1985). The probit model is consistent with assuming that each individual has a tolerance-dose below which no dose-related tumors occur during the study, and the statistical distribution of tolerances over individuals is lognormal. The Mantel-Bryan model is a probit model with the restriction that the lognormal tolerance distribution has a geometric standard deviation equal to 10.

To evaluate the degree to which our risk estimates were study dependent, the quantal form of the one-stage model was also used to produce risk estimates using published data from other rat inhalation bioassays (Brightwell et al., 1986, Heinrich et al., 1986, Ishinishi et al., 1986, Iwai et al., 1986, Mauderly et al., 1987). Estimates were produced from each individual bioassay and from analyzing the pooled data from these bioassays.

Extrapolation to Estimates of Human Risk

A number of assumptions must be made to extend the risk estimates derived from our models of tumor response in rats to the risks for humans. These assumptions fall into three categories: (1) those concerning the development of biologically equivalent doses for rats and humans, (2) those relating external exposure to internal dose, and (3) those concerning the scaling of age between rats and humans to account for the temporal aspects of exposure. Table II summarizes the assumptions made in this analysis about the biologic differences between humans and rats.

The biologically equivalent dose is based on milligrams of particulate deposited in the lungs per kilogram of body weight per day (mg/kg per day). This dose is a function of body weight, lung deposition fractions, inhalation rates, and the fraction of time exposed during the exposure period. Body weight was used as a surrogate for lung mass, since lung mass varies in direct proportion to body weight across various species (Calabrese 1983). The biologically equivalent dose was derived from the following equation:

$$D = \frac{F_d\ F_x\ I}{W}\ E \qquad (1)$$

where

D = biologic equivalent dose (mg/kg per day)

E = concentration of airborne diesel particles (mg/m^3)

I = inhalation rate during the exposure (m^3/day)

F_x = fraction of the time between the beginning and end of exposure during which exposure actually occurs

F_d = fraction of inhaled mass deposited in lungs.

W = body weight (kg)

Equation 1 was used to convert the concentrations of airborne particles used for rats to an equivalent exposure for humans as follows:

$$\frac{F_{dr}\ F_{xr}\ I_r}{W_r}\ (E_r) = \frac{F_{dh}\ F_{xh}\ I_h}{W_h}\ (E_h) \qquad (2)$$

or equivalently,

$$E_r = CE_h \qquad (3)$$

where $C = \dfrac{F_{dh}\ F_{xh}\ I_h\ W_r}{F_{dr}\ F_{xr}\ I_r\ W_h}$.

For this analysis we assumed body weights (W) of 0.35 kg for rats and 70 kg for humans. We used a lung deposition fraction (F_d) of 0.23 for humans based upon a respiratory deposition model developed by Yu and Xu (1986)[1], and of 0.15 for rats based upon experimental data (Wolff et al., 1984, and McClellan et al., 1982). The inhalation rate (I) was assumed to be 0.19 L/min for rats, based upon an approximate average ventilation rate reported by Mauderly (1986) in rats after 1 hour in an inhalation exposure tube. The inhalation rate for humans was assumed to be 21 L/min based on the average ventilation rate reported in a study of British coal miners (Jones et al., 1981). The rats in the Mauderly et al. (1987) study were exposed for 35 hr/week, and thus the fraction of time exposed (F_x) was assumed to be 0.21 (35/168) for rats. Based upon a report by MSHA (1989) it is estimated that on average coal workers spend 240 days per year underground. Thus the fraction of time exposed for miners was assumed to be approximately 0.22 (240/365 X 8/24). The value for C based on these assumptions is 0.89.

Estimates of risk for occupational lung cancer were developed on the basis of a 40-hr/wk exposure to diesel exhaust between the ages of 18 and 65. The excess risk of lung cancer for this population was evaluated at age 70.

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[1]The 0.23 value for deposition in humans was obtained through personal communication with C.P. Yu and was based upon the assumption of a mass median diameter of 0.2 μm with a geometric standard deviation of 4.5, a ventilation rate of 21 L/min and a tidal volume of 1.04 L.

Scaling of age between rats and humans was accomplished using information reported by Mauderly and Hahn (1982), who estimated this relationship based on age-related changes in lung function and structure. This scaling was used to identify the rat ages corresponding with the human ages associated with occupational exposure. For example, 59, 822, and 903 days are the rat ages that correspond with the human ages of 18, 65, and 70 years, respectively. Using this approach the age at which rats actually began exposure (120 days) corresponds with a human age of 22 years. Although the model was fitted to data from rats whose exposure continued throughout life, the estimates of excess risk are adjusted for the termination of occupational exposure at age 65.

Estimation of Excess Risk

After we determined the air concentration for rats (E_r) corresponding with that for humans (E_h) and the rat ages associated with the pertinent human ages, we estimated excess risk (ER) from the ToxRisk program (Crump et al., 1989), or for the Armitage-Doll model by the difference in the estimated proportions of exposed and unexposed rats with lung tumors:

$$ER(t) = \exp\{ -q_0 t^k \} - \exp\{ -q_0 t^k - q_r Z_{rk}(t) \}$$

$$= \exp\{ -q_0 t^k \} [1 - \exp\{ - q_r Z_{rk}(t) \}] \qquad (4)$$

The excess risk is well approximated by a linear function of the exposure concentration derived from the first order Maclaurin series expansion of Equation 4 in terms of the exposure concentration. The approximation holds quite well for air concentrations that are not too high (e.g.,< 2 mg/m^3). This approximation may be represented by the following simple linear equation when age is fixed:

$$ER = \beta E_h \qquad (5)$$

The risk coefficient β represents the increase in risk of developing a lung neoplasm per unit of air particulate concentration, and is thus an estimate of the potency of occupational diesel particulate exposure. It must be emphasized that this potency estimate is dependent upon the age-related aspects of exposure and the assumptions regarding biologic equivalency discussed earlier.

Separate risk estimates were developed in this assessment from modeling the data with and without the inclusion of the benign neoplasms. Inclusion of the benign neoplasms may be justified from the viewpoint that these neoplasms may

progress to malignancy, and that benign neoplasms may be fatal and thus are not always truly "benign." It is particularly unclear whether the squamous cysts would progress to malignancy and whether these benign neoplasms are relevant for estimating human risk.

We evaluated the sensitivity of our excess risk estimates to alterations in several of the key assumptions made in our assessment. We assessed the effect on our excess risk estimates of varying the rate of human lung ventilation rates and of varying length of exposure to diesel exhaust. As previously described, we also evaluated the effects of using other rat inhalation bioassay data sets and other statistical models for estimating risk.

RESULTS

Figure 1 illustrates the maximized likelihood for the models evaluated (all tumors and exposure groups) as a function of the number of stages (k) and the affected stage. The likelihood of the data from all exposure groups was maximized when exposure affected the first stage regardless of the number of stages assumed. The maximum of the likelihood with respect to k occurred when k=5.

Detailed results from the time-to-tumor models of lung tumor risk among rats are presented in Table III. Separate results are presented from fitting the model to data on all tumors (benign and malignant), and from fitting the model to malignant tumors alone. Tumor prevalence for rats by age derived from these models are displayed in Figure 2. These models assume 5 stages, with exposure acting on the first stage. The effect of diesel particles was significant ($p<0.001$) based on the likelihood ratio test; this result agrees with the report of a significant dose-related effect by Mauderly et al. (1987). Extra parameters for sex or for each dose group (separate q_rs) did not significantly improve the fit of this model ($P > 0.05$).

Figure 3 illustrates extrapolated estimates of excess risk for miners and 90% confidence intervals as a function of airborne particulate concentration from the models presented in Table III. The risk estimates based on malignant

tumors were less than half of the corresponding estimates based on all tumors.

The exposure-response relationships displayed in Figure 3 are well approximated by lines through the origin. This fact illustrates that a potency estimate based on the slope of the curve at the origin is useful for summarizing the excess risk for concentrations up to 2 mg/m^3. Table IV presents the potency estimates derived from the two models and the estimated concentrations associated with specific levels of excess risk.

Figures 4 and 5 illustrate how varying the inhalation rate and the length of the exposure period affects the relationship between excess risk and airborne particulate concentration. The risk associated with a given concentration clearly depends on the level of physical activity and the associated inhalation rate, and with the length of time exposed to that concentration.

Figures 6 and 7 present estimates of risk derived from fitting different models and from using different rat bioassay studies. As is usually the case, the maximum likelihood estimates of risk are very sensitive to the choice of the statistical model used for the risk assessment, particularly at the lower exposure concentrations. For instance at 0.050 mg/m^3 the risk estimates presented in Figure 5 vary from 5×10^{-4} based on the 1-stage model to 3×10^{-11} based on the probit model. All of the models evaluated appeared to provide an adequate fit to the data based upon the chi-square goodness of fit

test. The upper 95% confidence limits for risk are much less sensitive to the choice of model although the confidence limits from the probit model remain considerably lower.

