

7. CARCINOGENICITY OF DIESEL EXHAUST

7.1. INTRODUCTION

Initial health hazard concerns regarding the potential carcinogenicity of diesel exhaust were based on the reported induction of skin papillomas by diesel particle extracts (Kotin et al., 1955), evidence for mutagenicity of extracts (Huisinigh et al., 1978), evidence that components of diesel extract act as weak tumor promoters (Zamora et al., 1983), and the knowledge that diesel particles and their associated organics are respirable. During the 1980s, both human epidemiologic studies and long-term animal cancer bioassays were initiated. In 1981, Waller published the first epidemiologic investigation, a retrospective mortality study of London transport workers. Since then a large number of cohort and case-control studies have been carried out with railroad workers, dockworkers, truck drivers, construction workers, miners, and bus garage employees. During 1986 and 1987, several chronic animal cancer bioassays were published. These studies and numerous laboratory investigations carried out since then have been directed toward assessing the carcinogenic potential of whole exhaust, evaluating the importance of various exhaust components in the induction of cancer, and understanding the mode of action and implications of deposition, retention, and clearance of diesel exhaust particles.

7.1.1. Overview

This chapter evaluates the carcinogenic potential of diesel exhaust in both humans (Section 7.2) and animals (Section 7.3), determines likely mode/s of action (Section 7.4), and provides an overall weight of evidence (Section 7.5) for carcinogenicity in humans. This assessment focuses on diesel exhaust, although diesel particles comprise a portion of ambient particulate matter (PM). In 1998, diesel emissions constituted 72% (521,000 tons) of mobile sources PM₁₀ and 18% of total PM₁₀ in ambient air (excluding natural and miscellaneous emissions). Diesel emissions made up 77% (473,000 tons) of mobile source PM_{2.5} emissions, and 23% of total PM_{2.5} in ambient air (excluding natural and miscellaneous emissions) in 1998. Ambient PM, notably PM₁₀, has been known for many years to potentially affect human health; these effects have been evaluated in a separate document (U.S. EPA, 1996a). This document is also undergoing revision.

7.1.2. Ambient PM-Lung Cancer Relationships

A quick overview of the data regarding exposure to ambient PM and lung cancer is provided as background information. With DE being part of ambient PM, the question of what is

1 seen in the ambient PM data is of interest, since insight about the ambient PM exposure lung
2 cancer relationships may contribute to evaluation of DE-specific epidemiologic data.

3 Chapter 5 noted that (a) DPM, consisting mostly of fine particles (<1.0 µm diameter),
4 represents a toxicologically important component of typical ambient fine particle mixes, and (b)
5 health risk estimates for ambient fine particles would, logically, likely represent an upper limit for
6 estimates of the health risks associated with exposures to DPM as a subset of ambient fine PM.
7 Chapter 5 (and Appendix C) went on to summarize key epidemiologic findings from studies of
8 ambient PM noncancer effects, which provided important inputs to the setting, in 1997, of new
9 ambient fine particle standards (PM_{2.5} NAAQS) to protect against mortality and morbidity effects
10 of airborne fine particles. Several large-scale prospective studies (Harvard Six City Study;
11 American Cancer Society or ACS Study; Adventist Health Study of Smog or AHSMOG) were
12 highlighted in Chapter 5 and Appendix C as providing important evidence regarding associations
13 between chronic exposures to ambient fine particles and increased risks of noncancer
14 mortality/morbidity effects (e.g., cardiorespiratory-related deaths or hospital admissions). The
15 same studies also evaluated relationships between chronic PM exposures and lung cancer
16 mortality and/or incidence, evaluations of much pertinence here to consideration of ambient PM
17 cancer risks as possibly representing upper limits for DPM-related cancer risks.

18 The Harvard Six City Study (Dockery et al., 1993), of approximately 8,000 adults in six
19 cities comprising a transect across the northcentral and northeastern United States, found
20 markedly increased relative risks (RR) of lung cancer mortality for current (RR = 8.00, 95% CL
21 2.97-21.6) and former (RR = 2.54, CL 0.90-7.18) smokers. Also, elevated but statistically
22 nonsignificant associations of lung cancer mortality risks (RR = 1.37, CL 0.81-2.31) were found
23 by the Six City Study analyses (which included data for both males and females) to be related to
24 ambient fine particles indexed by a range of annual mean PM_{2.5} concentrations from the least to
25 the most polluted of the six cities.

26 The ACS Study (Pope et al., 1995), of 550,000 adults in 151 cities across all U.S.
27 geographic regions, also found markedly elevated lung cancer risks for current smokers (RR =
28 9.73, CL 5.96-15.9) and somewhat elevated and statistically significant lung cancer risk (RR =
29 1.36, CL 1.11-1.66) associations with a range (19.9 mg/m³) of annual average sulfate (SO₄)
30 concentrations as one index of chronic exposures to ambient fine particles, in combined analyses
31 of data for both males and females. However, in further analyses of subgroups broken out by sex
32 and smoking status (and thus having smaller sample sizes in each than for the above overall
33 combined analyses), only the lung cancer mortality risks for male “ever-smokers” (RR = 1.44, CL
34 1.14-1.83) were statistically significant in relation to sulfate concentrations as the fine particle
35 indicator in the 151 cities. Note that the analogous adjusted risk ratios (and 95% CL) for the
36 most polluted versus least polluted cities in terms of sulfate levels were statistically

1 nonsignificant for male “never-smokers” (RR = 1.36, CL 0.40 - 4.66), for female “ever-smokers”
2 (RR = 1.10, CL 0.72-1.68) and female “never-smokers” (RR = 1.61; CL 0.66 -3.92). Also, lung
3 cancer mortality risks (RR = 1.03; CL 0.80-1.33) were not statistically significantly associated
4 with ambient PM_{2.5} concentrations (across a range of 24.5 µg/m³ from least to most polluted of a
5 subset of 50 of the 151 cities) in overall combined analyses of data for both males and females.
6 Nor were the relative risk ratios statistically significant for smaller sample size subgroups broken
7 out by sex and smoking status in relation to PM_{2.5} concentrations, as a second index of ambient
8 airborne fine PM. Hence, the ACS Study provides only very limited evidence hinting at a possible
9 lung cancer mortality association with one indicator (sulfates) of ambient fine particles, but not
10 with another such index (PM_{2.5}).

11 In the first of an ongoing series of reports on AHSMOG data analyses, Abbey et al.
12 (1991) described the results of initial analyses related to the AHSMOG evaluation of air pollution
13 effects on the health of 6,338 nonsmoking, long-term California adult residents. Of a variety of
14 health endpoints evaluated, only respiratory symptoms and female cancers (any site) but not
15 respiratory cancer for either sex, were reported by Abbey et al. (1991) to be associated with
16 concentrations of total suspended particulate (TSP) matter (which includes not only fine particles
17 indexed by PM_{2.5} but also larger coarse mode particles ranging up to 25-50 µm). Later follow-up
18 analyses (Abbey et al., 1995) considered chronic exposures to PM₁₀ (estimated from TSP data),
19 PM_{2.5} (estimated from visibility data), and SO₄, but found no statistically significant associations
20 with nonexternal mortality. Subsequent AHSMOG analyses reported out by Abbey et al. (1999)
21 and Beesan et al. (1998) do, however, hint at possible associations of increased risk of lung
22 cancer mortality and/or incidence in males with ambient PM exposures. More specifically,
23 chronic exposures to ambient PM₁₀ (which includes both fine particle and <2.5 µm and coarse
24 particles 2.5 to 10 µm in size) were reported to be significantly associated with markedly
25 increased lung cancer mortality risks in the nonsmoking AHSMOG males (RR = 23.39, CL 2.55-
26 60.10), but not for the females (RR = 9.8; CL 0.34-9.52). Male lung cancer mortality was also
27 reported to be significantly associated with numbers of days per year that PM₁₀ exceeded 100
28 mg/m³ (RR = 1.055, CL 0.66-1.69). Other analyses of AHSMOG data were reported by Beeson
29 et al. (1998) also showing statistically significant associations of increased lung cancer incidence
30 (especially PM₁₀ > 100 µg/m³) for males, but not for females.

