# 11. QUALITATIVE AND QUANTITATIVE EVALUATION OF THE CARCINOGENICITY OF DIESEL ENGINE EMISSIONS

## 11.1. INTRODUCTION

Concern about the carcinogenic risk of exposure to diesel engine emissions was stimulated in the late 1970s by a report indicating that diesel particle extracts are mutagenic (Huisingh et al., 1978), by the knowledge that diesel exhaust (DE) contains known carcinogens, and by the projected increase in the use of diesel engines in passenger vehicles. This concern culminated in a U.S. Environmental Protection Agency (EPA)-sponsored quantitative cancer risk estimate for diesel engine emissions (Albert et al., 1983). Its estimate was based on a "comparative potency" approach because of a lack of either chronic animal cancer bioassays or definitive epidemiologic data. Since 1983, several chronic animal inhalation studies and epidemiologic investigations designed to assess the carcinogenicity of diesel engine emissions have been completed. These studies are summarized in Chapters 7 and 8. Data relating to mechanisms of DE-induced carcinogenicity are summarized in Chapter 10. Because of the increase in the availability of such data and because of the need to provide an up-to-date evaluation of the hazards of DE inhalation for U.S. EPA's Office of Mobile Sources, a qualitative as well as a quantitative assessment of the cancer risk from exposure to DE was undertaken. These assessments are presented in this chapter.

## 11.2. QUALITATIVE EVALUATION OF THE CARCINOGENIC RISK OF EXPOSURE TO DIESEL EXHAUST

### 11.2.1. Hazard Evaluation Based on EPA 1986 Guidelines for Carcinogen Risk Assessment

Lung cancer incidence has been studied in human populations exposed to diesel engine exhaust. An increased incidence of lung cancer was observed in 6 mortality studies (Howe et al., 1983; Wong et al., 1985; Boffetta and Stellman, 1988; Garshick et al., 1988; Gustavsson et al., 1990; Ahlman et al., 1991) and in 10 case-control studies (Williams et al., 1977; Hall and Wynder, 1984; Damber and Larsson, 1987; Garshick et al., 1987; Benhamou et al., 1988; Hayes et al., 1989; Gustavsson et al., 1990; Steenland et al., 1990; Burns and Swanson, 1991; Emmelin et al., 1993). A dose-response trend was observed in three of the cohort studies (Howe et al., 1983; Wong et al., 1985; Boffetta and Stellman, 1988) and in three of the case-control studies (Garshick et al., 1987; Steenland et al., 1990; Emmelin et al., 1993). An increased incidence of lung cancer was not observed in some other studies (Waller, 1981; Rushton et al., 1983; Wong et al., 1985; Edling et al., 1987; Lerchen et al., 1987), but each had several methodologic limitations, such as small sample sizes, short follow-up, and lack of adjustment for confounding factors. The studies reporting increased incidences also had some major limitations even though some of them,

especially those reported by Garshick and co-workers (1987, 1988), were able to eliminate most of the confounding variables.

An association between DE exposure and lung cancer is therefore suggested by the results of a number of epidemiologic studies. Because of the uncertainties created by limited exposure data and the possibility of exposure to other agents, the evidence for carcinogenicity of diesel engine emissions in humans is considered to be limited under the EPA Cancer Assessment Guidelines (U.S. EPA, 1986).

In animal experiments, inhalation of whole DE resulted in the induction of lung tumors in F344 rats (Ishinishi et al., 1986; Iwai et al., 1986; Mauderly et al., 1987; Brightwell et al., 1989; Nikula et al., 1995), in Wistar rats (Heinrich et al., 1986a; Heinrich et al., 1995), in Sencar mice (Pepelko and Peirano, 1983), in NMRI mice (Heinrich et al., 1986a; Stöber, 1986), and in C57BL mice (Takemoto et al., 1986). It should be noted, however, that lung tumor incidences did not exceed those of historical controls in the 1986 NMRI mouse study, and in a later study reported by Heinrich et al. (1995), using both NMRI and C57BL mice, significant increases in lung tumors were not seen. Lung tumors also were induced by implantation of DE condensate in Osborne-Mendel rats (Grimmer et al., 1987) and by intratracheal instillation of diesel particulate matter in Wistar rats (Pott and Roller, 1994). Skin painting of diesel particle extracts induced dermal tumors in strain A mice (Kotin et al., 1955) and in Sencar mice following promotion with tetradecanoylphorbol-13-acetate (Nesnow et al., 1982). Extensive studies with *Salmonella* mutagenesis assays have, in most cases, demonstrated direct-acting mutagenic activity in both particle extracts and gaseous fractions of DE. Positive results also have been reported for gene mutations and chromosome effects in mammalian cell systems after exposure to diesel particle extracts.

Based on the induction of lung tumors via inhalation in at least two strains of rats and two strains of mice and by lung implantation of DE condensate, subcutaneous tumors following injection of exhaust particle organic extracts, and skin tumors following dermal application of exhaust particle organic extracts and supported by positive mutagenicity results, the evidence for carcinogenicity of DE in animals is considered to be sufficient under U.S. EPA's Cancer Assessment Guidelines (U.S. EPA, 1986).

The International Agency for Research on Cancer (IARC) (1989) also evaluated the evidence for carcinogenicity of DE and concluded that the evidence for carcinogenicity in humans is limited. This conclusion was based primarily on cohort studies of railroad workers in the United States (Garshick et al., 1988) and Canada (Howe et al., 1983) and two case-control studies (Howe et al., 1983; Garshick et al., 1988) using individuals drawn from the same group of workers. Three further studies of cohorts with less certain exposure to diesel engine exhaust also were considered: two studies of London bus company employees (Raffle, 1957; Rushton et al.,

1983) and one of Swedish dock workers (Edling et al., 1987). IARC concluded that the evidence for carcinogenicity of whole engine exhaust in experimental animals was adequate. The conclusions were based on positive tumorigenic effects in two different strains of rats in five of six experiments (Karagianes et al., 1981; Heinrich et al., 1986b; Ishinishi et al., 1986; Iwai et al., 1986; Mauderly et al., 1987) and on positive effects in mice in two studies (Pepelko and Peirano, 1983; Stöber, 1986).

The IARC conclusions are thus in general agreement with those of EPA. Both agencies concluded that human evidence is limited. IARC considered the animal evidence to be adequate for whole DE as well as for extracts of exhaust particles but inadequate for the gaseous phase. Although EPA has not specifically evaluated the gaseous phase and did not consider whole exhaust and particle extracts separately, both agencies agree that whole diesel engine exhaust is carcinogenic in animals.

On the basis of limited evidence for carcinogenicity in humans, diesel engine emissions are considered to best fit into the cancer weight-of-evidence Category B1, according to 1986 EPA Cancer Assessment Guidelines. This classification is supported by sufficient evidence in animals and positive results in mutagenicity studies and is consistent with the presence of known carcinogens on diesel particles. Chemicals classified in Category B1 are considered to be probable human carcinogens. IARC (1989) also considers DE to be probably carcinogenic in humans and has therefore classified it as Category 2A.

### 11.2.2. Hazard Evaluation Based on EPA Proposed Guidelines for Carcinogen Risk Assessment

Under EPA's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), DE is considered to be a likely human carcinogen by the inhalation route of exposure. Its carcinogenic potential is indicated by limited evidence for carcinogenicity in occupationally exposed humans, positive carcinogenicity in laboratory animal studies, positive evidence for mutagenicity, and the presence of known human carcinogens in the mixture. In comparison with other agents designated as likely carcinogens, the overall weight of evidence for this agent places it at the upper end of this grouping. This is because of positive data on tumor responses in both humans and animals.

Concerning humans, increases in relative risks for lung cancer have been reported in a variety of populations occupationally exposed to DE. These increases have been small, generally less than 2. While the inability to eliminate all confounding variables increases uncertainty, most of the variables have been eliminated in at least one large study. Moreover, the reporting of increased relative risk in a number of studies with differing confounding factors increases the likelihood that a true response has occurred.

Concerning animals, clear evidence for induction of lung tumors in rats was reported in several well-designed and well-conducted experiments. Results in mice were equivocal with the only definitive response occurring in a sensitive strain of mice exposed from conception. Syrian hamsters did not show a positive response but are known to be resistant to induction of deep lung tumors. Experiments with cats, monkeys, and Chinese hamsters, while negative for tumor induction, were of insufficient exposure duration and/or exposure level.

In addition, DE contains a variety of compounds that are considered to be known or likely human carcinogens. These include several polycyclic aromatic compounds such as benzo[a]pyrene and nitroaromatics such a dintropyrene, 1,3-butadiene, and benzene. This evidence is limited because of the low concentration of most of these compounds and because of their uncertain bioavailability. Extracts of diesel exhaust particulate matter (DPM) are also genotoxic in most tests.

Biological information on DE is contradictory in terms of how to quantitate potential cancer risks. Among animal species, only rats have shown unequivocal tumor responses, raising the possibility that this response may be unique to rats. Tumor induction also was noted only at exposure concentrations resulting in lung particle overload and accompanying pathological effects. Because of limited sensitivity of the studies, however, the possibility of tumor induction at exposure levels below those responsible for particle overload still exists. Mechanistic studies support the concept that high-dose induction of lung cancer is a result of lung particle overload resulting in release of inflammatory cytokines, proteolytic enzymes, and reactive oxygen species, resulting in genotoxic effects with increased likelihood of fixing harmful mutations because of rapid cell turnover. On one hand, while epidemiologic data are limited because of small increases in relative risk ratios and an inability to eliminate all confounding factors, the data nevertheless suggest that humans are likely to respond with lung cancer under nonparticle-overload conditions. Low-dose effects are more likely due to elution of organics from the diesel particle, although direct effects of particles cannot be ruled out.