With the exception of the Ishinishi (1986) study, the risk estimates derived from analyses of the different rat bioassay studies were remarkably similar (Figure 7). Analysis of the pooled data from these studies provided risk estimates that were nearly identical to the risk estimates derived from the modeling of the data from the study by Mauderly et al. (1987). However, the chi-square goodness of fit statistic for the pooled analysis was highly significant, indicating a lack of fit to the data. The lack of fit for the pooled data was not eliminated when higher order terms were added to the model, or by fitting the other quantal models. Thus, the lack of fit was probably related to the heterogeneity that was introduced by combining studies with different tumor-response rates.

DISCUSSION

Findings

The estimates of risk to miners of lung cancer per unit increase in air particulate levels (potency) ranged from 0.01 to 0.02 per mg/m^3 from the two time-to-tumor models evaluated in our analysis. Limited information is available on current levels of diesel particulate exposures for miners and other occupational groups. McCawley et al. (1989) estimated that exposures of coal miners to diesel exhaust particles ranged from approximately 0.3 to 0.7 mg/m^3. MSHA has reported measurements of diesel particulate exposures in coal mines ranging from 0.2-1.0 mg/m^3, and in metal and nonmetal mines from 0.3-1.5 mg/m^3 (Haney, 1990). Based on our analysis, the excess risk estimated at the upper range of the diesel particulate exposure reported (1.5 mg/m^3) is approximately 1.5 to 3 in 100.

The likelihoods for the models evaluated in this investigation were always maximized with the first stage affected regardless of the number of stages assumed. With the first stage affected, the multistage model gives greater weight to early exposures than to later ones. This weighting implies that exposures sustained early in life have a greater impact on lung cancer risk than later exposures. However, the likelihoods for the models with the first stage affected were generally not markedly different from the likelihoods for the models with other stages affected. Thus, at best, our results provide

only suggestive evidence for a first-stage (initiating) effect of diesel exhaust on the risk of lung cancer.

The likelihoods were also maximized when five stages were used in the Armitage-Doll model. This implies that the fitted lung tumor incidence of unexposed rats is proportional to the fourth power of age. Doll (1971) in an analysis of smoking and lung cancer risk among British physicians, has also reported that smoking appears to act on the first stage of a 5 stage Armitage-Doll model[2]. This suggests that the production of lung tumors in rats exposed to diesel exhaust may share some similarities with smoking-related lung cancer. However, it must be emphasized that this suggestion is speculative, given the inability of the bioassay data to rule out models with other numbers of stages and other affected stages.

Assumptions and Underlying Uncertainties

Estimates of human risk always involve great uncertainty when they are derived from models based on studies of animals. Such estimates require numerous assumptions about (1) the shape of the dose-response curve in the low dose

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[2]There is evidence suggesting that smoking affects a late stage as well as an early stage within the Armitage-Doll model. Doll (1978) reported an approximately constant relative risk of lung cancer among exsmokers which is consistent with a late stage effect. Breslow and Day (1987) have examined the incidence rate predicted by a 5-stage Armitage-Doll model when exposure affects the first and fourth stages and indicated that the rates of lung cancer among smokers and exsmokers are consistent with this model.

region and (2) biologic differences between animals and humans. There are several sources of uncertainty that make these estimates of risk even more tentative than usual.

A major source of uncertainty in this analysis is related to the strong evidence that high doses of diesel particles compromise pulmonary clearance mechanisms. In the high-exposure groups, total lung particulate burdens were reported to be appreciably greater than predicted on the basis of extrapolation from the low-exposure group in the study by Mauderly et al. (1987). Decreases in alveolar clearance rates following chronic exposure to high levels of diesel exhaust particles have been demonstrated in experimental studies using radioactive tracers (Chan et al., 1984, Heinrich et al., 1986, Vostal et al., 1982, Wolff et al., 1986). Morrow (1988) has hypothesized that the reduction of pulmonary clearance observed with high particulate exposures reflects a breakdown in alveolar macrophage (AM) mediated removal of particles as the result of an overloading of the alveolar macrophages and the loss of AM mobility.

Reduced pulmonary clearance after prolonged exposure to high concentrations of diesel particles suggests that the target tissue (biologic) dose will not be directly proportional to air concentration if the carcinogenic potency of deposited particles depends on residence time. Thus, risk estimates based upon extrapolation from high concentrations of airborne particles may produce inappropriately large risk estimates for exposures to lower concentrations.

This potential bias may be counterbalanced by the fact that rats are believed to have faster pulmonary clearance rates than humans (Pepelko 1987). Unfortunately, additional information is needed before adjustments to this risk assessment could be made for the effects of high particulate concentrations, and interspecies differences in pulmonary clearance rates.

Using the results from exposing animals to high concentrations of diesel exhaust, which appears to reduce pulmonary clearance, may be justifiable for estimating the risk from exposure to low concentrations for certain occupational groups. Unlike experimental animals, workers exposed to diesel exhaust may be exposed to nondiesel sources of particulate matter. The adverse effects of prolonged exposure to high particulate concentrations on lung clearance mechanisms do not appear to be limited to diesel particulate exposure; they have also been observed in relation to asbestos (Bolton et al., 1983), coal dust (Le Bouffant 1971), quartz (Klosterkotter and Buneman, 1961), titanium dioxide (Muhle et al., 1988), and manmade mineral fibers (Muhle et al., 1988). Thus, the pulmonary clearance mechanisms of some workers may already be overburdened from other exposures and exposure to diesel exhaust may further aggravate this preexisting condition. This is of particular concern for miners, who under current standards may be exposed to total particulate levels of up to 2 mg/m^3 in coal mines and 10 mg/m^3 in other mines. Pulmonary clearance of particles has been reported to be decreased among smokers and individuals with chronic obstructive lung disease (Bohning et al., 1982) or emphysema (Freedman et al., 1988). Exposure to coal and other dusts

has been associated with the development of chronic bronchitis and emphysema (Merchant et al., 1986).

In addition to the possible compromise of pulmonary clearance mechanisms, a second major source of uncertainty in this analysis is our choice of particulate concentration as the exposure index. We chose this measure based on the findings from studies of rats, which indicate that the carcinogenic activity of diesel exhaust resides in the particulate fraction (Brightwell et al., 1986, Heinrich et al., 1986, Ishinishi et al., 1986, Iwai et al., 1986). However, one study did demonstrate a statistically significant excess of lung cancer among mice exposed to filtered diesel exhaust (Heinrich et al., 1986). Sulfur dioxide, a component of diesel exhaust, has been demonstrated to promote the carcinogenicity of polycyclic aromatic hydrocarbons in rodents (Pott and Stober 1983). Formaldehyde, another component of diesel exhaust, has been demonstrated to be a carcinogen in experimental studies (Albert et al., 1982, Swenberg et al., 1980). Thus, although the results from most research suggests that the polycyclic aromatic hydrocarbons (PAHs) adsorbed to the diesel particles are the primary cause of the excess of tumors observed in rodents, components of the gas phase of diesel exhaust may also have carcinogenic or cocarcinogenic activity.

The ability to generalize from our risk assessment is further limited by the fact that the relative composition of the compounds found in diesel exhaust varies greatly depending on factors such as the engine type and condition, load, temperature, and fuel composition (NIOSH 1988). Huisingh et al. (1978)

reported that the mutagenicity of extracts of diesel exhaust also varied with the type of engine and fuel used. Based on discussions with a MSHA official (personal communication, Peter Turcic, MSHA), it is estimated that approximately two-thirds of the engines used in the mines are of the light-duty type. It is worth noting that a light-duty diesel engine was used as the exposure source in the study by Mauderly et al. (1987). The one study that exposed rats to the exhaust from a large diesel engine under conditions meant to simulate as closely as possible diesel exhaust exposures in the mines failed to detect an increased incidence of lung tumors (Lewis et al., 1989). However, these negative findings may be related to the fact that the highest exposure was only 2 mg/m^3, and that the experiment was terminated at 24 months.