31 In summary, the three key prospective cohort studies (discussed in more detail in
32 Appendix C) provide an equivocal array of results with regard to possible associations between
33 chronic exposures to ambient PM and lung cancer mortality and/or incidence. Only the ACS
34 Study found a statistically significant association of increased risk of lung cancer with one
35 indicator of ambient fine particles (sulfates), but not with another such indicator (PM_{2.5})—the latter

1 being consistent with Harvard Six City Study results for PM_{2.5}. Also, the AHSMOG results hint
2 at possible increased lung cancer risks in males, but not females, in relation to PM₁₀ levels.
3 Overall, then, these studies are not conclusive and appear, at best, only to provide some indication
4 of possible associations between increased lung cancer risk and chronic ambient fine PM
5 exposures.

7 7.2. EPIDEMIOLOGIC STUDIES OF THE CARCINOGENICITY OF EXPOSURE TO 8 DIESEL EXHAUST

9 An increased risk from malignancies of the lung, bladder, and lymphatic tissue has been
10 reported in populations potentially exposed to diesel emissions. Isolated authors have reported
11 other malignancies, including testicular cancer (Garland et al., 1988), gastrointestinal cancer
12 (Balarajan and McDowall, 1988; Guberan et al., 1992), and prostate cancer (Aronsen et al.,
13 1996). A detailed review of lung cancer studies is presented in this section. A detailed review of
14 other health effect studies is not presented because findings are equivocal.

15 Excess risk of bladder cancer has been reported in several studies (Howe et al., 1980;
16 Wynder et al., 1985; Hoar and Hoover et al., 1985; Silverman et al., 1983; Vineis and Magnani
17 1985; Silverman et al., 1986; Jensen et al., 1987; Steenland et al., 1987; Isocovich et al., 1987;
18 Risch et al., 1988; Iyer et al., 1990; Steineck et al., 1990; Cordier et al., 1993; Notani et al.,
19 1993). Very few studies found significant excesses after adjustment for cigarette smoking. Most
20 studies failed to show any association between exposure to diesel exhaust and occurrence of
21 bladder cancer. Some authors have reported excess mortality from lymphohematopoietic system
22 cancers in people potentially exposed to diesel fumes. Rushton and Alderson (1983) and Howe
23 and Lindsay (1983) found increased mortality from lymphatic neoplasms. Balarajan and
24 McDowall (1983) found raised mortality for malignant lymphomas. Flodin et al. (1987) observed
25 increased risk for multiple myeloma, and Bender et al. (1989) reported excess mortality from
26 leukemia. Because evidence for bladder cancer and lymphohematopoietic cancer was found to be
27 equivocal, detailed reviews of these studies are not presented here.

28 In this section, various mortality and morbidity studies of lung cancer from potential
29 exposure to diesel engine emissions are reviewed. Although an attempt was made to cover all the
30 relevant studies, a number of studies are not included for several reasons. The change from steam
31 to diesel engines in locomotives began after World War II. By 1946 about 10% of the
32 locomotives in service were diesel, by 1952 55% were diesel, and dieselization was about 95%
33 complete by 1959 (Garshick et al., 1988). Therefore, exposure to diesel exhaust was less
34 common, and the follow-up period for studies conducted prior to 1960 (Raffle, 1957; Commins et
35 al., 1957; Kaplan, 1959) was not long enough to cover the long latency period of lung cancer.

1 The usefulness of these studies in evaluating the carcinogenicity of diesel exhaust is greatly
2 reduced; thus, they are not considered here.

3 On the other hand, the trucking industry changed to diesel trucks by the 1960s. In the
4 1960s sales of diesel-powered Class 8 trucks (long-haul trucks) were 48% of the market, and by
5 the 1970s sales had risen to 85%. Thus, studies conducted among truck drivers prior to the
6 1970s may reflect exposures to gasoline exhaust as well as diesel exhaust. Hence, studies with
7 ambiguous exposures or studies that examined several occupational risk factors were excluded
8 because they would have contributed little to the evaluation of the carcinogenicity of diesel
9 exhaust (Waxweiler et al., 1973; Williams et al., 1977; Ahlberg et al., 1981; Stern et al., 1981;
10 Buiatti et al., 1985; Gustafsson et al., 1986; Siemiatycki et al., 1988). A study by Coggon et al.
11 (1984) was excluded because occupational information abstracted from death certificates had not
12 been validated; this would have resulted in limited information.

13 Several types of studies of the health effects of exposure to diesel engine emissions are
14 reviewed in this chapter, such as cohort studies, case-control studies, and studies that conducted
15 meta-analysis. In the cohort studies, cohorts of heavy construction equipment operators, railroad
16 and locomotive workers, bus garage employees, and miners were studied retrospectively to
17 determine increased mortality and morbidity resulting from exposures to varying levels of diesel
18 emissions in the workplace. The evaluation of each study presents the study population,
19 methodology used for the study, i.e., data collection and verification, analysis, results, and a
20 critique of the study. There are some methodologic limitations that are common to studies with
21 similar design. The total evidence, including limitations, is discussed at the end of the chapter in
22 the summary and discussion section.

23 24 **7.2.1. Cohort Studies**

25 **7.2.1.1. *Waller (1981): Trends in Lung Cancer in London in Relation to Exposure to Diesel*** 26 ***Fumes***

27 A retrospective mortality study of a cohort of London transport workers was conducted
28 to determine if there was an excess of deaths from lung cancer that could be attributed to diesel
29 exhaust exposure. From nearly 20,000 male employees in the early years, those aged 45 to 64
30 were followed for the 25-year period between 1950 and 1974 (the actual number of employees is
31 not given in the paper), constituting a total of 420,700 man-years at risk. These workers were
32 distributed among five job categories: drivers, garage engineers, conductors, motormen or
33 guards, and engineers (works). Lung cancer were ascertained from death certificates of
34 individuals who died while still employed, or if retired, following diagnosis. Expected death rates
35 were calculated by applying greater London death rates to the population at risk within each job
36 category. Data were calculated in 5-year periods and 5-year age ranges, and the results were

1 combined to obtain the total expected deaths in the required age range for the calendar period. A
2 total of 667 cases of lung cancer was reported, compared with 849 expected, to give a cancer
3 mortality ratio of 79%. In each of the five job categories, the observed numbers were below
4 those expected. Engineers in garages had the highest mortality ratio, 90%, motormen and guards
5 had a mortality ratio of 87%, and both the bus drivers and conductors had mortality ratios of
6 75%. The engineers in the central works had a mortality ratio of 66%. These mortality ratios did
7 not differ significantly from each other. Environmental sampling was done at one garage, on one
8 day in 1979, for benzo[a]pyrene concentrations and was compared with corresponding values
9 recorded in 1957. Concentrations of benzo[a]pyrene recorded in 1957 were at least 10 times
10 greater than those measured in 1979.