## 11.3. QUANTITATIVE ESTIMATION OF THE CARCINOGENIC RISK OF EXPOSURE TO DIESEL EXHAUST

### 11.3.1. Review of Previous Quantitative Risk Estimates

Early attempts to quantitatively assess the carcinogenicity of diesel engine emissions were hindered by a lack of both positive epidemiologic studies and long-term animal studies. One means of overcoming these obstacles was the use of the “comparative potency” method (Albert et al., 1983). A second involved estimating risk based on equivocal epidemiologic evidence (Harris, 1983).

In the comparative potency method, a combustion or pyrolysis product was selected that had a previously determined cancer potency estimate based on epidemiologic data. The ratios of the potency of this agent (e.g., coke oven emissions) to diesel exhaust particulate matter (DPM) extract in a variety of in vivo and in vitro tests are then multiplied by the epidemiology-based potency estimate for coke oven emissions and averaged. If epidemiology-based estimates from more than one pollutant are used, the derived potencies are generally averaged to obtain an overall mean.

The comparative potency estimate of Albert et al. (1983) is probably the best known. Their results were obtained using epidemiology-based unit cancer risk estimates for coke oven emissions, cigarette smoke condensate, and roofing tar. Samples of particulate matter were collected from three light-duty engines (a Nissan 220 C, an Oldsmobile 350, and a Volkswagen turbocharged Rabbit), all run on a highway fuel economy test cycle, and from a heavy-duty engine (Caterpillar 3304), run under steady-state, low-load conditions. The particulate matter was extracted with dichloromethane and tested in a variety of assays. Dose-dependent increases in response were obtained for the four assays listed below:

- Ames *Salmonella typhimurium* (TA98) reverse mutation,
- Gene mutation in L5178Y mouse lymphoma cells,
- Sencar mouse skin tumor initiation test, and
- Viral enhancement of chemical transformation in Syrian hamster embryo cells.

Only the first three assays were used to develop comparative potency estimates because of variability of responses in the enhancement of the viral transformation assay. The in vitro studies were carried out both in the presence and absence of metabolic activators. The potency, defined as the slope of the dose-response curve, was measured for each sample in each short-term assay.

The skin tumor initiation test was positive for all the engines tested except the Caterpillar engine. Only the Nissan engine, however, gave strong dose-response data. Because skin tumor initiation was considered to be the most biologically relevant test, it was used to derive potency estimates for the Nissan engine. An estimate for the Nissan engine was then derived by multiplying the epidemiology-based potency estimates for each of the three agents (coke oven emissions, roofing tar, and cigarette smoke condensate) by the ratios of their potencies in the skin tumor initiation test to that of the Nissan diesel engine. According to this method, three 95% upper-bound estimates of lifetime cancer risk per microgram per cubic meter of extractable organic matter were derived for the Nissan diesel, based on potency comparisons with each of the three agents. These values are: coke oven emissions, $2.6 \times 10^{-4}$; roofing tar, $5.2 \times 10^{-4}$; and cigarette smoke condensate, $5.4 \times 10^{-4}$. The average of the three equals $4.4 \times 10^{-4}$.

The potency of the other diesel emission samples was not estimated directly because of the weak response in the skin tumor initiation test. Instead, their potency relative to the Nissan

engine was estimated as the arithmetic mean of their potency relative to the Nissan in the *Salmonella* assay in strain TA98, the sister chromatid exchange assay in Chinese hamster ovary cells, and the mutation assay in mouse lymphoma cells. The estimated lifetime cancer risk per microgram per cubic meter of extractable organic matter for extracts from these engines are as follows: Volkswagen, $1.3 \times 10^{-4}$; Oldsmobile $1.2 \times 10^{-4}$; and Caterpillar, $6.6 \times 10^{-6}$.

To convert these values to a lifetime risk per microgram per cubic meter of total DPM, the results were multiplied by the fraction of extractable organic matter in the particles. This conversion was based on the assumption that the carcinogenic effects were caused solely by the organic fraction. These fractions were as follows: Nissan, 0.08; Volkswagen, 0.18; Oldsmobile, 0.17; and Caterpillar, 0.27. After this adjustment, the resulting estimated potencies per microgram per cubic meter of inhaled DPM varied from $3.5 \times 10^{-5}$ for the Nissan to $1.8 \times 10^{-6}$ for the Caterpillar.

Harris (1983) developed comparative potency estimates for the same four engines used by Albert et al. (1983) but used only two epidemiology-based potency estimates: those for coke oven emissions and for roofing tar. He employed preliminary data from three of the same assays used by Albert et al. (1983)—the Sencar mouse skin tumor initiation assay, enhancement of viral transformation in Syrian hamster embryo cells, and the L5178 mouse lymphoma test. The mouse lymphoma test was used both with and without metabolic activation, whereas the *Salmonella* assay was not used.

The diesel cancer potency estimates by Harris (1983) were then derived by multiplying the epidemiology-based cancer potency estimates for both coke oven emissions and roofing tar by the ratio of their potencies compared with DE particles in each of the four bioassays. For example, the epidemiology-based relative risk of exposure to 1 $\mu g/m^3$ of coke oven emissions was estimated to equal $4.4 \times 10^{-4}$. In the skin tumor initiation test, 2.1 papillomas per mouse were reported for the coke oven sample, compared with 0.53 for the Nissan engine extract. The benzene-extractable fraction was assumed to equal 0.06 (slightly less than that in the Albert et al., 1983, studies). The diesel potency estimate using this comparison is then equal to $(0.53/2.1) \times 0.06 \times 4.4 \times 10^{-4}/\mu g/m^3$, or $6.6 \times 10^{-6}/\mu g/m^3$ DPM. A total of eight comparisons were made for each engine, four bioassays times two epidemiology-based potency estimates.

The Harris (1983) estimates are not comparable to those of Albert et al. (1983) without adjustment. The unit risk estimates of Albert and co-workers are based on absolute risk during lifetime exposure, whereas Harris reported his values in terms of relative risk per year of exposure. To adjust this to lifetime risk for continuous exposure, it is necessary to multiply Harris' values by a factor of $2.7 = (70 \times 0.039)$, where 70 reflects the lifetime exposure (70 years) and 0.039 is the lifetime lung cancer mortality rate in the U.S. population.

The range of potencies varied from $0.2 \times 10^{-5}$ to $0.6 \times 10^{-5}$ for the Nissan sample,

$0.1 \times 10^{-5}$ to $2.4 \times 10^{-5}$ for the Oldsmobile 350, $0.2 \times 10^{-5}$ to $27.8 \times 10^{-5}$ for the Volkswagen Rabbit, and $0.1 \times 10^{-5}$ to $2.5 \times 10^{-5}$/µg/m$^3$ DPM for the Caterpillar sample. Harris (1983) derived an overall mean relative risk value of $3.5 \times 10^{-5}$/µg/m$^3$ for the three light-duty engines with a 95% upper confidence limit of $2.5 \times 10^{-4}$. Individual mean values for each engine were not reported. After multiplying by 2.7 to convert to a unit risk, the upper-bound estimate of potency from the three light-duty engines was equal to $6.8 \times 10^{-4}$/µg/m$^3$ DPM. McClellan (1986), Cuddihy et al. (1981, 1984), and Cuddihy and McClellan (1983) estimated a risk of about $7.0 \times 10^{-5}$/µg/m$^3$ DPM using a comparative potency method similar to those reported in the preceding paragraph. The database was similar to that used by Albert et al. (1983) and Harris (1983). This estimate agrees quite well those reported by Albert et al. (1983). Although the Harris (1983) estimate is somewhat greater, it should be remembered that it was based on preliminary data.

With the availability of chronic cancer bioassays, more recent assessments were based on lung tumor induction in rats. Albert and Chen (1986) reported a risk estimate based on the chronic rat bioassay conducted by Mauderly et al. (1987). Using a multistage model and assuming equivalent deposition efficiency in humans and rats, they derived a 95% upper confidence limit of $1.6 \times 10^{-5}$ for lifetime risk of exposure to 1 µg/m$^3$. Pott and Heinrich (1987) used a linear extrapolation, including data reported by Brightwell et al. (1989), Heinrich et al. (1986a), and Mauderly et al. (1987). They reported risk estimates of $6 \times 10^{-5}$ to $12 \times 10^{-5}$/µg/m$^3$. More recently, Smith and Stayner (1990), using time-to-tumor models based on the data of Mauderly et al. (1987), derived 95% upper confidence limits ranging from $1.5 \times 10^{-5}$ to $3 \times 10^{-5}$/µg/m$^3$. Pepelko and Chen (1993) developed unit risk estimates based on the data of Brightwell et al. (1989), Ishinishi et al. (1986), and Mauderly et al. (1987) using a detailed dosimetry model to extrapolate dose to humans and a linearized multistage model. Taking the geometric mean of individual estimates from the three bioassays, they derived unit risk estimates of $1.4 \times 10^{-5}$/µg/m$^3$ when dose was based on carbon particulate matter per unit lung surface area rather than whole DPM and $1.2 \times 10^{-4}$/µg/m$^3$ when based on lung burden per unit body weight. Hattis and Silver (1994) derived a maximum likelihood estimate for occupational exposure of $5.2 \times 10^{-5}$/µg/m$^3$ based on lung burden and bioassay data reported by Mauderly et al. (1987) and use of a five-stage Armitage-Doll low-dose extrapolation model.