A third source of uncertainty for this analysis is our choice of values for respiratory deposition. Although lung deposition fractions were treated as known constants in this analysis, a great deal of uncertainty actually surrounds the estimate of deposition fraction for humans. The deposition fraction was derived for this assessment from a predictive model developed for predicting deposition of diesel particulates (Yu and Xu, 1986). The deposition fraction for humans derived from this model (0.23) agrees well with experimental results from studies of human volunteers (Chan and Lippman, 1980; Rudoph et al., 1988). However, it is known that respiratory deposition varies with breathing rate and particle size distribution (Yu and Xu, 1986; Rudolph et al., 1988) both of which may change in different mining operations. Furthermore, there appears to be a large degree of interindividual variability

in deposition rates. For example, in one study of 26 nonsmoking volunteers, the deposition fractions of 0.2 μm mass median diameter ferric oxide particles varied approximately 6 fold (Chan and Lippmann, 1980).

The implications of several other assumptions made in our analysis need to be recognized. First, we have assumed a ventilation rate of 21 L/min for workers based upon one published report on ventilation rates in coal miners. These measurements were taken in British coal mines, which may not be representative of all American mining operations. It is likely that ventilation rates may be substantially higher among some miners working in less mechanized mines. Figure 4 demonstrates that raising the ventilation rate would considerably increase our estimates of excess risk.

Second, our risk estimates were based upon an assumption that workers would be exposed for a working lifetime (47 years). This assumption reflects the philosophy underlying the Occupational Safety and Health Act of 1970 that "no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life." Obviously, using a shorter length of exposure (e.g., 20 years) does reduce our estimates of excess risk as demonstrated in Figure 5, although the reduction is not proportional to the reduced length of exposure assumed. This lack of proportional reduction in risk is a direct consequence of the greater weight given to earlier exposures when exposure acts at the first stage in the Armitage-Doll model.

Finally, in extrapolating between rat and man we adjusted for body mass. Higher estimates of risk (approximately 6 fold) would have resulted if surface area (e.g. weight $^{2/3}$) had been used for this extrapolation. It is impossible to determine which adjustment (body mass or surface area) is correct, but for a respiratory toxicant acting at the site of exposure (e.g. diesel), we consider it more appropriate to use body weight, which is proportional to the lung (target tissue) mass, than to use surface area, which is related to metabolic rate.

Choice of Model and Data

Alternative mathematical models and animal studies were also evaluated for comparative purposes. The results from these analyses show that estimates of risk are highly dependent on the choice of the model, and are much less dependent on the choice of data used for the analysis. All of the models provided a reasonable fit to the data reported by Mauderly et al. (1987), and thus it is not possible from a statistical viewpoint to determine which model provides the "best" estimate of risk from these data alone.

The Armitage-Doll multistage model, which was selected for this assessment, is a mechanistic model based on the assumption that a cell must pass through several stages leading to the production of cancer. As previously mentioned, reported epidemiologic observations of lung cancer in relation to smoking are consistent with this model.

In contrast to the multistage models, the probit model does not have any biologic justification; there is no mechanistic model of carcinogenesis that yields this mathematical model. The assumption of a tolerance for each individual below which carcinogenesis does not occur and above which it becomes nearly certain is questionable and the assumption that these tolerances are lognormally distributed is arbitrary. The probit model produces excess risk estimates that approach zero very rapidly. In an attempt to yield low-dose risk estimates that do not underestimate the true risk, the Mantel-Bryan procedure has a restriction on the probit model that the tolerance distribution has a geometric standard deviation of 10. Even so, this model can produce estimated risks that are lower than estimates based on multistage models at low doses.

As shown in Figure 6, the low-dose maximum likelihood estimates of risk derived from the Weibull model are also considerably lower than the multistage estimates. However, they are also very imprecise. This imprecision is reflected by the large difference between these estimates and the corresponding 95% upper confidence limits for this model; the confidence limits are at least two orders of magnitude above the maximum likelihood estimates for concentrations below 0.100 mg/m^3. This discrepancy indicates that the maximum likelihood estimates derived from this model are sensitive to relatively minor fluctuations of the data that could reasonably occur by chance. In this instance, a reasonable interpretation is that the "best" (i.e., maximum likelihood) estimates from the Weibull model may not be very good estimates even if the model is correct.

In contrast to the maximum likelihood estimates, the 95% upper confidence limits from the Weibull model agree very well with the corresponding limits from the multistage models. This implies that a 95% confidence interval estimate derived from one of these models is insensitive to which of these model forms was selected. It should be noted that the confidence interval estimates of risk offer protection only against underestimating risk as a result of random fluctuations in the data. Confidence interval estimate do not necessarily protect against underestimation if underlying assumptions are incorrect.

The multistage models produced excess risk estimates that are characteristically linear in the lose-dose range. The Weibull, probit, and Mantel-Bryan models evaluated are notably sublinear in the low-dose range. In the absence of information to the contrary, it has been the policy for most governmental agencies in evaluating the risks of carcinogens to use modeling techniques that incorporate low-dose linearity such as the multistage model (Office of Science and Technology Policy, 1985). The multistage model is also an attractive alternative, because it appears to fit human cancer data quite well for most solid tumors (e.g., lung cancer). The time-to-tumor version of the multistage model used in this analysis is an appropriate method for analyzing data with information on age of examination for tumor status from studies conducting serial sacrifices (e.g. , Mauderly et al., 1987).

Comparison with Results from Other Risk Assessments

The unit risk (potency) estimates we developed are compared with the estimates developed by previous reports (Harris 1983, Cuddihy et al., 1984, Albert and Chen 1986, Pott and Heinrich 1988) in Table V. Several of these authors (Harris 1983, Cuddihy et al., 1984, Albert and Chen 1986) relied on information from bioassays to estimate the potency of diesel exhaust relative to other complex mixtures of combustion products with similar chemical composition (i.e., coke ovens and roofing tar) for which epidemiologic information was available to estimate respiratory cancer risks. This approach was developed prior to the availability of the studies demonstrating an increased incidence of lung tumors in rodents exposed to diesel engine exhaust. Two of the previous reports did provide estimates of unit risk based upon a fit of the quantal form of the multistage model to rat inhalation studies (Albert and Chen 1986, Pott and Heinrich 1988). One of the reports (Harris 1983) provided risk estimates based upon an analysis of the results from an epidemiologic study of London bus garage workers (Waller 1981). As can be seen from Table V, the unit risk estimates developed from our analysis are quite close to the estimates produced by the other reports with the exception of the estimates developed by Harris (1983), which are approximately two orders of magnitude higher.

In conducting risk assessments, preference should generally be given to using suitable epidemiologic information rather than to data from animal experiments. However, the information published in the epidemiologic reports

is inadequate for estimating risks, and thus we have relied on animal bioassay information. However, the results from the study by Garshick et al. (1987) may be used to provide crude estimates of risk for comparison. In a recent report, McClellan et al. (1990) used information from Garshick et al. (1987) to predict the number of excess cancer cases expected per year based upon general environmental levels of diesel particulates. For this analysis they used the regression coefficient for duration of exposure among younger workers (age < 65) from a conditional logistic regression model from the case-control study reported by Garshick et al. (1987), and assumed that the average exposure levels for the cohort ranged between 0.1 and 0.5 mg/m^3.

Using an essentially similar approach as McClellan et al. (1990), and assuming a background risk for lung cancer of 0.04 for age 18 to 70, estimates of unit risk of lung cancer risk per mg/m^3 (potency) for 47 years of exposure may be estimated using the following formula: ([exp(47 X Beta) - 1] X 0.04)/C where C is the average concentration of particulate exposure, and Beta (=0.01719) is the regression coefficient for young workers after controlling for asbestos exposure and cigarette smoking from the case-control study by Garshick et al. (1987). Using this formula the potency based on the study by Garshick et al. (1987), may be estimated to range from 0.099 to 0.497 per mg/m^3. The lower bound of the potency estimate (0.099) derived from this exercise is approximately 4 times the upper bound estimate of potency (0.022) derived from our analysis of the rat bioassay data.

Thus the limited epidemiologic information available suggests that the results from our analysis of the rat bioassay study may in fact underestimate the true risk in humans. However, it should be recognized that the analysis presented above is based upon crude assumptions regarding average exposures to diesel exhaust among railroad workers, and that it is possible that exposures to other carcinogens may in part explain the excessive risk observed in this group. Furthermore, duration of exposure in the railroad study may have been inaccurately estimated, since information was unavailable to identify which study subjects were exposed to diesel exhaust during the transition from steam to diesel locomotives. It is our understanding that plans are currently being made for an exposure-response analysis of the U.S. railroad study based upon improved estimates of diesel particulate exposures (personal communication Dr. Mark Schenker, University of California at Davis). This study could provide the basis for a future risk assessment, although uncertainties related to some of the issues discussed above may still be present.