11 This study failed to find any association between diesel exhaust and occurrence of lung
12 cancer, which may be due to several methodologic limitations. The lung cancer deaths were
13 ascertained while the workers were employed (the worker either died of lung cancer or retired
14 after lung cancer was diagnosed). Although man-years at risk were based on the entire cohort, no
15 attempt was made to trace or evaluate the individuals who had resigned from the London
16 transport company for any other reason. Hence, information on resignees who may have had
17 significant exposure to diesel exhaust, and on lung cancer deaths among them, was not available
18 for analysis. This may have led to a dilution effect, resulting in underascertainment of observed
19 lung cancer deaths and underestimation of mortality ratios. Eligibility criteria for inclusion in the
20 cohort, such as starting date and length of service with the company, were not specified.
21 Therefore, there may not have been sufficient latency for the development of lung cancer. Use of
22 greater London population death rates to obtain expected number of deaths may have resulted in
23 a deficit in mortality ratios reflecting the “healthy worker effect.” Investigators did not categorize
24 the five job categories either by qualitative or quantitative levels of diesel exhaust exposure;
25 neither did they use an internal comparison group to derive risk estimates.

26 The age range considered for this study was limited (45 to 64 years of age) for the period
27 between 1950 and 1974. It is not clear whether this age range was applied to calendar year 1950
28 or 1974, or at the midpoint of the 25-year follow-up period. No analyses were presented either
29 by latency or by duration of employment (surrogate for exposure). The environmental survey
30 based on benzo[a]pyrene concentrations suggests that the cohort in its earlier years was exposed
31 to much higher concentrations of environmental contaminants than currently exist. It is not clear
32 when the reduction in benzo[a]pyrene concentration occurred, because there are no environmental
33 readings available between 1957 and 1979. It is also important to note that the concentrations of
34 benzo[a]pyrene inside the garage in 1957 were not very different from those outside the garage,
35 thus indicating that exposure for garage workers was not much different from that of the general

1 population. Thus, this study fails to provide any negative association between the diesel exhaust
2 exposure and the occurrence of lung cancer.

3
4 **7.2.1.2. *Howe et al. (1983): Cancer Mortality (1965 to 1977) in Relation to Diesel Fumes and***
5 ***Coal Exposure in a Cohort of Retired Railroad Workers***

6 This is a retrospective cohort study of the mortality experience of 43,826 male pensioners
7 of the Canadian National Railroad (CNR) between 1965 and 1977. Members of this cohort
8 consisted of male CNR pensioners who had retired before 1965 and who were known to be alive
9 at the start of that year, as well as those who retired between 1965 and 1977. The records were
10 obtained from a computer file that is regularly updated and used by the company for payment of
11 pensions. To receive a pension, each pensioner must provide, on a yearly basis, evidence that he
12 is alive. Specific cause of death among members of this cohort was ascertained by linking these
13 records to the Canadian Mortality Data Base, which contains records of all deaths registered in
14 Canada since 1950. Of the 17,838 deaths among members of the cohort between 1965 and 1977,
15 16,812 (94.4%) were successfully linked to a record in the mortality file. A random sample
16 manual check on unlinked data revealed that failure to link was due mainly to some missing
17 information on the death records.

18 Occupation at time of retirement was used by the Department of Industrial Relations to
19 classify workers into three diesel fume and coal dust exposure categories: (1) nonexposed, (2)
20 possibly exposed, and (3) probably exposed. Person-years of observation were calculated and
21 classified by age at observation in 5-year age groups (35 to 39, 40 to 44, . . . , 80 to 84, and ≥ 85
22 years). The observed deaths were classified by age at death for different cancers, for all cancers
23 combined, and for all causes of death combined. Standard mortality ratios (SMRs) were then
24 calculated using rates of the Canadian population for the period between 1965 and 1977. The
25 relative risks were calculated using the three exposure categories: nonexposed, possibly exposed,
26 and probably exposed.

27 Both total mortality (SMR = 95, $p < 0.001$) and all cancer deaths (SMR = 99, $p > 0.05$)
28 were close to that expected for the entire cohort. Analysis by exposure to diesel fume levels in
29 the three categories (nonexposed, possibly exposed, and probably exposed) revealed an increased
30 relative risk for lung cancer among workers with increasing exposure to diesel fumes. The
31 relative risk for nonexposed workers was presumed to be 1.0; for those possibly exposed, the
32 relative risk was significantly elevated to 1.2 ($p = 0.013$); and for those probably exposed, it was
33 significantly elevated to 1.35 ($p = 0.001$). The corresponding rates for exposure to varying levels
34 of coal dust were very similar at 1.00, 1.21 ($p = 0.012$), and 1.35 ($p = 0.001$), respectively. The
35 trend tests were highly significant for both exposures ($p < 0.001$). Analysis performed after the
36 exclusion of individuals who worked in the maintenance of steam engines, and hence were

1 exposed to high levels of asbestos, yielded a risk of lung cancer of 1.00, 1.21, and 1.33 for those
2 nonexposed, possibly exposed, and probably exposed to diesel exhaust, respectively, with a highly
3 significant trend ($p<0.001$).

4 An analysis done on individuals who retired prior to 1950 showed the relative risk of lung
5 cancer among nonexposed, possibly exposed, and probably exposed to be 1.00, 0.70, and 0.44,
6 respectively, based on fewer than 15 deaths in each category. A similar analysis of individuals
7 who retired after 1950 found the results in the same categories to be 1.00, 1.23, and 1.40,
8 respectively. Although retirement prior to 1950 indicated exposure to coal combustion fumes
9 alone, retirement after 1950 shows the results of mixed exposure to coal combustion fumes and
10 diesel fumes. As there was considerable overlap between occupations involving probable
11 exposure to diesel fumes and probable exposure to coal, and as most members of the cohort were
12 employed during the years in which the transition from coal to diesel occurred, it was difficult to
13 distinguish whether lung cancer was associated with exposure to coal combustion fumes or diesel
14 fumes or a mixture of both.

15 Although this study showed a highly significant dose-response relationship between diesel
16 fumes and lung cancer, it has some methodological limitations. There were concurrent exposures
17 to both diesel fumes and coal combustion fumes during the transition period; therefore,
18 misclassification of exposure may have occurred, because only occupation at retirement was
19 available for analysis. It is possible that the elevated response observed for lung cancer was due
20 to the combined effects of exposure to both coal dust/coal combustion products and diesel fumes
21 and not just one or the other. However, deaths due to lung cancer were not elevated among
22 workers who retired prior to the 1950s and thus would have been primarily exposed to coal
23 dust/coal combustion products. Furthermore, it should be noted that so far coal dust has not been
24 demonstrated to be a pulmonary carcinogen in studies of coal miners. This study was restricted to
25 deaths among retired workers; therefore, it is unclear if a worker who developed lung cancer
26 when actively employed and filed for a disability claim instead of retirement claim would be
27 included in the study or not. Thus, it is possible that workers with heavy exposure might have
28 been excluded from the study. Neither information on duration of employment in diesel work, nor
29 coal dust-related jobs other than those held at retirement, nor details of how the exposure
30 categories were created was provided. Therefore, it was not possible to evaluate whether this
31 omission would have led to an under- or overestimate of the true relative risk. Although
32 information on potential confounders such as smoking is lacking, the use of an internal
33 comparison group to compute the relative risks minimizes the potential for confounding by
34 smoking, as there is no reason to assume different smoking patterns among individuals exposed to
35 diesel exhaust versus those not exposed. Despite these limitations, this study provides suggestive
36 evidence toward a causal association between exposure to diesel exhaust and excess lung cancer.