Lung cancer risk estimates based on epidemiologic data were derived by two investigators. Harris (1983) assessed the risk of exposure to diesel engine emissions using data from the London Transport Worker Study reported by Waller (1981). Five groups of employees from the London Transport Authority (LTA) were used: bus garage engineers, bus drivers, bus conductors, engineers in central works, and motormen and guards. The first group was considered to have received the highest exposure; the next two, intermediate; and the last two, none. When cancer death rates for the high-exposure group were compared with those of

London males, there was no increase in the observed-to-expected (O/E) ratios. The author, in fact, considered the results to be negative. However, because the low rate of lung cancer in all the LTA exposure groups may have been the result of a "healthy worker" effect, Harris (1983) compared the exposed groups with internal controls. He merged the three exposed groups and compared them with the two groups considered to be unexposed. An adjustment was made for the estimated greater exposure levels of garage engineers compared with bus drivers and conductors. Using this method, the relative risk of the exposed groups was greater than 1 but was statistically significant only for garage engineers exposed from 1950 to 1960. In this case, the O/E ratio was 29% greater than the presumed unexposed controls.

Harris (1983) identified a variety of uncertainties relative to potency assessment based on this study. These included:

- Small unobserved differences in smoking incidences among groups, which could have a significant effect on lung cancer rates;
- Uncertainty about the magnitude of exposure in the exposed groups;
- Uncertainty regarding the extent of change in exposure conditions over time;
- Random effects arising from the stochastic nature of the cancer incidence; and
- Uncertainty in the mathematical specification of the model.

Taking the uncertainties into account, he derived a maximum likelihood relative risk estimate of $1.23 \times 10^{-4}$ with a 95% upper confidence limit of $5 \times 10^{-4}/\mu g/m^3$ DPM per year. These estimates are equal to $5 \times 10^{-4}$ and $2 \times 10^{-3}$, respectively, when converted to an absolute risk for lifetime exposure to 1 $\mu g/m^3$ particulate matter. It should be noted that, because of the high degree of uncertainty, the 95% lower confidence limit would predict no risk.

More recently, McClellan et al. (1989) reported risk estimates based on the Garshick et al. (1987) case-control study in which lung cancer in railroad workers was evaluated. Using a logistic regression, the expected relative risk of lung cancer death was estimated to rise 0.016 per year of exposure to DE. Adjustments were made to convert to continuous exposure (168 vs. 40 hours) for 70 years. Because exposure levels could not be defined exactly, two sets of calculations were made, assuming inhaled DPM concentrations of either 500 or 125 $\mu g/m^3$ DPM. Using a 95% upper confidence limit, the number of excess cancer deaths per year in the United States was estimated to range from 1,900 to 7,400. These values could then be converted to a lifetime 95% upper confidence limit of the risk of exposure to 1 $\mu g/m^3$ DE, by dividing the estimated excess number of annual cancer deaths in the United States by the total population and multiplying by 70, the estimated mean lifespan. Using this approach, unit risks of $0.6 \times 10^{-3}$ to $2 \times 10^{-3}$ were derived. Even using the 95% lower confidence limits, an excess of 100 to 400 deaths is

predicted, unlike the Harris (1983) study in which no excess deaths could be predicted based on the lower confidence limit. The estimates discussed in this section are listed in Table 11-1.

Each of the methods used to assess cancer risk has differing strengths and weaknesses, which will be discussed later in this chapter.

**Table 11-1. Estimated 95% upper confidence limits of the lifetime risk of cancer from inhalation of 1 μg/m$^3$ diesel particulate matter (DPM)**

| Method | Potency | Comments | Reference |
|---|---|---|---|
| Comparative potency | $3.5 \times 10^{-5}$ | Nissan engine | Albert et al., 1983 |
| Comparative potency | $2.6 \times 10^{-5}$ | Average of 3 engines | Albert et al., 1983 |
| Comparative potency | $7.0 \times 10^{-5}$ | Light-duty engines | Cuddihy et al., 1984 |
| Comparative potency | $6.8 \times 10^{-4}$ | Average of 3 engines | Harris, 1983 |
| Multistage model | $1.6 \times 10^{-5}$ | Lung cancer rats[a] | Albert and Chen, 1986 |
| Straight-line extrapolation | $6\text{-}12 \times 10^{-5}$ | Lung cancer rats[b] | Pott and Heinrich, 1987 |
| Time-to-tumor model | $2\text{-}3 \times 10^{-5}$ | Lung cancer rats[a] | Smith and Stayner, 1990 |
| Logistic regression | $8 \times 10^{-5}$ | Lung cancer rats[c] | McClellan et al., 1989 |
| Multistage model | $1.4 \times 10^{-5}$ | Lung cancer rats[d] | Pepelko and Chen, 1993 |
| Armitage-Doll model | $5.2 \times 10^{-5}$ | Lung cancer rats[a,e] | Hattis and Silver, 1994 |
| Epidemiologic analysis | $1.4 \times 10^{-3}$ | London transport study | Harris, 1983 |
| Epidemiologic analysis | $.6\text{-}2 \times 10^{-3}$ | Railroad workers | McClellan et al., 1989 |

[a]Used data from studies by Mauderly et al., 1987.
[b]Used data from studies by Brightwell et al., 1989; Heinrich et al., 1986a; and Mauderly et al., 1987.
[c]Used data from studies by Brightwell et al., 1989; Ishinishi et al., 1986; Iwai et al., 1986; and Mauderly et al., 1987.
[d]Used data from studies by Brightwell et al., 1989; Ishinishi et al., 1986; and Mauderly et al., 1987.
[e]Maximum likelihood estimate based on 53 years of exposure, 8 hours/day, 240 days/year.

### 11.3.2. Current Approaches to Quantitation of Human Cancer Risk From Exposure to Diesel Exhaust

#### 11.3.2.1. *Dose-Response Estimates Using Human Epidemiologic Data*

In an attempt to quantitatively estimate risk using humans, a detailed analysis of the Garshick et al. (1988) study of railroad workers was carried out by ICF Clements (Crump et al., 1991). This study was selected because the cohort was quite large, significant increases in relative risk ratios were reported, exposure data collected during the later years of exposure were available, and some estimates of early exposures were available (Woskie et al., 1988a,b). The investigators were also able to eliminate many of the confounding factors present in earlier studies. Garshick et al. (1988) analyzed information obtained from the Railroad Retirement Board on 55,407 white males who began railroad employment between 1939 and 1949, who were between the ages of 40 and 64 in 1959, and who in 1959 worked at 1 of the 39 jobs selected to represent a range of potential DE exposure. Two analyses that indicated effects of exposure to DE on lung cancer risk in this cohort were reported: (1) A relative risk for lung cancer of 1.45 (95% confidence interval [CI] = 1.11, 1.89) was observed for DE-exposed workers who were 40 to 44 years of age in 1945 and who consequently had the longest potential exposure to DE; relative risk was progressively lower among DE-exposed workers who were older in 1959 and who had potentially shorter exposures to DE; and (2) the relative risk of lung cancer increased monotonically with increasing duration of work in 1959 or later in a job involving DE exposure (disregarding exposures in the current year and in the most recent 4 years); this risk was 1.72 (95% CI = 1.29, 2.23) in the group with the longest exposure (15 to 17 years).

The Garshick et al. (1988) database was used by two groups of investigators for the purpose of quantitating cancer risk from exposure to diesel engine emissions (Crump et al., 1991, unpublished; Dawson, California EPA, personal communication to William Pepelko, U.S. EPA). The results of these analyses were not in agreement. While Crump and co-workers failed to derive a positive dose-response relationship, Dawson did report increasing incidence of lung cancer with exposure level. These differences have not been resolved. Until they are resolved, utilization of the Garshick et al. (1988) study to quantitate cancer risk from DE is not anticipated. It should be noted, however, that despite the decision to not use this study for quantitative analysis at this time, it still provides the strongest qualitative evidence for a causal association between DE exposure and lung cancer.

As described previously, McClellan et al. (1989) estimated annual lung cancer mortality in the U.S. population, per $\mu g/m^3$ DPM, using the Garshick et al. (1987) case-control study, which minimizes the issue of the dose response by assuming a single exposure level for all the cases. Mean exposure levels of 125 or 500 $\mu g/m^3$ DPM were used for deriving risk estimates because exposure data, while limited, indicated that actual exposures were unlikely to fall outside this

range (Woskie et al., 1988a,b). The unit risk estimate of $2 \times 10^{-3}/(\mu g/m^3)$, assuming a mean exposure concentration of 125 $\mu g/m^3$, is then quite conservative because it is based not only on the upper-bound estimate of lung cancer mortality, but also on the lower estimate of mean exposure. The risk estimates of either 0.6 or $3 \times 10^{-3}/(\mu g/m^3)$, depending on the level of exposure assumed, will be approximately halved if maximum likelihood estimates of mortality are used.

#### 11.3.2.2. *Dose-Response Estimates Based on Animal Bioassay Data*

Several cancer potency estimates for DE have been developed by U.S. EPA and others. Most of them used somewhat similar approaches, and as a result most of the estimates did not differ greatly. The approaches used here are an extension of these efforts. To develop unit risk estimates, it was necessary to address several issues, including (a) determination of the critical target site for DE; (b) determination of the fraction of exhaust responsible for tumor induction; (c) use of existing methods or development of new dosimetric methods for accurately extrapolating dose from experimental animals chronically exposed to high concentrations of exhaust to humans exposed at ambient concentrations; and (d) selection of the most suitable low-dose risk extrapolation model.

The critical target organ was considered to be the lung. Although Iwai et al. (1986) reported the induction of malignant lymphomas in the spleen as well as lung tumors in rats following DE exposure, the lung was the only target site in other experimental studies with this species. Potential carcinogenic agents present in DE may be adsorbed from the lungs, enter the bloodstream, and be transported systemically. Although increases in DNA adduct levels in peripheral lymphocytes have been reported in workers occupationally exposed to DE (Hemminki et al., 1994), there is insufficient evidence for induction of cancer in humans at systemic locations. Particle-adsorbed organics also may reach systemic targets via the gastrointestinal tract. Particles deposited in the conducting airways are cleared to the mouth quite rapidly and swallowed. A considerable volume of particles are also likely to be ingested as a result of grooming during whole animal exposures (Wolff et al., 1982), resulting in the possible uptake of carcinogens by the gastrointestinal tract. Because half-times for elution of organics from the particles are considerably longer than passage through the gastrointestinal tract, however, the fraction adsorbed is expected to be small.