CONCLUSIONS

Based on our analysis, the excess risk to miners of lung cancer at the upper range of the diesel particulate exposure reported (1.5 mg/m^3) is approximately 1.5 to 3 in 100. We wish to emphasize that the risk estimates presented in this paper are based on a series of assumptions and involve considerable uncertainty. Most notably, uncertainties about the effects of exposure on lung clearance mechanisms, the deposition rates in humans, and about the relationship between exposure and tissue dose limit our confidence in these estimates of risk. Because of these uncertainties, this risk assessment should be viewed as an exploratory effort. Future efforts should be directed towards developing better estimates of the relevant tissue dose, and to developing estimates of risk based on epidemiologic findings. The results from this risk assessment are consistent with previous recommendations made by NIOSH that diesel exhaust be regarded as a potential human carcinogen and that efforts be made to reduce exposures to the lowest feasible concentrations (NIOSH 1988).

APPENDIX

The notation and methodology closely follows that of the appendix of Crump and Howe (1984) with some readily apparent modifications. An explicitly noted modification is that a parameter included by Crump and Howe to represent a constant delay between tumor initiation and expression is set equal to zero in this implementation. The delay between tumor initiation and expression is ascribed to later stages of the Armitage-Doll model.

Let $E_i(t)$ denote the ambient airborne concentration (mg/m^3) of the i^{th} rat at age t, measured in years = days/365. All exposures began at age t_0 = 120/365 years, giving the following:

$$E_i(t) = \begin{cases} 0, & t < t_0 \\ e_i, & t \geq t_0 \end{cases} \qquad \text{(A.1)}$$

where e_i is one of (0, 0.35, 3.47, 7.08) depending on the exposure group of the i^{th} rat.

When a single stage (r) of k total stages is dose-related, Crump and Howe [1984] show that the cumulative incidence is

$$H_i(t) = q_0 t^k + q_r Z_{rki}(t)$$

where

$$Z_{rki}(t) = \frac{k!}{(k-r)!(r-1)!} \int_0^t E_i(u)\ (t-u)^{k-r} u^{r-1}\ du, \quad t \geq t_0$$

(See especially equations A6 through A11 of Crump and Howe (1984).)

When $t \geq t_0$,

$$Z_{rki}(t) = e_i \frac{k!}{(k-r)!(r-1)!} \int_{t_0}^t (t-u)^{k-r} u^{r-1}\ du, \quad t \geq t_0.$$

$$= e_i \frac{k!\ t^{k-1}}{(k-r)!(r-1)!} \int_{t_0}^t (1-(u/t))^{k-r} (u/t)^{r-1}\ du, \quad t \geq t_0.$$

Making the substitution, v=u/t in the integral gives

$$Z_{rki}(t) = e_i \frac{k!\, t^k}{(k-r)!(r-1)!} \int_{t_0/t}^{1} (1-v)^{k-r} v^{r-1}\, dv, \quad t \geq t_0.$$

$$= e_i\, t^k\, Pr[ß > t_0/t],$$

where ß is a random variable having a beta distribution with shape parameters r, k-r+1 and 'Pr' denotes the probability of the event inside of the brackets. Hastings and Peacock (1974) give the following relationship between the beta distribution and binomial distribution for positive integer values of r and k:

$$Pr[ß{:}r,k-r+1 > t_0/t] = Pr[B{:}k,(t_0/t) \leq r-1],$$

where B is a binomial random variable with Bernoulli trial parameter k and Bernoulli probability parameter (t_0/t).

Hence,

$$Z_{rki}(t) = \begin{cases} 0, & t < t_0 \\ e_i\, t^k \sum_{j=0}^{r-1} \left(k!/(j!(k-j)!)\, (t_0/t)^j\, [1 - (t_0/t)]^{k-j} \right), & t \geq t_0 \end{cases} \qquad (A.2)$$

Equation (A.2) was derived for the case where exposure continued indefinitely once started. This pertains to the actual experience of the rats in the study. When exposure of the i^{th} individual ends at age t_1, similar reasoning leads to:

$$Z_{rki}(t) = \begin{cases} 0, & t < t_0 \\ e_i\, t^k \sum_{j=0}^{r-1} \left\{ k!/(j!(k-j)!)\ (t_0/t)^j\ [1 - (t_0/t)]^{k-j} \right\}, & t_0 \le t \le t_1 \\ e_i\, t^k \sum_{j=0}^{r-1} \left\{ k!/(j!(k-j)!) \left[(t_0/t)^j\ [1 - (t_0/t)]^{k-j} - (t_1/t)^j\ [1 - (t_1/t)]^{k-j} \right] \right\}, & t_1 < t \end{cases} \qquad (A.3)$$

Comparison of special cases of (A.3) for r=1, r=k-1, and r=k to equations (A19), (A20), and (A21) in Crump and Howe (1984) shows that the expressions are in agreement.

When tumors are occult and nonlethal, the death (and sacrifice) times are treated as a random sample of examination times for the presence of a tumor. Rats found to be tumor-free contribute right-censored data on time-to-tumor. Rats found to have a tumor at examination contribute left-censored data on time-to-tumor. The likelihood, which reflects only right-censored or left-censored data is given by

$$L = \prod_i [P(t_i)]^{y_i} [1-P(t_i)]^{1-y_i}$$

where

t_i is the age of examination of the i^{th} rat and y_i is equal to 1 (one) if a tumor was present; otherwise y_i is equal to 0 (zero), and

$P(t_i) = 1 - \exp\{ -q_0 t_i^k - q_r Z_{rki}(t_i) \}$ is the probability that a tumor has occurred by t_i. The likelihood is identical with that given by Crump and Howe (1984) in their equations (5) through (7).

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Table I
Observed Numbers of Tumor-Bearing Rats Exposed to Diesel Exhaust
By Sex and Particulate Exposure Level

Sex	Exposure Level mg/m^3	Number Examined	Adenoma	Adeno-Carcinoma	Adenocar-cinoma + Squam. Cyst	Squamous Cyst	Squamous Cell Carcinoma
F	0	113	-	-	-	-	-
	0.35	111	-	2	-	-	-
	3.47	114	2	-	-	2	-
	7.08	108	-	7	2	7	-
M	0	117	-	2	-	-	-
	0.35	112	-	1	-	-	-
	3.47	108	3	1	-	-	-
	7.08	119	1	6	-	4	2

Table II

Summary of Assumptions Made for Extrapolating Estimates of Risk from Rats to Humans

ASSUMPTION	RATS	HUMANS
Body Weight (W)	0.35 kg	70 kg
Lung Deposition Fraction (F_d)	0.15	0.23
Inhalation Rate (I)	0.19 L/min	21 L/min
Fraction of Time Exposed (F_x)	0.21	0.22

Table III

Information Derived from 5-Stage Armitage-Doll Models with Exposure Acting on the First Stage Fitted to Data on Age of Death or Sacrifice and Tumor Status.

Data Used	Parameter	Estimate	Std Error	Cov(q0,q1)
All Tumors[a]	q_0	0.811×10^{-4}	0.484×10^{-4}	-0.1015×10^{-8}
	q_1	3.80×10^{-4}	0.697×10^{-4}	
Malignancies	q_0	0.850×10^{-4}	0.456×10^{-4}	-0.7529×10^{-9}
	q_1	1.67×10^{-4}	0.477×10^{-4}	

a. The four tumor types reported by Mauderly et al [1987] are adenomas, adenocarcinomas, squamous cysts, squamous cell carcinomas.

Table IV

Estimates of Potency and Exposure Concentrations Corresponding to Levels of Excess Risk[a] Derived from Data and Models Given in Table 3 for an Inhalation Rate of 21 L/min During Exposure Which Occurs Between Ages 18 and 65.

Data Used	Potency Estimate $(mg/m^3)^{-1}$	Standard Error	Excess Risk Level	Concentration (mg/m^3)	Standard Error
All Tumors	0.022	0.0067	0.0001	0.005	0.001
			0.001	0.045	0.008
			0.01	0.45	0.082
Malignancies	0.010	0.0046	0.0001	0.010	0.003
			0.001	0.10	0.029
			0.01	1.0	0.29

a. Evaluated at age 70 years

Table V
Summary of Unit Risk Estimates for Working Lifetime
Exposures (47 years) from Diesel Risk Assessments Performed to Date.[a]

Reference	Method	Unit Risk per $\mu g/m^3$
Harris	Epidemiologic Analysis[b]	5.6×10^{-3}
(1983)	Comparative Potency[c]	1.6×10^{-3}
Cuddihy et al.	Comparative Potency[c]	4.7×10^{-5}
(1984)		
Albert et al.	Comparative Potency[c]	1.7×10^{-5}
(1986)	Multistage Model[d]	0.7×10^{-5}
Pott and Heinrich	Multistage Model[d]	$4\text{-}8 \times 10^{-5}$
(1988)		
Smith and Stayner	Time-to-tumor Model	$1\text{-}2 \times 10^{-5}$
(1990)		

a. All reported risk estimates were adjusted to the equivalent for a 47 years of exposure to diesel exhaust.
b. Based upon an upper bound estimate of risk derived from an analysis of the London bus driver study (Waller 1981).
c. Based upon comparing the relative potency of extracts of diesel exhaust in bioassays to the potency of other complex mixtures with similar chemical composition (e.g. coke oven emissions) for which epidemiologic information on risk was available.
d. Based upon fit of the quantal form of the multistage model. The paper by Albert et al. (1986) fit this model to the study by Mauderly et al. (1987); whereas, the paper by Pott and Heinrich (1988) fit this model to the studies by Mauderly et al. (1987), Brightwell et al. (1986) and Heinrich et al. (1986).