1 **7.2.1.3. *Rushton et al. (1983): Epidemiological Survey of Maintenance Workers in the***
2 ***London Transport Executive Bus Garages and Chiswick Works***

3 This is a retrospective mortality cohort study of male maintenance workers employed for
4 at least 1 continuous year between January 1, 1967, and December 31, 1975, at 71 London
5 transport bus (also known as rolling stock) garages and at Chiswick Works. The following
6 information was obtained from computer listings: surname with initials, date of birth, date of
7 joining company, last or present job, and location of work. For those individuals who left their
8 job, date of and reason for leaving were also obtained. For those who died in service or after
9 retirement, and for men who had resigned, full name and last known address were obtained from
10 an alphabetical card index in the personnel department. Additional tracing of individuals who had
11 left was carried out through social security records. The area of residence was assumed to be
12 close to their work; therefore place of work was coded as residence. One hundred different job
13 titles were coded into 20 broader groups. These 20 groups were not ranked for diesel exhaust
14 exposure, however. The reason for leaving was coded as died in service, retired, or other. The
15 underlying cause of death was coded using the eighth revision of the International Classification
16 of Diseases (ICD). Person-years were calculated from date of birth and dates of entry to and exit
17 from the study using the man-years computer language program. The workers were then
18 subdivided into 5-year age and calendar period groups. The expected number of deaths was
19 calculated by applying the 5-year age and calendar period death rates of the comparison
20 population with the person-years of corresponding groups. The mortality experience of the male
21 population in England and Wales was used as the comparison population. Significance values
22 were calculated for the difference between the observed and expected deaths, assuming a Poisson
23 distribution.

24 The person-years of observation totaled 50,008 and were contributed by 8,490 individuals
25 in the study, with a mean follow-up of 5.9 years. Only 2.2% (194) of the men were not traced.
26 Observed deaths from all causes were significantly lower than expected ($O = 495, p < 0.001$).
27 Observed deaths from all neoplasms and cancer of the lung were approximately the same as those
28 expected. The only significant excess observed, for cancer of the liver and gall bladder at
29 Chiswick Works, was based on four deaths ($p < 0.05$). A few job groups showed a significant
30 excess of risks for various cancers. All the excess deaths observed for the various job groups,
31 except for the general hand category, were based on very small numbers (usually fewer than five)
32 and merited cautious interpretation. Only a notable excess in the general hand category for lung
33 cancer was based on as many as 48 cases ($SMR = 133, p < 0.03$).

34 This mortality study did not demonstrate any cancer excess. Details of work history were
35 not obtained to permit any analysis by diesel exhaust exposure. The study's limitations, including

1 small sample size, short duration of follow-up (average of only 6 years), and lack of sufficient
2 latency period, make it inadequate to draw any conclusions.

3 4 **7.2.1.4. Wong et al. (1985): Mortality Among Members of a Heavy Construction Equipment** 5 **Operators Union With Potential Exposure to Diesel Exhaust Emissions**

6 This retrospective mortality study was conducted on a cohort of 34,156 male members of
7 a heavy construction equipment operators union with potential exposure to diesel exhaust
8 emissions. Study cohort members were identified from records maintained at Operating
9 Engineers' Local Union No. 3-3A in San Francisco, CA. This union has maintained both work
10 and death records on all its members since 1964. Individuals with at least 1 year of membership in
11 this union between January 1, 1964, and December 31, 1978, were included in the study. Work
12 histories of the cohort were obtained from job dispatch computer tapes. The study follow-up
13 period was January 1964 to December 1978. Death information was obtained from a trust fund,
14 which provided information on retirement dates, vital status, and date of death for those who
15 were entitled to retirement and death benefits. Approximately 50% of the cohort had been union
16 members for less than 15 years, whereas the other 50% had been union members for 15 years or
17 more. The average duration of membership was 15 years. As of December 31, 1978, 29,046
18 (85%) cohort members were alive, 3,345 (9.8%) were dead, and 1,765 (5.2%) remained untraced.
19 Vital status of 10,505 members who had left the union as of December 31, 1978, was ascertained
20 from the Social Security Administration. Death certificates were obtained from appropriate State
21 health departments. Altogether, 3,243 deaths (for whom death certificates were available) in the
22 cohort were coded using the seventh revision of the ICD. For 102 individuals, death certificates
23 could not be obtained, only the date of death; these individuals were included in the calculation of
24 the SMR for all causes of death but were deleted from the cause-specific SMR analyses.
25 Expected deaths and SMRs were calculated using the U.S. national age-sex-race cause-specific
26 mortality rates for 5-year time periods between 1964 and 1978. The entire cohort population
27 contributed to 372,525.6 person-years in this 5-year study period.

28 A total of 3,345 deaths was observed, compared with 4,109 expected. The corresponding
29 SMR for all causes was 81 ($p=0.01$), which is consistent with the "healthy worker effect." A total
30 of 817 deaths was attributed to malignant neoplasms, slightly fewer than the 878 expected based
31 on U.S. white male cancer mortality rates ($SMR = 93, p=0.05$). Mostly there were SMR deficits
32 for cause-specific cancers, including lung cancer for the entire cohort ($SMR = 99, O = 309$). The
33 only significant excess SMR was observed for cancer of the liver ($SMR = 167, O = 23, p<0.05$).

34 Analysis by length of union membership as a surrogate of duration for potential exposure
35 showed statistically significant increases in SMRs of cancer of the liver ($SMR = 424, p<0.01$) in
36 the 10- to 14-year membership group and of the stomach ($SMR = 248, p<0.05$) in the 5- to 9-

1 year membership group. No cancer excesses were observed in the 15- to 19-year and 20+-year
2 membership groups. Although the SMR for cancer of the lung had a statistically significant deficit
3 in the less-than-5-year duration group, it showed a positive trend with increasing length of
4 membership, which leveled off after 10 to 14 years.

5 Cause-specific mortality analysis by latency period showed a positive trend for SMRs of
6 all causes of death, although all of them were statistically significant deficits, reflecting the
7 diminishing “healthy worker effect.” This analysis also demonstrated a statistically significant
8 SMR excess for cancer of the liver (10- to 19-year group, SMR = 258). The SMR for cancer of
9 the lung showed a statistically significant deficit for a <10-year latency but showed a definite
10 positive trend with increasing latency.

11 In addition to these analyses of the entire cohort, similar analyses were carried out in
12 various subcohorts. Analyses of retirees, 6,678 individuals contributing to 32,670 person-years,
13 showed statistically significant increases ($p<0.01$) in SMRs for all cancers; all causes of death;
14 cancers of the digestive system, large intestine, respiratory system, and lung; emphysema; and
15 cirrhosis of the liver. The other two significant excesses ($p<0.01$) were for lymphosarcoma and
16 reticulosarcoma and nonmalignant respiratory diseases. Further analysis of the 4,075 retirees
17 (18,678 person-years) who retired at age 65 or who retired earlier but had reached the age of 65
18 revealed statistically significant SMR increases ($p<0.05$) for all cancers, cancer of the lung, and
19 lymphosarcoma and reticulosarcoma.

20 To analyze cause-specific mortality by job held (potential exposure to diesel exhaust
21 emissions), 20 functional job titles were used, which were further grouped into three potential
22 categories: high exposure, low exposure, and unknown exposure. A person was classified in a
23 job title if he ever worked on that job. Based on this classification system, if a person had ever
24 worked in a high-exposure job title he was included in that group, even though he may have
25 worked for a longer time in a low-exposure group or in an unknown exposure group.
26 Information on length of work in any particular job, hence indirect information on potential length
27 of exposure, was not available either.

28 For the high-exposure group a statistically significant excess was observed for cancer of
29 the lung among bulldozer operators who had 15 to 19 years of membership and 20+ years of
30 follow-up (SMR = 343, $p<0.05$). This excess was based on 5 out of 495 deaths observed in this
31 group of 6,712 individuals, who contributed 80,328 person-years of observation.