The site of action in the lungs is assumed to be the epithelial lining of the alveoli and small airways. According to Mauderly et al. (1987) and others, inflammation and tumors appear to arise from this tissue. Although a connection between interstitial events and lung tumors has been suggested for particles (i.e., fibrosis as a precondition for lung tumors [Kuschner, 1984]), data are unavailable to support this view with respect to DE-induced tumors.

Accurate extrapolation of dose from experimental studies using animals exposed at high concentrations of exhaust to humans exposed to ambient concentrations requires a variety of adjustments. These include adjustments for species differences in deposition efficiency and respiratory exchange rates. An important factor is the rate of particle clearance from the deep lung. Normal clearance half-times from the alveolar region are several times longer in humans than in rats (Chan et al., 1981; Bohning et al., 1982; Griffis et al., 1983). This may result in an underestimate of lung burden when extrapolating to humans. On the other hand, the high exposure concentrations used in some of the animal studies resulted in greatly slowed or even complete cessation of macrophage-based clearance (Chan et al., 1984).

To more accurately extrapolate dose from experimental studies to humans, detailed dosimetry modeling was used to account for these factors. One of these models (Yu et al., 1991) is listed in Appendix C. A second approach reported by Hattis and Silver (1994) was also employed for comparison. Hattis and Silver determined area under the curve/time, using observed lung burden data reported by Mauderly et al. (1987). Human lung burden in the Hattis and Silver approach was calculated using a one-compartment model suggested by Smith (1992), assuming that at low doses the lung burden is at steady state. Dose for both approaches was estimated in terms of either particle concentration per unit of lung surface area or lung burden/body surface area.

The use of whole particle lung burden as the dosimeter is based on the assumption that both the diesel particle as well as its surface-adsorbed constituents are responsible for the carcinogenic effects of DE. A particle-based assessment was considered to be reasonable for two principal reasons. First, exposure to the vapor phase alone did not result in detectable tumor induction in rats (Ishinishi et al., 1986; Iwai et al., 1986; Stöber, 1986; Brightwell et al., 1989; Heinrich et al., 1995). Second, while tumor induction at high doses is considered to be primarily a particle effect (Heinrich, 1990; Heinrich et al., 1995; Nikula et al., 1995), the particle-associated organics are likely to play a greater role at lower doses. Particle concentration is also the most practical measure of dose because of the large number of surface-associated compounds and because their concentrations are seldom reported.

As reviewed in Chapter 7, several bioassay studies showed positive lung tumor responses in rats (Ishinishi et al., 1986; Iwai et al., 1986; Stöber, 1986; Mauderly et al., 1987; Brightwell et al., 1989; Heinrich et al., 1995; Nikula et al., 1995). Three of these studies (Tables 11-2 through 11-4) were used for unit risk calculations because they were designed using multiple exposure groups and thus are more appropriate for risk calculations. Use of these studies also allows comparison with earlier risk estimates. The time-to-event (i.e., death with or without tumors) data are available for the Mauderly et al. (1987) study. These time-to-event data are used in all

**Table 11-2. Incidence of lung tumors in Fischer 344 rats (males and females combined) exposed to heavy-duty engine exhaust**

| Exposure concentration ($mg/m^3$) | Dose metric: Weekly exposure ($mg/m^3 \times h$)[a] | Dose metric: Lung particle burden ($mg/cm^2$ lung surface)[b] | Lung tumor incidence[c] |
|---|---|---|---|
| 0 | 0 | 0 | 2/230 |
| 0.35 | 12 | $6.4 \times 10^{-5}$ | 3/223 |
| 3.50 | 122 | $2.8 \times 10^{-3}$ | 6/222 |
| 7.08 | 248 | $6.0 \times 10^{-3}$ | 18/227 |

[a]Exposures were 7 hours/day, 5 days/week for 30 months. Numbers include those dying or moribund prior to 30 months.
[b]Calculated using mathematical models in Appendix C.
[c]Does not include squamous cysts.

Source: Mauderly et al., 1987.

**Table 11-3. Incidence of lung tumors in Fischer 344 rats (males and females combined) exposed to heavy-duty engine exhaust**

| Exposure concentration ($mg/m^3$) | Dose metric: Weekly exposure ($mg/m^3 \times h$)[a] | Dose metric: Lung particle burden ($mg/cm^2$ lung surface)[b] | Lung tumor incidence[c] |
|---|---|---|---|
| 0 | 0 | 0 | 1/123 |
| 0.46 | 44 | $2.5 \times 10^{-4}$ | 1/123 |
| 0.96 | 92 | $2.0 \times 10^{-3}$ | 0/125 |
| 1.84 | 177 | $4.2 \times 10^{-3}$ | 4/123 |
| 3.72 | 357 | $8.8 \times 10^{-3}$ | 8/124 |

[a]Exposures were 16 hours/day, 6 days/week for 30 months. Numbers include those dying or sacrificed moribund before 30 months.
[b]Calculated using mathematical models in Appendix C.
[c]All tumors reported were carcinomas.

Source: Ishinishi et al., 1986.

**Table 11-4. Incidence of lung tumors in Fischer 344 rats (males and females combined) exposed to diesel engine exhaust**

| Exposure concentration ($mg/m^3$) | Dose metric: Weekly exposure ($mg/m^3 \times h$)[a] | Dose metric: Lung particle burden ($mg/cm^2$ lung surface)[b] | Lung tumor incidence[c] |
|---|---|---|---|
| 0 | 0 | 0 | 4/250 |
| 0.7 | 56 | $3.5 \times 10^{-4}$ | 1/112 |
| 2.2 | 176 | $4.2 \times 10^{-3}$ | 14/112 |
| 6.6 | 248 | $1.3 \times 10^{-2}$ | 55/111 |

[a]Exposures were 16 hours/day, 5 days/week.
[b]Calculated using mathematical models listed in Appendix C.
[c]The number of animals sacrificed at 6 and 12 months is excluded from the denominators.

Source: Brightwell et al., 1989.

the risk calculations based on the Mauderly et al. (1987) data. Use of a time-to-tumor model, when data are available, allows more accurate modeling of dose response.

Risk estimates were derived using two models. The first one is the linearized low-dose extrapolation model. The linearized multistage (LMS) model is adopted by U.S. EPA as a default procedure to provide an upper bound estimate of risk when data useful to incorporate plausible mechanisms are not available. This model was selected as one of the approaches because, although mechanisms of carcinogenesis have been proposed (see Chapter 10), they remain largely unproven.

The LMS model has the mathematical form $P = 1 - \exp(-Z)$, where Z is either $Z = q_0 + q_1xd + ... + q_mxd^m$, a polynomial of concentration d, or $Z = (Q_0 + Q_1xd + ... + Q_mxd^m)\ xt^k$, a polynomial of concentration d multiplied by a time factor $t^k$ when time-to-event data are used. The range of extrapolation is about three orders of magnitude in the present study. Because the extra risk $(P - P_0)/(1 - P_0)$ is dominated by the linear term $q_1xd$ at low concentration, the 95% upper bound of $q_1$ is used to represent unit risk when d is expressed in $\mu g/m^3$. $P_0$ denotes the lifetime cancer risk at concentration 0. The resulting unit risk estimates are listed in Table 11-5.

Table 11-5. Unit risk estimates per µg/m $^3$ of diesel exhaust based on the Yu et al. (1991) dosimetry model

| | Lung burden/lung surface area | Lung burden/body weight $^{3/4}$ |
|---|---|---|
| Mauderly et al., 1987 | $3.4 \times 10^{-5}$ | $9.9 \times 10^{-5}$ |
| Ishinishi et al., 1986 | $1.6 \times 10^{-5}$ | $4.6 \times 10^{-5}$ |
| Brightwell et al., 1989 | $7.1 \times 10^{-5}$ | $2.1 \times 10^{-5}$ |
| Geometric mean of three studies | $3.4 \times 10^{-5}$ | $9.9 \times 10^{-5}$ |

The potency estimates derived using the LMS model are an improvement over most of the earlier estimates because of improved methods for extrapolating dose from experimental animals to humans. These assessments as well as earlier ones, however, are based on the premise that carcinogenic effects are a function of the whole particle concentration. Moreover, risk estimates are calculated using the default assumption that responses vary linearly with particle concentration even at ambient exposure concentrations. As noted in Chapter 10, however, while particle effects may be dominant at large lung burdens, other components such as polycyclic aromatic compounds, nitroaromatics, and surface-associated reactive oxygen species are likely to play a more important role as exposure concentrations approach those found in the ambient air.

In an attempt to account for the effects of particles as well as particle-associated components of DE, a biologically based two-stage model with piecewise constant parameters was developed. This model assumes that both the carbon and the organic fraction have initiating properties and that the carbon fraction also has effects on the proliferation, conversion and progression steps of carcinogenesis. In addition, it accounts for the tumor initiating and promoting effects at high exposure concentrations. A description of this model has been published by Chen and Oberdörster (1996). (See Appendix B for details.) The resultant two-stage model is then used to predict tumor responses under various exposure scenarios and to investigate the impacts of different biological assumptions on risk projection.