Figure 1

Maximized Likelihood of All Tumors vs. the Number of Stages and the Stage Affected by Exposure for the Armitage-Doll Model

Symbol Plotted = Number of Stages

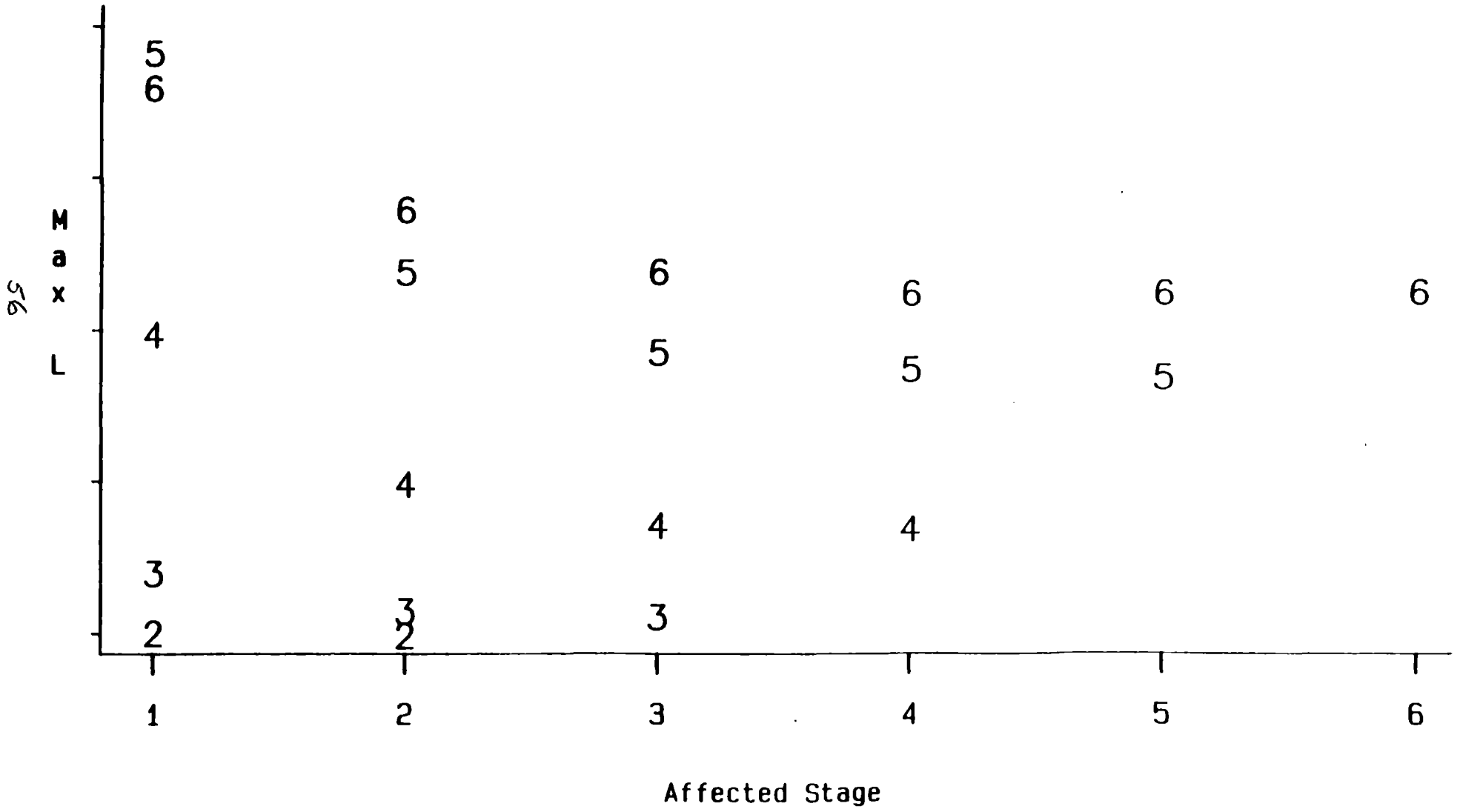
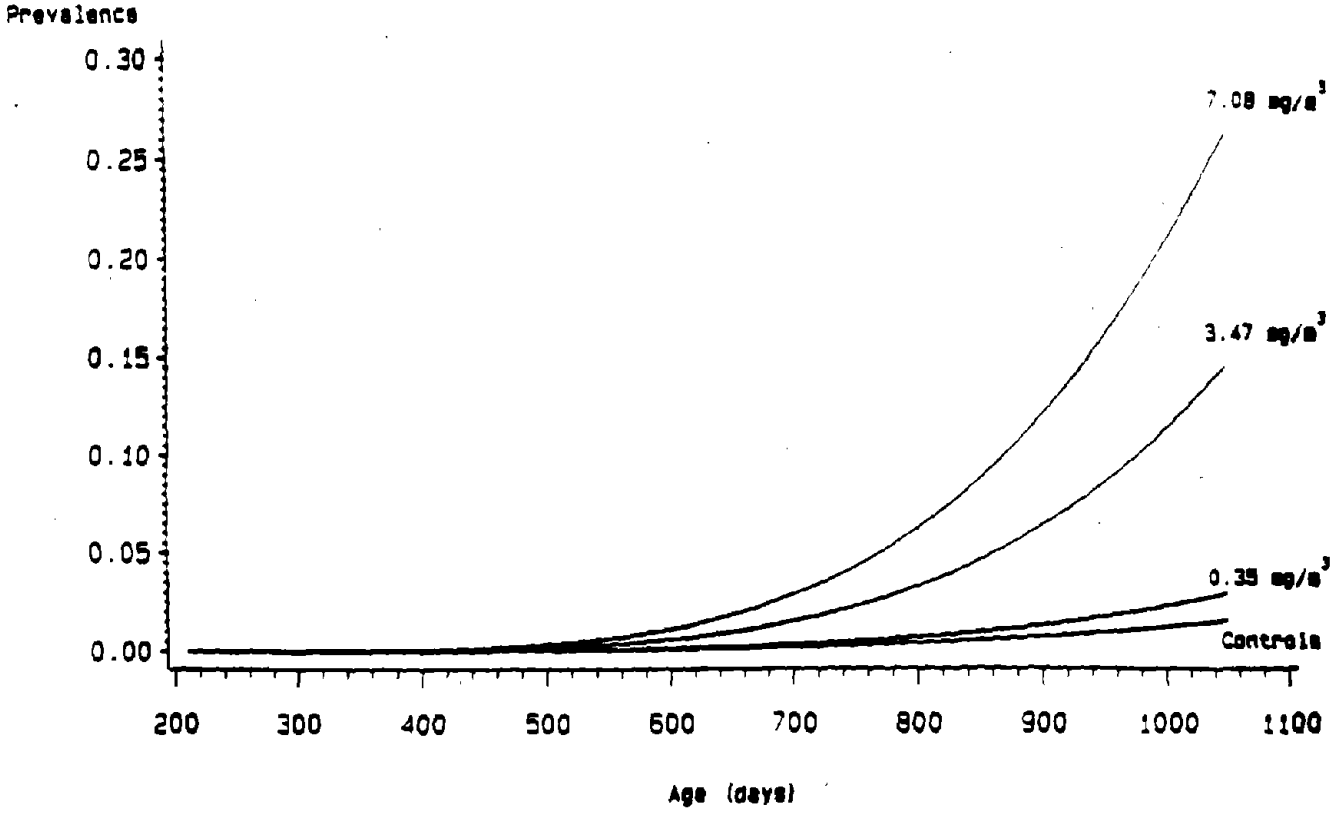


Figure 2

Fitted Tumor Prevalences of Rats by Age and Exposure Concentration
Using Data on All Tumors