32 The cause-specific mortality analysis in the low-exposure group revealed statistically
33 significant SMR excesses in individuals who had ever worked as engineers. These excesses were
34 for cancer of the large intestine (SMR = 807, O = 3, $p<0.05$) among those with 15 to 19 years of
35 membership and length of follow-up of at least 20 years, and cancer of the liver (SMR = 872, O =
36 3, $p<0.05$) among those with 10 to 14 years of membership and length of follow-up of 10 to 19

1 years. There were 7,032 individuals who contributed to 78,403 person-years of observation in the
2 low-exposure group.

3 For the unknown exposure group, a statistically significant SMR was observed for motor
4 vehicle accidents only (SMR = 174, O = 21, $p < 0.05$). There were 3,656 individuals who
5 contributed to 33,388 person-years of observation in this category.

6 No work histories were available for those who started their jobs before 1967 and for
7 those who held the same job prior to and after 1967. This group comprised 9,707 individuals
8 (28% of the cohort) contributing to 104,448 person-years. Statistically significant SMR excesses
9 were observed for all cancers (SMR = 112, O = 339, $p < 0.05$) and cancer of the lung (SMR = 119,
10 O = 141, $p < 0.01$). A significant SMR elevation was also observed for cancer of the stomach
11 (SMR = 199, O = 30, $p < 0.01$).

12 This study demonstrates a statistically significant excess for cancer of the liver but also
13 shows statistically significant deficits in cancers of the large intestine and rectum. It may be, as
14 the authors suggested, that the liver cancer cases actually resulted from metastases from the large
15 intestine and/or rectum, as tumors of these sites will frequently metastasize to the liver. The
16 excess in liver cancer mortality and the deficits in mortality that are due to cancer of the large
17 intestine and rectum could also, as the authors indicate, be due to misclassification. Both
18 possibilities have been considered by the investigators in their discussion.

19 Cancer of the lung showed a positive trend with length of membership as well as with
20 latency, although none of the SMRs were statistically significant except for workers without any
21 work histories. The individuals without any work histories may have been the ones who were in
22 their jobs for the longest period of time, because workers without job histories included those
23 who had the same job before and after 1967 and thus may have worked 12 to 14 years or longer.
24 If they had belonged to the category in which heavy exposure to diesel exhaust emissions was
25 very common for this prolonged time, then the increase in lung cancer, as well as stomach cancer,
26 might be linked to diesel exhaust. Further information on those without work histories should be
27 obtained if possible, because such information may be quite informative with regard to the
28 evaluation of the carcinogenicity of diesel exhaust.

29 The study design is adequate, covers about a 15-year observation period, has a large
30 enough population, and is appropriately analyzed; however, it has too many limitations to permit
31 any conclusions. First, no exposure histories are available; one has to make do with job histories,
32 which provide limited information on exposure level. Any person who ever worked at the job, or
33 any person working at the same job over any period of time, is included in the same category; this
34 would have a dilution effect, because extremely variable exposures were considered in the study.
35 Second, the length of time worked in any particular job is not available. Third, work histories
36 were not available for 9,707 individuals, who contributed 104,448 person-years, a large

1 proportion of the study cohort (28%). These individuals happen to show the most evidence of a
2 carcinogenic effect. Confounding by alcohol consumption for cancer of the liver and smoking for
3 emphysema and cancer of the lung was not ruled out. Fourth, 15 years' follow-up may not
4 provide sufficient latency to observe excess lung cancer. Last, although 34,156 members were
5 eligible for the study, the vital status of 1,765 individuals was unknown. Nevertheless, they were
6 still considered in the denominator of all the analyses. The investigators fail to mention how the
7 person-year calculation for these individuals was handled. Also, some of the person-years might
8 have been overestimated, as people may have paid the dues for a particular year and then left
9 work. These two causes of overestimation of the denominator may have resulted in some or all
10 the SMRs being underestimated.

11 12 **7.2.1.5. *Edling et al. (1987): Mortality Among Personnel Exposed to Diesel Exhaust***

13 This retrospective cohort mortality study of bus company employees investigated a
14 possible increased mortality of cardiovascular diseases and cancers from diesel exhaust exposure.
15 The cohort comprised all males employed at five different bus companies in southeastern Sweden
16 between 1950 and 1959. Based on information from personnel registers, individuals were
17 classified into one or more categories and could have contributed person-years at risk in more
18 than one exposure category. The study period was from 1951 to 1983; information was collected
19 from the National Death Registry, and copies of death certificates were obtained from the
20 National Bureau of Statistics. Workers who died after age 79 were excluded from the study
21 because diagnostic procedures were likely to be more uncertain at higher ages (according to
22 investigators). The cause-, sex-, and age-specific national death rates in Sweden were applied to
23 the 5-year age categories of person-years of observation to determine expected deaths for all
24 causes, malignant diseases, and cardiovascular diseases. A Poisson distribution was used to
25 calculate *p*-values and confidence limits for the ratio of observed to expected deaths. The total
26 cohort of 694 men (after loss of 5 men to follow-up) was divided into three exposure categories:
27 (1) clerks with lowest exposure, (2) bus drivers with moderate exposure, and (3) bus garage
28 workers with highest exposure.

29 The 694 men provided 20,304 person-years of observation, with 195 deaths compared
30 with 237 expected. A deficit in cancer deaths largely accounted for this lower-than-expected
31 mortality in the total cohort. Among subcohorts, no difference between observed and expected
32 deaths for total mortality, total cancers, or cardiovascular causes was observed for clerks (lowest
33 diesel exposure), bus drivers (moderate diesel exposure), and garage workers (high diesel
34 exposure). The risk ratios for all three categories were less than 1 except for cardiovascular
35 diseases among bus drivers, which was 1.1.

1 When the analysis was restricted to members who had at least a 10-year latency period
2 and either any exposure or an exposure exceeding 10 years, similar results were obtained, with
3 fewer neoplasms than expected, whereas cardiovascular diseases showed risk around or slightly
4 above unity.

5 Five lung cancer deaths were observed among bus drivers who had moderate diesel
6 exhaust exposure, whereas seven were expected. The only other lung cancer death was observed
7 among bus garage workers who had the highest diesel exhaust exposure. This study's major
8 limitations, including small size and poor data on diesel exhaust exposure, make it inadequate to
9 draw any conclusions.

10
11 **7.2.1.6. Boffetta and Stellman (1988): Diesel Exhaust Exposure and Mortality Among Males**
12 ***in the American Cancer Society Prospective Study***

13 Boffetta and Stellman conducted a mortality analysis of 461,981 males with known
14 smoking history and vital status at the end of the first 2 years of follow-up. The analysis was
15 restricted to males aged 40 to 79 years in 1982 who enrolled in the American Cancer Society's
16 prospective mortality study of cancer. Mortality was analyzed in relation to exposure to diesel
17 exhaust and to employment in selected occupations related to diesel exhaust exposure. In 1982,
18 more than 77,000 American Cancer Society volunteers enrolled more than 1.2 million men and
19 women from all 50 States, the District of Columbia, and Puerto Rico in a long-term cohort study,
20 the Cancer Prevention Study II (CPS-II). Enrollees were usually friends, neighbors, or relatives
21 of the volunteers; enrollment was by family groups, with at least one person in the household 45
22 years of age or older. Subjects were asked to fill out a four-page confidential questionnaire and
23 return it in a sealed envelope. The questionnaire included history of cancer and other diseases;
24 use of medications and vitamins; menstrual and reproductive history; occupational history; and
25 information on diet, drinking, smoking, and other habits. The questionnaire also included three
26 questions on occupation: (1) current occupation, (2) last occupation, if retired, and (3) job held
27 for the longest period of time, if different from the other two. Occupations were coded to an ad
28 hoc two-digit classification in 70 categories. Exposures at work or in daily life to any of the 12
29 groups of substances were also ascertained. These included diesel engine exhausts, asbestos,
30 chemicals/acids/solvents, dyes, formaldehyde, coal or stone dusts, and gasoline exhausts.
31 Volunteers checked whether their enrollees were alive or dead and recorded the date and place of
32 all deaths every other year during the study. Death certificates were then obtained from State
33 health departments and coded by a trained nosologist according to a system based on the ninth
34 revision of the ICD.