The parameters for the two-stage model were statistically estimated initially, using tumor response data from animals exposed to high concentrations of DE and assuming particles continue to exert effects at low concentrations (i.e., nonthreshold for particle effects). When the two-stage biologically based dose-response model (BBDr) was compared with results derived with the LMS model, using malignant tumor data from the Mauderly et al. (1987) study, the results were nearly identical (Table 11-6). The maximum likelihood estimate (MLE) of cancer risk for the BBDr model at an exposure concentration of 1 µg/m$^3$ was calculated to be $8.2 \times 10^{-6}$

Table 11-6. Relative importance of particles and organics at different exposure concentrations assuming either threshold or nonthreshold effects of particles

| Excess risk in humans (MLE) | | | |
|---|---|---|---|
| Concentration | Threshold effect of particles | Nonthreshold effect of particles | Ratio [a] |
| 0.1 | $1.8 \times 10^{-7}$ | $8.1 \times 10^{-7}$ | 4.5 |
| 1.0 | $1.8 \times 10^{-6}$ | $8.2 \times 10^{-6}$ | 4.6 |
| 100 | $1.2 \times 10^{-2}$ | $5.6 \times 10^{-4}$ | 4.9 |
| 1,000 | $1.9 \times 10^{-3}$ | $2.6 \times 10^{-2}$ | 14.1 |

[a]Ratio =ratio of column 3 and column 2.

with an upper 95% confidence limit of $1.7 \times 10^{-5}$. The 95% upper confidence limits using the LMS model were also $1.7 \times 10^{-5}$ when rounded to two significant numbers.

Table 11-6 demonstrates that risk is much smaller if the assumption is made that particles do not exert effects below a certain concentration. As can be seen in Table 11-6, risk is decreased 4.6-fold at an exposure concentration of 1 µg/m$^3$ if a threshold is assumed for particles. Importantly, not only is risk decreased if a threshold is assumed for particle effects, but while particles play a major role in tumor induction at high exposure concentrations, organics and other components of DE play an increasingly dominant role as concentrations become lower.

An alternative approach that avoids the controversies related to lung overload with concomitant pathology involves calculation of an upper-bound risk based only on animals exposed to low diesel particle concentrations (e.g., below 0.5 mg/m$^3$). This modeling is designed to cap a theoretical upper-bound estimate on a nonobservable rat resonse to organics, while assuming organics and possibly free radicals are driving carcinogenicity at low exposure concentrations. As a general matter, the newly proposed Carcinogenicity Risk Assessment Guidelines suggest identifying a point of departure on the dose-response curve, perhaps an $ED_{10}$ or some other $ED_x$, and then extrapolating risk from that point of departure. The low-dose groups from the Mauderly et al. (1987) and Ishinishi et al. (1986) studies are the most suitable for this purpose. Both include exposure groups at less than 0.5 mg/m$^3$, and have the same duration follow-up (30 mo). By combining studies, statistical power is increased, resulting in a smaller upper-bound estimate of risk than by either study alone. The resultant upper-bound estimate is equal to $1.9 \times 10^{-5}$/µg/m$^3$.

While this approach has the advantage of avoiding controversies related to lung particle overload, it also has disadvantages. First, because lung tumors were not significantly increased at

the doses used, the estimated risk is considered unlikely to exceed the upper bound, but may be as low as zero. Second, the upper-bound estimate of risk is greater than the unit risk estimates derived using data from animals exposed to all concentrations of DE.

#### 11.3.2.3. *Dose-Response Estimation Using Benzo(a)pyrene as a Dosimeter*

Pike and Henderson (1981) found good agreement when relating the concentration of benzo(a)pyrene (B[a]P) to lung cancer risk in smokers, British gas workers, U.S. coke oven workers, and U.S. hot pitch workers and when comparing residents of rural and urban locations. They concluded that while B[a]P is unlikely to be the only carcinogen present and perhaps not even the most important one present in combustion emissions, nevertheless it serves as a reasonably accurate dosimeter. Based on an estimated cancer risk of 1/1,500 per ng/m$^3$ B[a]P and a reported B[a]P concentration of 3.9 ng/µg DPM in exhaust from a Volkswagen engine (Heinrich et al., 1995), a maximum likelihood estimate of cancer risk from lifetime exposure to 1 µg/m$^3$ can be calculated to be $3 \times 10^{-6}$. The 95% upper bound was not derived, but is estimated to be near $1 \times 10^{-5}$.

### 11.3.3. Strengths and Weaknesses of Differing Approaches for Quantitating Cancer Risk

#### 11.3.3.1. *Dose-Response Estimates Based on Human Epidemiologic Data*

A major advantage in the use of human data is the elimination of uncertainty due to possible differences in sensitivity to cancer induction by DE among species. As will be discussed later, there is some evidence that rats may respond differently from humans to DE. Second, epidemiology studies are based on occupational exposures, which generally occur at concentrations insufficient to result in lung particle overload. Thus, lung cancer in the human studies is likely to be induced by non-particle-overload mechanisms under either occupational or ambient exposure levels. Cancer induction in the rat bioassays, on the other hand, was observed only under particle-overload conditions, with concomitant pathology. Uncertainty in extrapolating from occupational studies is therefore decreased, not only because low-dose extrapolation occurs over a smaller range, but because mechanisms of cancer induction are less likely to vary within this range with accompanying changes in the dose-response curve.

There is considerable evidence for nonoverload mechanisms of cancer induction by products of fossil fuel combustion. Mumford et al. (1989) reported greatly increased lung cancer mortality in Chinese communes burning so-called smoky coal containing high concentrations of PAHs. Demonstration of the carcinogenicity of coke oven emissions in humans (Lloyd, 1971) also provided evidence for a role by organics because coke oven PM contains a high concentration of PAHs but lacks an insoluble carbon core. Increased levels of aromatic DNA adducts were reported in bus maintenance and terminal workers by Hemminki et al. (1994) and in

garage workers and mechanics exposed to diesel exhaust (Nielson and Autrup, 1994). Studies by Sagai et al. (1993) have indicated that DPM could produce superoxide and hydroxyl radicals in vitro, without any biologically activating systems. On the basis of these findings, they suggested that most DE toxicity in lungs is due to active oxygen radicals. In a more recent study, these investigators reported that instillation of only 0.1 mg of DPM into mouse lungs resulted in the production of 8-hydroxyguanosine in lung cell DNA. The critical lesion may thus be induced by oxygen free-radicals generated from DPM (Nagashima et al., 1995).

An uncertainty associated with most of the diesel epidemiology studies was the inability to completely eliminate all confounding factors, resulting in possible errors in estimating relative risk ratios. Small errors in adjustment for smoking, for example, can result in considerable error because smoking has a much larger effect on relative cancer risk than is likely for DE. The likelihood of significant confounding errors in the Garshick et al. (1987 and 1988) studies is decreased by the considerable effort exerted to eliminate or reduce such factors, especially smoking. Moreover, a meta-analysis by the California EPA (Cal-EPA, 1997) and more recently one by Bhatia et al. (1998) using a number of diesel epidemiology studies resulted in relative risk ratios quite similar to the one reported by Garshick et al. (1987). Although exposure levels are likely to have differed somewhat among studies, the agreement still suggests that a relative risk near 1.4 is reasonable.

The greatest uncertainty in estimating DE-induced cancer risk from epidemiology studies is determination of exposure levels. Even though DPM concentrations were often measured near the end of the studies, historic exposure data are generally lacking. Such information is critical, since there is indirect evidence, based on other pollutant measurements such as nitrogen oxides, that exposure levels have decreased considerably in recent years, especially in the railroad industry (Woskie et al., 1988b). In the only historic study found in which DPM were measured, Heino et al. (1978) reported average concentrations of 2 $mg/m^3$ in Finnish roundhouses. Woskie et al. (1988a), by contrast, reported a mean of 134 $\mu g/m^3$ for roundhouse workers near the end of the Garshick et al. (1987, 1988) studies. While the relationship between DPM concentrations in Finnish and U.S. railroad roundhouses during the 1970s is uncertain, it does point to the likelihood that exposure levels have decreased over time.

Despite the uncertainties discussed above, the epidemiology data-based risk assessments are useful for bounding risk. The control of confounding factors in the Garshick et al. (1987) study and the general agreement of relative risk estimates with those of other studies renders it unlikely that the true risk is greatly different from the reported one. The mean DPM concentration for all the occupational groups was somewhat less than 125 $\mu g/m^3$. Historic exposures were undoubtedly greater, but unlikely to approach 2 $mg/m^3$ because the cases in this study included not only roundhouse workers but other occupational groups as well, who were

likely exposed at lower concentrations. Based on the evidence available, there is considerable confidence that mean exposures are in the range of 125-500 μg/m$^3$.

#### 11.3.3.2. *Dose-Response Estimate-Based Laboratory Animal Bioassays*

Cancer risk assessment from exposure to DE, based on available animal bioassays, has a variety of strengths. The studies selected are adequately designed, eliminating confounding factors often present in epidemiology studies. Exposure duration and exposure levels were precisely controlled and monitored. The presence or absence of tumors were verified by pathological evaluation. Although animal-to-human extrapolation of dose is required, the development of dosimetry models has eliminated much of the uncertainty in this area.

Nevertheless, two important uncertainties remain: the adequacy of the rat as a model for evaluating human risk of cancer from exposure to DE and the shape of the dose-response curve. It is believed by some that the rat may be unique in its response to particulate matter, and therefore its use for assessing human lung cancer risk is questionable (Mauderly, 1994; Watson and Valberg, 1995). As noted in Chapter 7, the rat is the only species that has unequivocally been shown to develop lung cancer in response to DE exposure. On the other hand, only two other species, Syrian hamsters and mice, have been tested adequately. Although responses in the hamster have been negative, this species is known to be resistant to induction of lung cancer (Heinrich, 1994). Mice also fail to respond in standard bioassays of DE (Heinrich et al., 1995; Mauderly et al., 1996). Positive results, however, have been reported in mice exposed from birth or conception (Pepelko and Peirano, 1983; Takemoto et al., 1986), a condition likely to increase sensitivity. In the case of the study reported by Pepelko and Peirano, Sencar mice were used, a strain sensitive to chemical induction of skin tumors. Since the alveolar lining of the lung is also epithelial tissue, it is possible these mice are more sensitive to the organic constituents of DPM. Ichinose et al. (1997a,b) reported increased lung tumors in mice following intratracheal instillation of DPM. Positive results in mice may have therefore been due to use of a sensitive strain, early exposure to increased sensitivity, or very high local concentrations due to the instillation procedure.