Using Data on Malignant Tumors

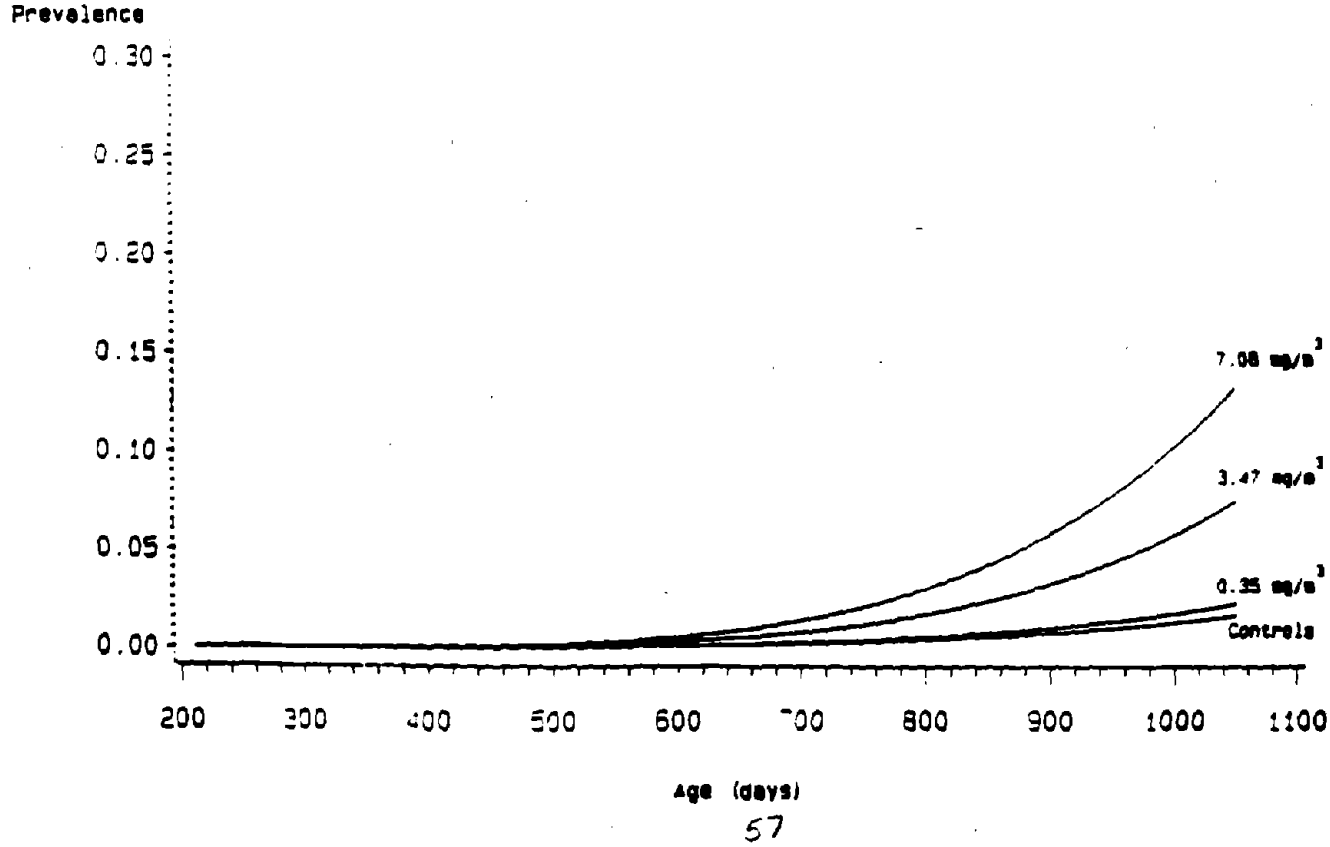
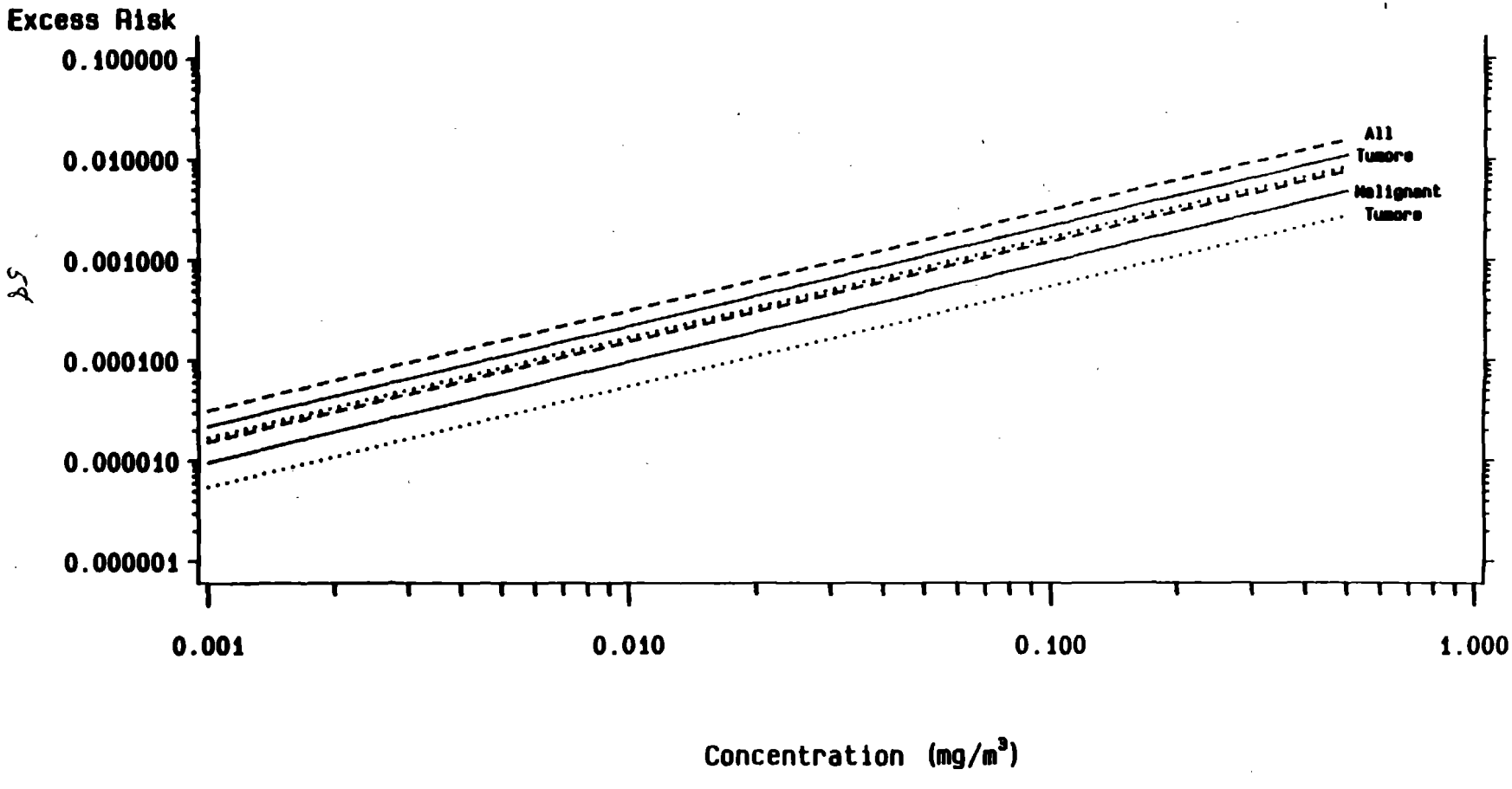
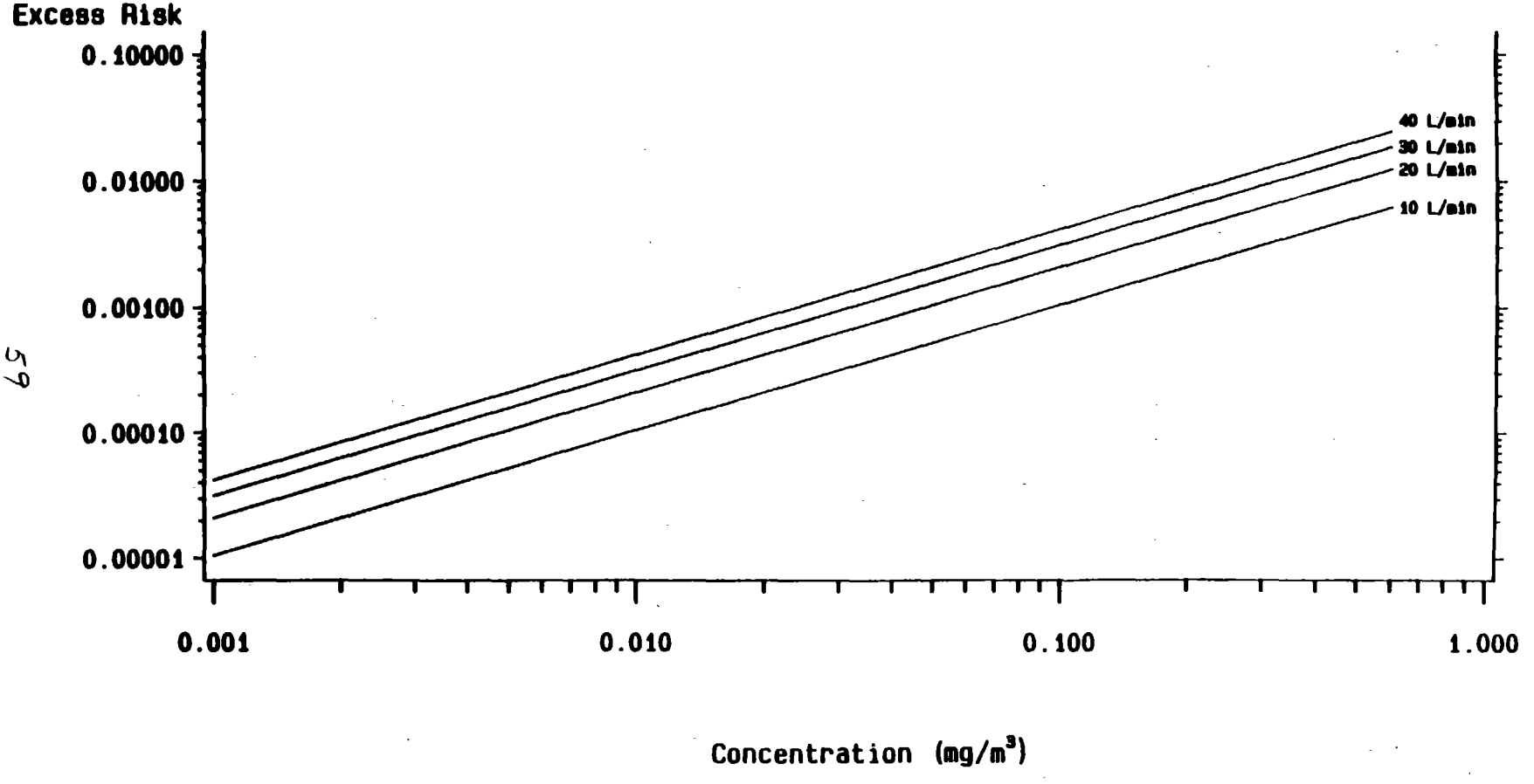