35 The data were analyzed to determine the mortality for all causes and lung cancer in
36 relation to diesel exhaust exposure, mortality for all causes and lung cancer in relation to

1 employment in selected occupations with high diesel exhaust exposure, and mortality from other
2 causes in relation to diesel exhaust exposure. The incidence-density ratio was used as a measure
3 of association, and test-based confidence limits were calculated by the Miettinen method. For
4 stratified analysis, the Mantel-Haenszel method was used for testing linear trends. Although data
5 on 476,648 subjects comprising 939,817 person-years of risk were available for analysis, 3% of
6 the subjects (14,667) had not given any smoking history, and 20% (98,026) did not give
7 information on diesel exhaust exposure and were therefore excluded from the main diesel exhaust
8 analysis. Among individuals who had provided diesel exhaust exposure history, 62,800 were
9 exposed and 307,143 were not exposed. Comparison of the population with known information
10 on diesel exhaust exposure with the excluded population with no information on diesel exhaust
11 exposure showed that the mean ages were 54.7 and 57.7 years, the nonsmokers were 72.4% and
12 73.2%, and the total mortality rates per 1,000 per year were 23.0% and 28.8%, respectively.

13 All-cause mortality was elevated among railroad workers (relative risk [RR] = 1.43, 95%
14 confidence interval [CI] = 1.2, 1.72), heavy equipment operators (RR = 1.7, 95% CI = 1.19,
15 2.44), miners (RR = 1.34, 95% CI = 1.06, 1.68), and truck drivers (RR = 1.19, 95% CI = 1.07,
16 1.31). The age-adjusted lung cancer relative risk was elevated significantly (RR = 1.41, 95% CI =
17 1.19,1.66), which was slightly decreased to 1.31 (95% CI = 1.10, 1.54). For lung cancer
18 mortality the age- and smoking-adjusted risks were significantly elevated for miners (RR = 2.67,
19 95% CI = 1.63, 4.37) and heavy equipment operators (RR = 2.60, 95% CI = 1.12, 6.06). Risks
20 were also elevated, but not significantly, for railroad workers (RR = 1.59, 95% CI = 0.94, 2.69)
21 and truck drivers (RR = 1.24, 95% CI = 0.93, 1.66). These risks were calculated with the
22 Mantel-Haenszel method, controlling for age and smoking. Although the relative risk was
23 nonsignificant for truck drivers, a small dose-response effect was observed when duration of
24 diesel exhaust exposure was examined. For drivers who worked for 1 to 15 years, the relative
25 risk was 0.87, whereas for drivers who worked for more than 16 years, the relative risk was 1.33
26 (95% CI = 0.64, 2.75). Relative risks for lung cancer were not presented for other occupations.
27 Mortality analysis for other causes and diesel exhaust exposure showed a significant excess of
28 deaths ($p < 0.05$) in the following categories: cerebrovascular disease, arteriosclerosis, pneumonia,
29 influenza, cirrhosis of the liver, and accidents.

30 The main strength of this study is detailed information on smoking. The two main
31 methodologic concerns are the representativeness of the study population and the quality of
32 information on exposure. The sample, though very large, was composed of volunteers. Thus, the
33 cohort was healthier and less frequently exposed to important risk factors such as smoking and
34 alcohol. Self-administered questionnaires were used to obtain data on occupation and diesel
35 exhaust exposure. None of this information was validated. Nearly 20% of the individuals had an
36 unknown exposure status to diesel exhaust, and they experienced a higher mortality for all causes

1 and lung cancer than both the diesel exhaust exposed and unexposed groups. This could have
2 introduced a substantial bias in the estimate of the association. Given that all diesel exhaust
3 exposure occupations, such as heavy equipment operators, truck drivers, and railroad workers,
4 showed elevated lung cancer risk, this study is suggestive of a causal association. It should be
5 noted that after adjusting for smoking, the RR reduced slightly from 1.41 to 1.31 and remained
6 significant, indicating that observed excess of lung cancer was associated mainly with diesel
7 exhaust exposure. This study did not find any association between exposure to diesel exhaust and
8 bladder cancer.

9
10 **7.2.1.7. *Garshick et al. (1988): A Retrospective Cohort Study of Lung Cancer and Diesel***
11 ***Exhaust Exposure in Railroad Workers***

12 An earlier case-control study of lung cancer and diesel exhaust exposure in U.S. railroad
13 workers by these investigators had demonstrated a relative odds of 1.41 (95% CI = 1.06, 1.88)
14 for lung cancer with 20 years of work in jobs with diesel exhaust exposure. To confirm these
15 results, a large retrospective cohort mortality study was conducted by the same investigators.
16 Data sources for the study were the work records of the U.S. Railroad Retirement Board (RRB).
17 The cohort was selected based on job titles in 1959, which was the year by which 95% of the
18 locomotives in the United States were diesel powered. Diesel exhaust exposure was considered
19 to be a dichotomous variable depending on yearly job codes between 1959 and death or
20 retirement through 1980. Industrial hygiene evaluations and descriptions of job activities were
21 used to classify jobs as exposed or unexposed to diesel emissions. A questionnaire survey of 534
22 workers at one of the railroads where workers were asked to indicate the amount of time spent in
23 railroad locations, either near or away from sources of diesel exhaust, was used to validate this
24 classification. Workers selected for this survey were actively employed at the time of the survey,
25 40 to 64 years of age, started work between 1939 and 1949 in the job codes sampled in 1959, and
26 eligible for railroad benefits. To qualify for benefits, a worker must have had 10 years or more of
27 service with the railroad and should not have worked for more than 2 years in a nonrailroad job
28 after leaving railroad work. Workers with recognized asbestos exposure, such as repair of
29 asbestos-insulated steam locomotive boilers, passenger cars, and steam pipes, or railroad building
30 construction and repairs, were excluded from the job categories selected for study. However, a
31 few jobs with some potential for asbestos exposure were included in the cohort, and the analysis
32 was done both ways, with and without them.

33 The death certificates for all subjects identified in 1959 and reported by the RRB to have
34 died through 1980 were searched. Twenty-five percent of them were obtained from the RRB and
35 the remainder from the appropriate State departments of health. Coding of cause of death was
36 done without knowledge of exposure history, according to the eighth revision of the ICD. If the

1 underlying cause of death was not lung cancer, but was mentioned on the death certificate, it was
2 assigned as a secondary cause of death, so that the ascertainment of all cases was complete.
3 Workers not reported by the RRB to have died by December 31, 1980, were considered to be
4 alive. Deceased workers for whom death certificates had not been obtained or, if obtained, did
5 not indicate cause of death, were assumed to have died of unknown causes.