It has also been argued that humans are resistant to particle-induced lung cancer; although coal miners develop pneumoconiosis, lung cancer seldom occurs. Rats, on the other hand, were reported to develop lung cancer in response to coal dust (Martin et al., 1977). This study, however, was poorly described, and the number of animals exposed was small (4/36 developed lung cancer). Moreover, exposure levels were very high and lung burdens were greater than those generally encountered in coal miners (Mauderly, 1994). Finally, although lung cancer has not been reported in most epidemiology studies of coal miners, Zhong and Dehong (1995)

reported that Chinese workers suffering coal miners' pneumoconiosis did have an increased risk of lung cancer.

The evidence for the uniqueness of the rat carcinogenic response to DE is therefore still equivocal. Nevertheless, the evidence to date does raise questions concerning the suitability of the rat for assessing human risk from exposure to DE. This concern is heightened by the fact that particle deposition patterns are different in the rat and human. Because of the absence of respiratory bronchioles in the rat, a greater fraction of inhaled particles deposit in the alveolar regions; in primates, deposition occurs to a large extent at the bifurcation of the small bronchi. Differing deposition patterns may result in different pathologic responses, as reported by Nikula et al. (1997) for rats and monkeys.

The other important uncertainty relating to use of rat bioassay data concerns low-dose extrapolation. Significant lung tumor increases in experimental animals have generally been obtained only at concentrations resulting in lung particle overload with concomitant pathological effects. A hypothesis first proposed by Vostal et al. (1986) is based on the belief that diesel particles themselves induce lung cancer, through a secondary effect. Driscoll (1995) suggested that the secondary effect was due to release of various inflammatory mediators by particle overloaded phagocytic cells. The resultant inflammatory response, with accompanying cell division, can increase the likelihood that any oxidant-induced or spontaneously occurring genetic damage becomes fixed in a dividing cell and is clonally expanded. In support of this hypothesis are the observations that lung cancer can be induced by inhalation of so-called "inert" particles, such as titanium dioxide (Lee et al., 1986) and coal dust (Martin et al., 1977), or by intratracheal instillation of activated carbon (Kawabata et al., 1986). Inhalation of carbon black that was virtually devoid of organics and is similar to the carbon core of diesel exhaust was also reported to induce lung cancer in rats (Heinrich, 1990; Heinrich et al., 1995; Nikula et al., 1995). Finally, Kawabata et al. (1993) induced lung tumors in rats through intratracheal instillation with DPM from which the organic components had been extracted.

Although considerable evidence for the particle-overload hypothesis exists, occupational exposures in which lung cancer induction has been reported in humans are generally considered insufficient to induce lung particle overload. This suggests that other mechanisms are also likely to be operating. Experimental evidence also provides support for low-dose mechanisms. Riebe-Imre et al. (1994) reported that carbon black is taken up by lung epithelial cells in vitro, inducing chromosomal damage and disruption of the cytoskeleton (lesions that closely resemble those in tumor cells) at concentrations that did not induce measurable toxicity. As noted in the previous section, diesel particles are capable of inducing toxicity and possible carcinogencity at low doses through production of oxygen free radicals. Finally, Dasenbrock et al. (1996) reported that extraction of the organic fraction from diesel particles decreased their carcinogenic potency, even

though specific particle surface area, a factor related to cancer potency, is increased following extraction.

In summary, the use of rat data for quantitating human lung cancer risk from exposure to DE results in considerable uncertainty. There is some doubt concerning the validity of the rat model for this purpose, although proof is still lacking. The greatest uncertainty concerns low-dose extrapolation of lung cancer risk. Information to date indicates that DE induces lung cancer by more than one means, including particle overload-induced pathology, carcinogenic organics present on the particle, and oxygen free radicals. While all these methods are likely to function at high doses, particle effects are likely to be absent or minimal at low exposures, resulting in a high degree of uncertainty regarding the shape of the dose-response curve.

Despite these uncertainties, rat data are still useful for comparison with other estimates, especially those derived using human epidemiology data. The greater risk estimates derived using epidemiology data, for example, suggest that even though rats are the only laboratory species in which lung cancer can be regularly induced by DE and other fine particulate matter, they may be less sensitive than humans to nonoverload mechanisms induced by DE at low concentrations. Unfortunately, limitations on animal numbers do not allow testing this possibility.

#### 11.3.3.3. *Dose-Response Estimates Based on the Biomarker Approach*

This approach provides reasonably good estimates of lung cancer risk in spite of the fact that B(*a*)P may constitute a relatively small fraction of the carcinogens present in combustion and pyrolysis products of coke ovens, hot pitch gas productions, etc. Risk estimates were also based on well-documented lung cancer rates in the occupationally exposed groups. On the other hand, while predictions are good for the pollutants tested, the particles present, unlike diesel particles, generally lack an insoluble carbon core. As noted below, adsorption to an insoluble particle core may influence risk estimates. Estimates of cancer risk will also vary based on B(*a*)P concentration on the particle. The variability in B(*a*)P concentration among different DE sources and its effect on cancer potency have not been evaluated.

#### 11.3.3.4. *Dose-Response Estimates Based on the Comparative Potency Approach*

In this method, the potency of diesel DPM extract is compared with other combustion or pyrolysis products, coke oven emissions, roofing tar, and cigarette smoke condensate for which epidemiology-based unit risk estimates have been developed. Comparisons are made using short-term tests such as skin painting, mutation, and mammalian cell transformation. The ratio of the potency of DPM extracts to each of these agents is then multiplied by their unit risk estimates to obtain the unit risk for DE. Because no new studies have been carried out since the early 1980s, the values considered are those published by Albert et al. (1983) and listed in Table 11-1.

This test is based on the belief that cancer induction at low doses is due to the organic fraction present on diesel particles. A major strength of this approach is avoidance of lung particle overload effects. The tests also have shown that the organic fraction of DE can induce cancer. A degree of uncertainty is due to the possibility that the presence of particles may alter the carcinogenicity of the organics. For example, particle-associated organics may deposit in different regions of the lungs than free organics do. Association with particles may increase residence time, thus increasing potency. On the other hand, a fraction of the organics may not be bioavailable because of tight adherence to the particle. Another uncertainty involves the assumption that cancer potency in short-term tests is the same as that for lung cancer induction. This is somewhat mitigated by the fact that the assessment is based to a large degree on skin painting studies. Skin and lung surfaces are both epithelial tissue, increasing the likelihood that responses will be similar. Nesnow et al. (1995) have, in fact, showed that for many polycyclic aromatic compounds relative cancer potency by skin painting and lung adenoma induction in strain A mice was quite similar.

## 11.4. SUMMARY AND RECOMMENDATIONS

Based on limited evidence from human epidemiologic studies and adequate evidence from animal experiments, DE is considered to be a probable human carcinogen. The evidence places DE in the upper range of agents classified as probable human carcinogens because of positive findings in both animal experiments and human data as well as the presence of known carcinogens in the mixture. The inability to completely eliminate confounding factors in most of the epidemiology studies, the lack of clearcut carcinogenic responses in more than one animal species, and the low concentration of organics precluded classifying DE as a known human carcinogen.

Cancer potency has been estimated using human epidemiology data, chronic animal cancer bioassays, a comparative potency approach, and use of B[a]P as a dosimeter. Each of these methods has important uncertainties that preclude recommendation of a point estimate of risk. Uncertainties relating to use of epidemiology studies include limited historical exposure data, inability to eliminate all possible confounding factors, and small increases in relative risk that can be more easily influenced by confounding factors. Uncertainties in use of chronic animal bioassays stem from questions regarding relative sensitivities of rats and humans to DE and shape of the low-dose response curve. In the comparative potency method, the assumption that relative potency in short-term tests accurately reflects relative cancer potency of different combustion emissions requires confirmation. While use of B[a]P as a dosimeter has been shown to reflect the potency of several combustion emissions reasonably well, DE differs from these emissions because of the presence of an insoluble carbon core.

Despite these uncertainties, they are considered, collectively, adequate to place reasonable bounds on risk. An upper-bound lung cancer risk from lifetime exposure to DE at a particulate matter concentration of 1 μg/m$^3$ of $2 \times 10^{-3}$, based on the estimate derived by McClellan et al. (1989), using the case-control study of Garshick et al. (1987) and assuming a mean exposure concentration of 125 μg/m$^3$ is recommended. It is considered to be a reasonable upper bound because relative risk ratios were either less or only slightly greater in other epidemiology studies with DE. Furthermore, exposures were unlikely average less than 125 μg/m$^3$ particulate matter assumed. A lower bound of $1 \times 10^{-5}$/(μg/m$^3$) is recommended. MLEs slightly less than this value were obtained from animal bioassay data by Chen and Oberdörster (1996) using a biologically based dose-response model and assuming nonthreshold effects for particles and by estimates based on use of B[a]P as a dosimeter according to the Pike and Henderson (1981) report and B[a]P content of DE reported by Heinrich et al. (1995). Most comparative potency estimates were only slightly greater than $1 \times 10^{-5}$/μg/m$^3$. The lower bound is considered to be reasonable for at least two reasons. First, the latter two approaches are based on effects of the organic constituents. Second, while they are likely to be the primary cause of lung cancer at low doses, other factors such as particle effects and reactive oxygen species may play some role. Thus, risk is unlikely to be significantly lower. This conclusion is supported by animal data-based calculations of Chen and Oberdörster (1996) using a biologically based, low-dose extrapolation model.