Figure 3
Estimated Relationship Between Excess Risk and Exposure to Diesel Exhaust
Using Data on All Tumors or Data on Malignant Tumors from Mauderly et al (1987)



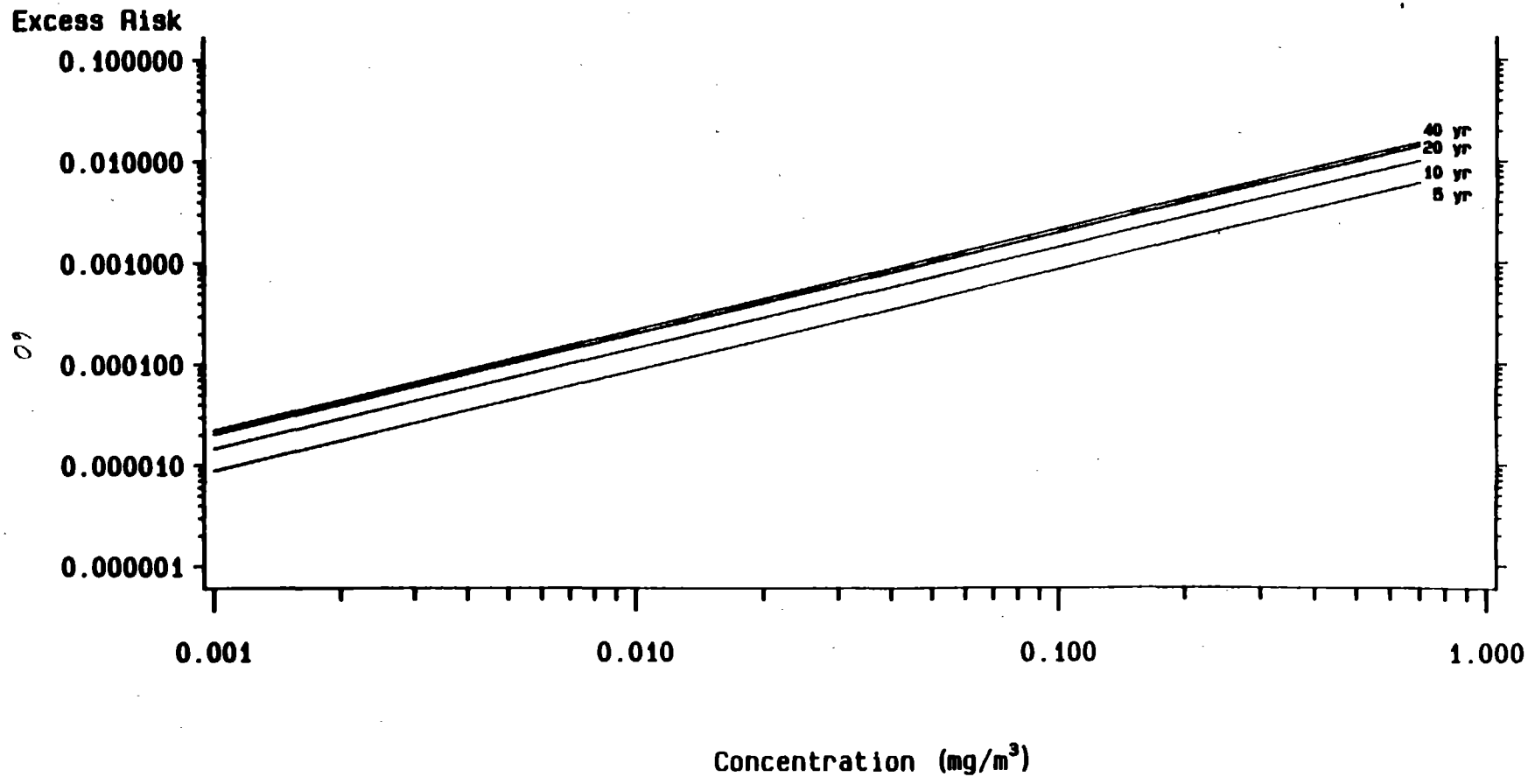
Based on a 5-stage Armitage-Doll model with the first stage affected. Exposure begins at age 18 and ends at age 65. The excess risk is evaluated at age 70 years. The inhalation rate during exposure is 21 L/min. Maximum likelihood estimates with approximate two-sided 90% confidence limits are illustrated.

Figure 4
Estimated Relationship Between Excess Risk and Exposure to Diesel Exhaust
As a Function of Particulate Concentration and Inhalation Rate During Exposure



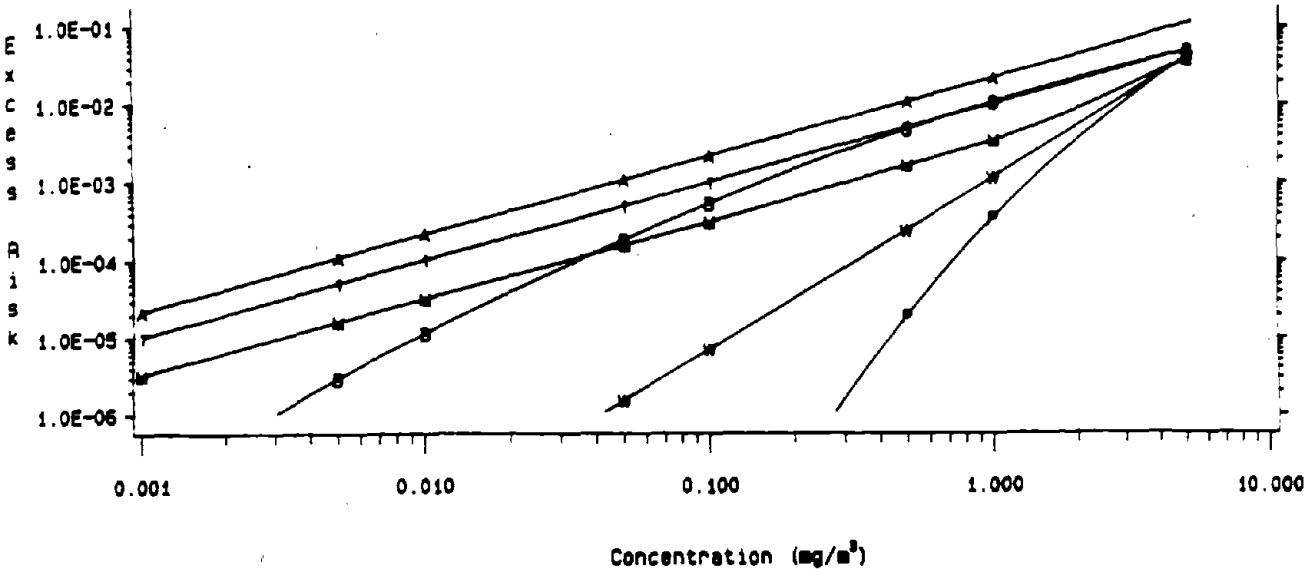
Maximum likelihood estimates for inhalation rates equal to 10, 20, 30, and 40 L/min are illustrated.
A 5-stage Armitage-Doll model with the first stage affected was fitted to data on all tumors.
Exposure begins at age 18 and ends at age 65. The excess risk is evaluated at age 70 years.