6 Proportional hazard models were fitted that provided estimates of relative risk for death
7 caused by lung cancer using the partial likelihood method described by Cox, using the time
8 dimension being the time since first entry into the cohort. The model also controlled for the birth
9 year and the calendar time. The 95% confidence intervals were constructed using the asymptotic
10 normality of the estimated regression coefficients of the proportional hazards model. Exposure
11 was analyzed by diesel exhaust-exposed jobs in 1959 and by cumulative number of years of diesel
12 exhaust exposure through 1980. Directly standardized rate ratios for deaths from lung cancer
13 were calculated for diesel exhaust exposed compared with unexposed for each 5-year age group
14 in 1959. The standardized rates were based on the overall 5-year person-year time distribution of
15 individuals in each age group starting in 1959. The only exception to this was between 1979 and
16 1980, when a 2-year person-year distribution was used. The Mantel-Haenszel analogue for
17 person-year data was used to calculate 95% confidence intervals for the standardized rate ratios.

18 The cohort consisted of 55,407 workers, 19,396 of whom had died by the end of 1980.
19 Death certificates were not available for 11.7% of all deaths. Of the 17,120 deaths for whom
20 death certificates were obtained, 48.4% were attributable to diseases of the circulatory system,
21 whereas 21% were attributable to all neoplasms. Of all neoplasms, 8.7% (1,694 deaths) were due
22 to lung cancer. A higher proportion of workers in the younger age groups, mainly brakemen and
23 conductors, were exposed to diesel exhaust, while a higher proportion of workers in the older age
24 groups were potentially exposed to asbestos. In a proportional hazards model, analyses by age in
25 1959 found a relative risk of 1.45 (95% CI = 1.11, 1.89) among the age group 40 to 44 years and
26 a relative risk of 1.33 (95% CI = 1.03, 1.73) for the age group 45 to 49 years. Risk estimates in
27 the older age groups 50 to 54, 55 to 59, and 60 to 64 years were 1.2, 1.18, and 0.99, respectively,
28 and were not statistically significant. The two youngest age groups in 1959 had workers with the
29 highest prevalence and longest duration of diesel exhaust exposure and lowest exposure to
30 asbestos. When potential asbestos exposure was considered as a confounding variable in a
31 proportional hazards model, the estimates of relative risk for asbestos exposure were all near null
32 value and not significant. Analysis of workers exposed to diesel exhaust in 1959 (n = 42,535),
33 excluding workers with potential past exposure to asbestos, yielded relative risks of 1.57 (95% CI
34 = 1.19, 2.06) and 1.34 (95% CI = 1.02, 1.76) in the 1959 age groups 40 to 44 years and 45 to 49
35 years. Directly standardized rate ratios were also calculated for each 1959 age group based on

1 diesel exhaust exposure in 1959. The results confirmed those obtained by using the proportional
2 hazards model.

3 Relative risk estimates were then obtained using duration of diesel exhaust exposure as a
4 surrogate for dose. In a model that used years of exposure up to and including exposure in the
5 year of death, no exposure duration-response relationship was obtained. When analysis was done
6 by disregarding exposure in the year of death and 4 years prior to death, the risk of dying from
7 lung cancer increased with the number of years worked in a diesel-exhaust-exposed job. In this
8 analysis, exposure to diesel exhaust was analyzed by exposure duration groups and in a model
9 entering age in 1959 as a continuous variable. The workers with greater than 15 years of
10 exposure had a relative risk of lung cancer of 1.72 (95% CI = 1.27, 2.33). The risk for 1 to 4
11 years of cumulative exposure was 1.20 (95% CI = 1.01, 1.44); for 5 to 9 years of cumulative
12 exposure, it was 1.24 (95% CI = 1.06, 1.44); and for 10 to 14 years of cumulative exposure, it
13 was 1.32 (95% CI = 1.13, 1.56).

14 The results of this study, demonstrating a positive association between diesel exhaust
15 exposure and increased lung cancer, are consistent with the results of the case-control study
16 conducted by the same investigators in railroad workers dying of lung cancer from March 1981
17 through February 1982. This cohort study has addressed many of the weaknesses of the other
18 epidemiologic studies. The large sample size (60,000) allowed sufficient power to detect small
19 risks and also permitted the exclusion of workers with potential past exposure to asbestos. The
20 stability of job career paths in the cohort ensured that of the workers 40 to 44 years of age in
21 1959 classified as diesel exhaust-exposed, 94% of the cases were still in diesel exhaust-exposed
22 jobs 20 years later.

23 The main limitation of the study is the lack of quantitative data on exposure to diesel
24 exhaust. This is one of the few studies in which industrial hygiene measurements of diesel exhaust
25 were done. These measurements were correlated with job titles to divide the cohort in
26 dichotomous exposure groups of exposed and nonexposed. This may have led to an
27 underestimation of the risk of lung cancer because exposed groups included individuals with low
28 to high exposure. The number of years exposed to diesel exhaust was used as a surrogate for
29 dose. The dose, based on duration of employment, was inaccurate because individuals were
30 working on steam and diesel locomotives during the transition period. It should be noted that the
31 investigators only included exposures after 1959; the duration of exposure prior to 1959 was not
32 known. If the categories of exposure to diesel exhaust had been set up as no, low, moderate, and
33 high exposure, the results would have been more meaningful, as would the dose-response
34 relationship. Another limitation of this study was its inability to examine the effect of years of
35 exposure prior to 1959 and latency. No adjustment for smoking was made in this study.
36 However, an earlier case-control study done in the same cohort (Garshick et al., 1987) showed no

1 significant difference in the risk estimate after adjusting for smoking. Despite these limitations,
2 the results of this study indicate that occupational exposure to diesel exhaust is associated with a
3 modest risk (1.5) of lung cancer.

4 The data of this study were reanalyzed by Crump et al. (1991), who found that the relative
5 risk can be positively or negatively related to the duration of exposure depending on how age was
6 controlled in a model. Garshick conducted some additional analyses (letter from E. Garshick,
7 Harvard Medical School, to Dr. Chao Chen, U.S. EPA, dated August 15, 1991) and reported that
8 the relationship between years of exposure, when adjusted for attained age, and calendar year is
9 flat to negative depending upon which model was used. They also found that in the years 1977-
10 1980 the death ascertainment was incomplete; approximately 20% to 70% of deaths were missing
11 depending upon the calendar year. Their analysis, based on job titles in 1959 and limited to deaths
12 occurring through 1976, showed that the youngest workers still had the highest risk of dying of
13 lung cancer. Crump (1999) reported that the negative dose-response continued to be upheld in
14 his latest analysis. California EPA (CalEPA, 1998) found a positive dose-response by using age at
15 1959 but allowing for an interaction term of age and calendar year in the model. A detailed
16 discussion of divergent results observed by Crump and CalEPA can be found in Chapter 8.

17 18 **7.2.1.8. *Gustavsson et al. (1990): Lung Cancer and Exposure to Diesel Exhaust Among Bus*** 19 ***Garage Workers***

20 A retrospective mortality study (from 1952 to 1986), cancer incidence study (from 1958
21 to 1984), and nested case-control study were conducted among a cohort of 708 male workers
22 from five bus garages in Stockholm, Sweden, who had worked for at least 6 months between
23 1945 and 1970. Thirteen individuals were lost to follow-up, reducing the cohort to 695.

24 Information was available on location of workplace, job type, and beginning and ending of
25 work periods. Workers were traced through a computerized register of the living population,
26 death and burial books, and data from the Stockholm city archives.

27 For the cohort mortality analyses, death rates of the general population of greater
28 Stockholm were used. Death rates of occupationally active individuals, a subset of the general
29 population of greater Stockholm, were used as a second comparison group to reduce the bias
30 from “healthy worker effect.” Mortality analysis was conducted using the “occupational mortality
31 analysis program” (OCMAP-PC). For cancer incidence analysis, the “epidemiology in Linköping”
32 (EPILIN) program was used, with the incidence rates obtained from the cancer registry.