Finally, the 95% lower-bound estimate of risk, assuming exposures of 500 μg/m$^3$, is $5 \times 10^{-5}$/μg/m$^3$. The range of human data-based risk estimates therefore encompasses a large portion of the recommended bounds of 1 to $200 \times 10^{-5}$/μg/m$^3$.

## 11.5. REFERENCES


Ahlman, K; Koskela, RS; Kuilla, P; Koponen, M; Annanmäki, M. (1991) Mortality among sulfide ore miners. Am J Ind Med 19:603-617.

Albert, RE; Chen, C. (1986) U.S. EPA diesel studies on inhalation hazards. In: Ishinishi, N; Koizumi, A; McClellan, R; Stöber, W, eds. Carcinogenicity and mutagenicity of diesel engine exhaust. Amsterdam: Elsevier, pp. 411-419.

Albert, RE; Lewtas, J; Nesnow, S; Thorslund, TW; Anderson, E. (1983) Comparative potency method for cancer risk assessment: application to diesel particulate emissions. Risk Anal 3:101-117.

Benhamou, S; Benhamou, E; Flamant, R. (1988) Occupational risk factors of lung cancer in a French case-control study. Br J Ind Med 45:231-233.

Bhatia, R; Lopipero, P; Smith, AH. (1998) Diesel exhaust exposure and lung cancer. Epidemiology 9:84-91.

Boffetta, P; Stellman, SD. (1988) Association between diesel exhaust exposure and multiple myeloma: an example of confounding. Prev Med 17:236-237.

Bohning, DE; Atkins, HL; Cohn, SH. (1982) Long-term particle clearance in man: normal and impaired. Ann Occup Hyg 26:259-271.

Brightwell, J; Fouillet, X; Cassano-Zoppi, AL; Bernstein, D; Crawley, F; Duchosal, F; Gatz, R; Perczel, S; Pfeifer, H. (1989) Tumours of the respiratory tract in rats and hamsters following chronic inhalation of engine exhaust emissions. J Appl Toxicol 9:23-31.

Burns, PB; Swanson, GM. (1991) The occupational cancer incidence surveillance study (OCISS): risk of lung cancer by usual occupation and industry in the Detroit metropolitan area. Am J Ind Med 19:655-671.

Chan, TL; Lee, PS; Hering, WE. (1981) Deposition and clearance of inhaled diesel exhaust particles on the respiratory tract of Fischer 344 rats. J Appl Toxicol 1:77-82.

Chan, TL; Lee, PS; Hering, WE. (1984) Pulmonary retention of inhaled diesel particles after prolonged exposure to diesel exhaust. Fundam Appl Toxicol 4:624-631.

Chen, CW; Oberdörster, G. (1996) Selection of models for assessing dose-response relationships for particle-induced lung cancer. Inhal Toxicol 8(suppl):259-278.

Crump, KS; Lambert, T; Chen, C. (1991) Assessment of risk from exposure to diesel engine emissions. Clement International Corporation. Prepared for U.S. EPA under contract no. 68-02-4601; 56 pp.

Cuddihy, RG; McClellan, RO. (1983) Evaluating lung cancer risks from exposures to diesel engine exhaust. Risk Anal 3:119-124.

Cuddihy, RG; Griffith, WC; Clark, CR; McClellan, RO. (1981) Potential health and environmental effects of light-duty diesel vehicles. Report No. LMF-89. Albuquerque, NM: Inhalation Toxicology Research Institute.

Cuddihy, RG; Griffith, WC; McClellan, RO. (1984) Health risks from light-duty diesel vehicles. Environ Sci Technol 18:14-21a.

Damber, LA; Larsson, LG. (1987) Occupation and male lung cancer: a case-control study in northern Sweden. Br J Ind Med 44:446-453.

Dasenbrock, C; Peters, L; Creutzenberg, O; Heinrich, U. (1996) The carcinogenic potency of carbon particles with and without PAH after repeated intratracheal administration in the rat. Toxicol Lett 88:15-21.

Driscoll, K. (1995) Role of inflammation in the development of rat lung tumors in response to chronic particle exposure. Inhal Toxicol 8(Suppl):139-153.

Edling, O; Anjou, CG; Axelson, O; Kling, H. (1987) Mortality among personnel exposed to diesel exhaust. Int Arch Occup Environ Health 59:559-565.

Emmelin, A; Nyström, L; Wall, S. (1993) Diesel exhaust exposure and smoking: a case-referent study of lung cancer among Swedish dock workers. Epidemiology 3:237-244.

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

Garshick, E; Schenker, MB; Munoz, A; Segal, M; Smith, TJ; Woskie, SR; Hammond, SK; Speizer, FE . (1988) A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. Am Rev Respir Dis 137:820-825.

Griffis, LC; Wolff, RK; Henderson, RF; Griffith, WC; Mokler, BV; McClellan, RO. (1983) Clearance of diesel soot particles from rat lung after subchronic diesel exhaust exposure. Fundam Appl Toxicol 3:99-103.

Grimmer, G; Brune, H; Deutsch-Wenzel, R; Dettbarn, G; Jacobs, J; Navjack, KW; Mohr, U; Ernst, H. (1987) Contribution of polycyclic aromatic hydrocarbons and nitro-derivatives to the carcinogenic impact of diesel exhaust condensate evaluated by implantation into the lungs of rats. Cancer Lett 37:173-180.

Gustavsson, P; Plato, N; Lidström, EB; Hogstedt, C. (1990) Lung cancer and exposure to diesel exhaust among bus garage workers. Scand J Work Environ Health 16:348-354.

Hall, NE; Wynder, E. (1984) Diesel exhaust exposure and lung cancer. Environ Res 34:77-86.

Harris, JE. (1983) Diesel emissions and lung cancer. Risk Anal 3:83-100.

Hattis, D; Silver, K. (1994) Use of mechanistic data in occupational health risk assessment: The example of diesel particulates. In: Smith, MC; Christiani, DC; Kelsey, KT eds. Chemical risk assessment and occupational health. Auburn House: Westport, CT, pp. 167-178.

Hayes, RB; Thomas T; Silverman, DT; Vineis, P; Blot, WJ; Mason, TJ; Pickle, LW; Correa, P; Fontham, ETH; Schoenberg, JB. (1989) Lung cancer in motor exhaust occupations. Am J Ind Med 16:685-695.

Heinrich, U. (1990) Carcinogenicity of carbon black “Printex 90" in female Wistar rats. Presented at: U.S. EPA Diesel Emissions Peer Review Workshop; July 18-19; Chapel Hill, NC.

Heinrich, U. (1994) Carcinogenic effects of solid particles. In: Mohr, U; Dungworth, DL; Mauderly, JL; Oberdorster, G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI, pp. 57-73.

Heinrich, U; Muhle, H; Takenaka, S; Ernst, H; Fohst, R; Mohr, U; Pott, F; Stöber, W. (1986a) Chronic effects on the respiratory tract of hamsters, mice and rats after long-term inhalation of high concentration of filtered and unfiltered diesel engine emissions. J Appl Physiol 6:383-395.

Heinrich, U; Pott, F; Rittinghausen, S. (1986b) Comparison of chronic inhalation effects in rodents after long-term exposure to either coal oven flue gas mixed with pyrolized pitch or diesel engine exhaust. In: Ishinishi, N; Koizumi, A; McClellan, RO; Stöber, W, eds. Carcinogenic and mutagenic effects of diesel engine exhaust. Amsterdam: Elsevier, pp. 441-457.

Heinrich, U; Fuhst, R; Rittinghausen, S; Creutzenberg, O; Bellmann, B; Koch, W; Levsen, K. (1995) Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. Inhal Toxicol 7:553-556.

Hemminki, K; Söderling, J; Ericson, P; Norbeck, HE; Segerbäck, D. (1994) DNA adducts among personnel servicing and loading diesel vehicles. Carcinogenesis 15:767-769.

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

Huisingh, J; Bradow, R; Jungers, R; Claxton, L; Zweidinger, R; Tejada, S; Bumgarner, J; Duffield, F; Waters, M; Simmon, V; Hare, C; Rodriguez, C; Snow, L. (1978) Application of bioassay to the characterization of diesel particle emissions. In: Waters, MD; Nesnow, S; Huisingh, JL; Sandhu, SS; Claxton, L, eds. Application of short-term bioassays in the fractionation and analysis of complex environmental mixtures. New York: Plenum Press, pp. 383-418.

Ichinose, T; Yajima, Y; Nagashima, M; Takenoshita, S; Nagamachi, Y; Sagai, M. (1997a) Lung carcinogenesis and formation of 8-hydroxyguanosine in mice by diesel exhaust particles. Carcinogenesis 18:185-192.

Ichinose, T; Yamanushi, T; Seto, H; Sagai, M. (1997b) Oxygen radicals in lung carcinogenesis accompanying phagocytosis of diesel exhaust particles. Int J Oncol 11:571-575.

International Agency for Research on Cancer. (1989) IARC monographs on the evaluation of carcinogenic risks to humans, vol. 46. Diesel and gasoline engine exhausts and some nitroarenes. Lyon, France: IARC, pp. 41-185.

Ishinishi, N; Kuwabara, N; Nagase, S; Suzuki, T; Ishiwata, S; Kohno, T. (1986) Long-term inhalation studies on effects of exhaust from heavy and light duty diesel engines on F344 rats. In: Ishinishi, N; Koizumi, A; McClellan, RO; Stöber, W, eds. Carcinogenic and mutagenic effects of diesel engine exhaust. Amsterdam: Elsevier, pp. 329-348.

Iwai, K; Udagawa, T; Yamaguchi, M; Yamada, H. (1986) Long-term inhalation studies of diesel exhaust on F344 SPF rats. Incidence of lung cancer and lymphoma. In: Ishinishi, N; Koizumi, A; McClellan, RO; Stöber, W, eds. Carcinogenic and mutagenic effects of diesel engine exhaust. Amsterdam: Elsevier, pp. 349-360.