Figure 5
Estimated Relationship Between Excess Risk and Exposure to Diesel Exhaust
As a Function of Particulate Concentration and Years of Exposure

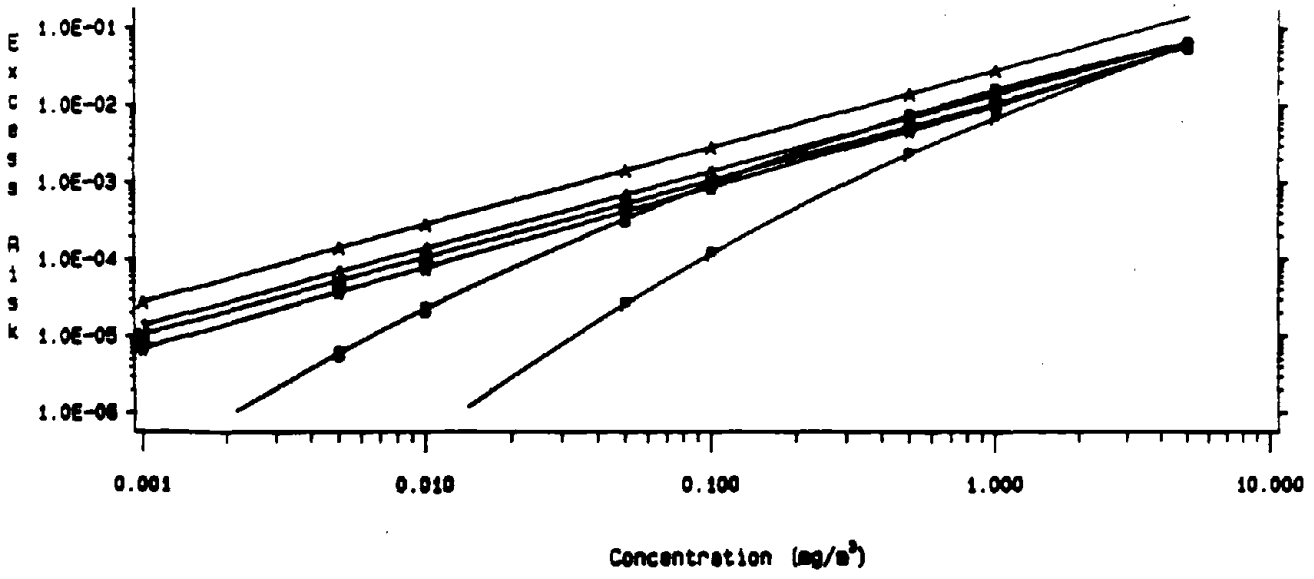


Maximum likelihood estimates for 5, 10, 20 and 40 years of exposure are illustrated. A 5-stage Armitage-Doll model with the first stage affected was fitted to data on all tumors. Exposure begins at age 18 and ends at ages 23, 28, 38, and 58 years. The excess risk is evaluated at age 70 years.

Figure 6
Excess Risk Estimates from Several Models Applied to Quantal Tumor Data
Maximum Likelihood Estimates



Upper 95% Confidence Limits



Symbols are: A - Armitage-Doll with the first of five stages affected
1 - One-Stage, M - Multistage,
B - Mantel-Bryan, W - Weibull, P - Probit
Data are on all tumors from Mauderly et al (1987). The One-Stage, Multistage, Mantel-Bryan, Weibull, and Probit models were applied to quantal data, ignoring age of examination. The Probit model was applied to $\log_{10}$(dose). The Armitage-Doll time-to-tumor model estimates are also shown.

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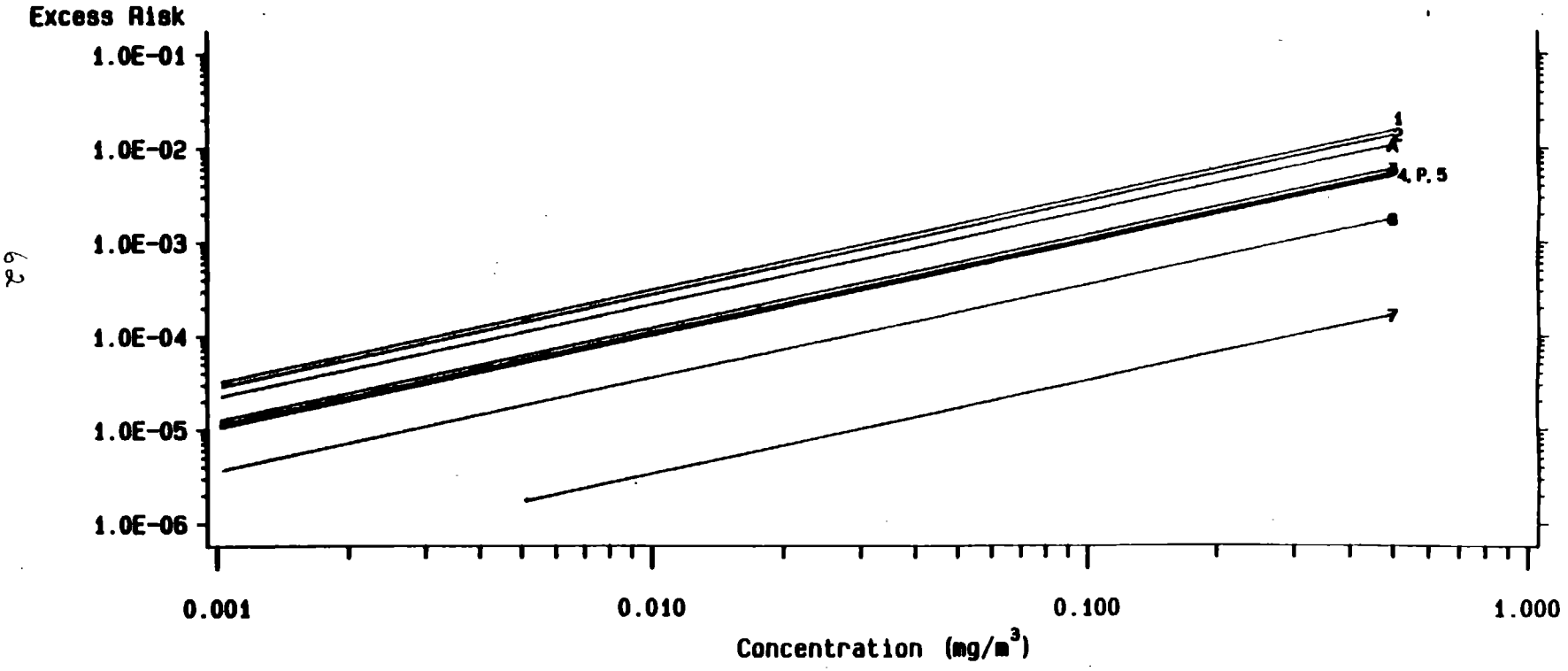
Figure 7

Excess Risk Estimates from Several Studies Applying a One-Stage Model to Quantal Tumor Data

Maximum Likelihood Estimates



Studies ordered from high to low estimates are:

1 - Brightwell et al (1986, Female rats). 2 - Iwai et al (1986). A - Armitage-Doll time-to-tumor.

3 - Heinrich et al (1986). 4 - Brightwell et al (1986, Male rats). P - Quantal data from these studies pooled. 5 - Maudsrly et al (1987, quantal data)

6 - Ishinishi et al (1986, Heavy Duty Engine). 7 - Ishinishi et al (1986, Light Duty Engine)

Data are on all tumors.