Karagianes, RF; Palmer, RF; Busch, RH. (1981) Effects of inhaled diesel emissions and coal dust in rats. Am Ind Hyg Assoc J 42:382-391.

Kawabata, Y; Iwai, K; Udagawa, T; Tukagoshi, K; Higuchi, K. (1986) Effects of diesel soot on unscheduled DNA synthesis of tracheal epithelium and lung tumor formation. In: Ishinishi, N; Koizumi, A; McClellan, R; Stöber, W, eds. Carcinogenic and mutagenic effects of diesel engine exhaust. Amsterdam: Elsevier, pp. 213-222.

Kawabata, Y; Udagawa, T; Iwai, K. (1993) One year exposure to diesel engine exhaust causes lung tumors. Toxic and carcinogenic effects of solid particles in the respiratory tract. Fourth International Inhalation Symposi, Hannover, 61 pp.

Kotin, P; Falk, H; Thomas, M. (1955) Aromatic hydrocarbons. III. Presence in the particulate phase of diesel engine exhausts and the carcinogenicity of exhaust extracts. Arch Ind Health 11:113-120.

Kuschner, M. (1984) The causes of cancer. Am Rev Respir Dis 98:573-590.

Lee, KP; Henry, NW, III; Trochimowicz, HJ; Reinhardt, CF. (1986) Pulmonary response to impaired lung clearance following excessive $TiO_2$ dust deposition. Environ Res 41:144-167.

Lerchen, ML; Wiggins, CL; Samet, JM. (1987) Lung cancer and occupation in New Mexico. J Natl Cancer Inst 79:639-645.

Lloyd, JW. (1971) Long-term mortality study of steelworkers V. Respiratory cancer in coke plant workers. J Occcup Med 13:53-68.

Martin, JC; Daniel, H; LeBouffant, L. (1977) Short- and long-term experimental study of the toxicity of coal mine dust and some of its components. In: Walton, WH, ed. Inhaled particles IV. Vol 1. Oxford, Pergamon: pp. 361-370.

Mauderly, JL. (1994) Contribution of inhalation bioassays to the assessment of human health risks from solid airborne particles. In: Mohr, U; Dungworth, DL; Mauderly, JL; Oberdörster, G, eds. Carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI, pp. 355-365.

Mauderly, JL; Jones, RK; Griffith, WC; Henderson, RF; McClellan, RO. (1987) Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. Fundam Appl Toxicol 9:208-221.

Mauderly, JL; Banas, DA; Griffith, WC; Hahn, FF; Henderson, RF; McClellan, RO. (1996) Diesel exhaust is not a pulmonary carcinogen under conditions carcinogenic to F344 rats. Fundam Appl Toxicol 30:233-242.

McClellan, RO. (1986) Health effects of diesel exhaust: a case study in risk assessment. Am Ind Hyg Assoc J 47:1-13.

McClellan, RO; Cuddihy, RG; Griffith, WC; Mauderly, JL. (1989) Integrating diverse data sets to assess the risks of airborne pollutants. In: Mohr, U, ed. Assessment of inhalation hazards. New York: Springer Verlag, pp. 3-22.

Mumford, JL; Chapman, RS; Harris, DB. (1989) Indoor air exposure to coal and wood combustion emissions associated with a high lung cancer rate in Xuan Wei, China. Environ Int 15:315-320.

Nagashima, M; Kasai, H; Yokata, J; Nagamachi, Y; Ichinose, T; Sagai, M. (1995) Formation of an oxidative DNA damage, 8-hydroxyguanosine, in mouse lung DNA after intratracheal instillation of diesel exhaust particles and effects of high dietary fat and beta carotene on this process. Carcinogenesis 6:1441-1445.

Nesnow, S; Evans, C; Stead, A; Creason, J; Slaga, TJ; Triplett, LL. (1982) Skin carcinogenesis studies of emission extracts. In: Lewtas, J, ed. Toxicological effects of emissions from diesel engines. Amsterdam: Elsevier, pp. 295-320.

Nesnow, S; Ross, JA; Stoner, GD; Mass, MJ. (1995) Mechanistic linkage between DNA adducts, mutations in oncogenes and tumorigenesis of carcinogenic environmental polycyclic aromatic hydrocarbons in strain A/J mice. Toxicology 105:403-413.

Nielsen, PS; Autrup, H. (1994) Diesel exhaust-related DNA adducts in garage workers. Clin Chem 40:1456-1458.

Nikula, KJ; Snipes, MB; Barr, EB; Griffith, WC; Henderson, RF; Mauderly, JL. (1995) Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. Fundam Appl Toxicol 25:80-94.

Nikula, KJ; Avila, KJ; Griffith, WC; Mauderly, JL. (1997) Lung tissue responses and sites of particle retention differ between rats and Cynomolgous monkeys exposed chronically to diesel exhaust and coal dust. Fundam Appl Toxicol 37:37-53.

Pepelko, WE; Chen, C. (1993) Quantitative assessment of cancer risk from exposure to diesel engine emissions. Reg Toxicol Pharmacol 17:52-65.

Pepelko, WE; Peirano, WB. (1983) Health effects of exposure to diesel engine emissions. J Am Coll Toxicol 2:253-306.

Pike, ME; Henderson, BE. (1981) Epidemiology of polycyclic aromatic hydrocarbons: quantifying the cancer risk from cigarette smoking and air pollution. In: Gellbond, HV; Tso, POP, eds. Polycyclic hydrocarbons and cancer. New York: Academic Press, pp. 317-334.

Pott, F; Heinrich, U. (1987) Dieselmotorabgas und Lungenk auf die Gefährdung des Menschen. In: Umwelthygiene, vol. 19. Med. Institut. f. Umwelthygiene, Annual Report 1986/87. Dusseldorf, F.R.G., pp. 130-167.

Pott, F; Roller, M. (1994) Relevance of nonphysiologic exposure routes for carcinogenicity studies of solid particles. In: Mohr, U; Dungworth, DL; Mauderly, JL; Oberdörster, G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI, pp. 109-125.

Raffle, PAB. (1957) The health of the worker. Br J Ind Med 14:73-80.

Riebe-Imre, M; Auferheide, M; Gärtner-Hübsch, S; Peraud, A; Straub, M. (1994) Cytotoxic and genotoxic effects of insoluble particles in vitro. In: Mohr, U; Dungworth, DL; Mauderly, JL; Oberdörster, G, eds. Toxic and carcinogenic effects of solid particles in the respiratory tract. Washington, DC: ILSI, pp. 519-523.

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

Sagai, M; Saito, H; Ichinose, T; Kodama, M; Mori, Y. (1993) Biological effects of diesel exhaust particles. I. In vitro production of superoxide and in vivo toxicity in mouse. Free Radic Biol Med 14:37-47.

Smith, TJ. (1992) Occupational exposure and dose over time: limitations of cumulative exposure. Am J Ind Med 21:35-51.

Smith, RA; Stayner, L. (1990) An exploratory assessment of the risk of lung cancer associated with exposure to diesel exhaust based on a study with rats. Final report. Division of Standards Development and Technology Transfer; Cincinnati, OH: NIOSH.

Steenland NK; Silverman, DT; Hornung, RW. (1990) Case-control study of lung cancer and truck driving in the Teamsters Union. Am J Public Health 80:670-674.

Stöber, W. (1986) Experimental induction of tumors in hamsters, mice and rats after long-term inhalation of filtered and unfiltered diesel engine exhaust. In: Ishinishi, N; Koizumi, A; McClellan, RO; Stöber, W, eds. Carcinogenic and mutagenic effects of diesel engine exhaust. Amsterdam: Elsevier, pp. 421-439.

Takemoto, K; Yoshimura, H; Katayama, H. (1986) Effects of chronic inhalation exposure to diesel exhaust on the development of lung tumors in di-isopropyl-nitropyrene-treated F344 rats and newborn C57Bl and ICR mice. In: Ishinishi, N; Koizumi, A; McClellan, RO; Stöber, W, eds. Carcinogenic and mutagenic effects of diesel engine exhaust. Amsterdam: Elsevier, pp. 311-327.

U.S. Environmental Protection Agency. (1986, Sept. 24) Guidelines for carcinogenic risk assessment. Federal Register 51(185):33992-43003.

U.S. Environmental Protection Agency. (1996, April 23) Proposed guidelines for carcinogen risk assessment. Federal Register 61(79):17960-18011.

Waller, RE. (1981) Trends in lung cancer in London in relation to exposure to diesel fumes. Environ Int 5:479-483.

Watson, AY; Valberg, PA. (1996) Particle-induced lung tumors in rats: evidence for species specificity in mechanisms. Inhal Toxicol 8(Suppl):227-257.

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

Wolff, RK; Griffis, LC; Hobbs, CH; McClellan, RO. (1982) Deposition and retention of 0.1 µm $^{67}Ga_2O^3$ aggregate aerosols in rats following whole body exposures. Fundam Appl Toxicol 2:195-200.

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

Woskie, SR; Smith, TJ; Hammond, SK; Schenker, MB; Garshick, E; Speizer, FE. (1988a) Estimation of the diesel exhaust exposures of railroad workers: I. Current exposures. Am J Ind Med 13:381-394.

Woskie, SR; Smith, TJ; Hammond, SK; Schenker, MB; Garshick, E; Speizer, FE. (1988b) Estimation of the diesel exhaust exposures of railroad workers: II. National and historical exposures. Am J Ind Med 13: 395-404.

Yu, CP; Yoon, KJ; Chen, YK. (1991) Retention modeling of diesel exhaust particles in rats and humans. J Aerosol Med 4:79-115.

Zhong, Y; Dehong, L. (1995) Potential years of lifework and tenure lost when silicosis is compared with pneumoconiosis. Scand J Work Environ Health 21(Suppl 2):91-94.