33 For the nested case-control study, both dead and incident primary lung cancers identified
34 in the register of cause of deaths and the cancer register were selected. Six controls matched on
35 age \pm 2 years, selected from the noncases at the time of the diagnosis of cases, were drawn at

1 random without replacements. Matched analyses were done to calculate odds ratios using
2 conditional logistic regression. The EGRET and Epilog programs were used for these analyses.

3 Diesel exhaust and asbestos exposure assessments were performed by industrial hygienists
4 based on the intensity of exposure to diesel exhaust and asbestos, specific for workplace, work
5 task, and calendar time period. A diesel exhaust exposure assessment was based on (1) amount of
6 emission (number of buses, engine size, running time, and type of fuel), (2) ventilatory equipment
7 and air volume of the garages, and (3) job types and work practices. Based on detailed historical
8 data and very few actual measurements, relative exposures were estimated (these were not
9 absolute exposure levels). The scale was set to 0 for unexposed and 1 for lowest exposure, with
10 each additional unit increase corresponding to a 50% increase in successive intensity (i.e., 1.5,
11 2.25, 3.38, and 5.06).

12 Based on personal sampling of asbestos during 1987, exposures were estimated and time-
13 weighted annual mean exposures were classified on a scale of three degrees (0, 1, and 2).
14 Cumulative exposures for both diesel exhaust and asbestos were calculated by multiplying the
15 level of exposure by the duration of every work period. An exposure index was calculated by
16 adding for every individual contribution from all work periods for both diesel exhaust and
17 asbestos. Four diesel exhaust index classes were created: 0 to 10, 10 to 20, 20 to 30, and >30.
18 The four asbestos index classes were 0 to 20, 20 to 40, 40 to 60, and >60. The cumulative
19 exposure indices were used for the nested case-control study.

20 Excesses were observed for all cancers and some other site-specific cancers using both
21 comparison populations for the cohort mortality study, but none of them was statistically
22 significant. Based on 17 cases, SMRs for lung cancer were 122 and 115 using Stockholm
23 occupationally active and general population, respectively. No dose-response was observed with
24 increasing cumulative exposure in the mortality study. The cancer incidence study reportedly
25 confirmed the mortality results (results not given).

26 The nested case-control study, on the other hand, showed increasing risk of lung cancer
27 with increasing exposure. Using 0 to 10 diesel exhaust exposure index as the comparison group
28 yielded RRs of 1.34 (95% CI = 1.09 to 1.64), 1.81 (95% CI = 1.20 to 2.71), and 2.43 (95% CI =
29 1.32 to 4.47) for the diesel exhaust indices 10 to 20, 20 to 30, and >30, respectively. The study
30 was based on 17 cases and 6 controls for each case matched on age \pm 2 years. Adjustment for
31 asbestos exposure did not change the lung cancer risk for diesel exhaust.

32 The main strength of this study is the detailed exposure matrices constructed for both
33 diesel exhaust and asbestos exposure, although they were based primarily on job tasks and very
34 few actual measurements. There are a few methodological limitations to this study. The cohort is
35 small and there were only 17 lung cancer deaths; thus the power is low. Exposure or outcome
36 may be misclassified, although any resulting bias in the relative risk estimates is likely to be

1 toward unity, because exposure classification was done independently of the outcome. Although
2 the analysis by dose indices was done, no latency analysis was performed. Although data on
3 smoking were missing, it is unlikely to confound the results because this is a nested case-control
4 study; therefore, smoking is not likely to be different among the individuals irrespective of their
5 exposure status to diesel exhaust. Overall, this study provides some support to the excess lung
6 cancer results found earlier among populations exposed to diesel exhaust.

7 8 **7.2.1.9. Hansen (1993): A Followup Study on the Mortality of Truck Drivers**

9 This is a retrospective cohort mortality study of unskilled male laborers, ages 15 to 74
10 years, in Denmark, identified from a nationwide census file of November 9, 1970. The exposed
11 group included all truck drivers employed in the road delivery or long-haul business (14,225).
12 The unexposed group included all laborers in certain selected occupational groups considered to
13 be unexposed to fossil fuel combustion products and to resemble truck drivers in terms of work-
14 related physical demands and various personal background characteristics (43,024).

15 Through automatic record linkage between the 1970 census register (the Central
16 Population Register 1970 to 1980) and the Death Certificate Register (1970 to 1980), the
17 population was followed for cause-specific mortality or emigration up to November 9, 1980.
18 Expected number of deaths among truck drivers was calculated by using the 5-year age group and
19 5-year time period death rates of the unexposed group and applying them to the person-years
20 accumulated by truck drivers. ICD Revision 8 was used to code the underlying cause of death.
21 Test-based CIs were calculated using Miettinen's method. A Poisson distribution was assumed
22 for the smaller numbers, and CI was calculated based on exact Poisson distribution (Ciba-Geigy).
23 Total person-years accrued by truck drivers were 138,302, whereas for the unexposed population,
24 they were 407,780. There were 627 deaths among truck drivers and 3,811 deaths in the
25 unexposed group. Statistically significant excesses were observed for all cancer mortality (SMR =
26 121, 95% CI = 104 to 140); cancer of respiratory organs (SMR = 160, 95% CI = 128 to 198),
27 which was due mainly to cancer of bronchus and lung (SMR = 160, 95% CI = 126 to 200); and
28 multiple myeloma (SMR = 439, 95% CI = 142 to 1,024). When lung cancer mortality was further
29 explored by age groups, excesses were observed in most age groups (30 to 39, 45 to 49, 50 to 54,
30 55 to 59, 60 to 64, and 65 to 74), but there were small numbers of deaths in each group when
31 stratified by age, and the excesses were statistically significant for the 55 to 59 (SMR = 229, O =
32 19, 95% CI = 138 to 358) and 60 to 64 (SMR = 227, O = 22, 95% CI = 142 to 344) age groups
33 only. No excess was observed for bladder cancer.

34 As acknowledged by the author, the study has quite a few methodologic limitations. The
35 exposure to diesel exhaust is assumed in truck drivers based on use of diesel-powered trucks, but
36 no validation of qualitative or quantitative exposure is attempted. It is also not known whether

1 any of these truck drivers or any other laborers had changed jobs after the census of November 9,
2 1970, thus creating potential misclassification bias in exposure to diesel exhaust. The truck
3 drivers and the unexposed laborers were from the same socioeconomic class and may have the
4 same smoking habits. Still, the lack of information on smoking data and a 36% rural population
5 (usually consuming less tobacco) in the unexposed group may potentially confound the lung
6 cancer results. However, a population survey carried out in 1988 showed very little difference in
7 smoking habits of residents of rural areas and the total Danish male population. The investigator
8 reports that diesel trucks were introduced in Denmark after World War II, and since the late
9 1940s the majority of the Danish fleet has been composed of diesel trucks. Consequently, even
10 though the follow-up period is relatively short, the truck drivers may have had exposure to diesel
11 exhaust for 20 to 30 years. Therefore, the finding of excess lung cancer in this study is consistent
12 with the findings of other truck driver studies.

14 **7.2.1.10. Saverin et al. (1999): Diesel Exhaust and Lung Cancer Mortality in Potash Mining**

15 This is a cohort mortality study conducted in male potash miners in Germany. The mines
16 began using mobile diesel-powered vehicles in 1969 and 1970. Miners who had worked
17 underground for at least 1 year after 1969 to 1991, when the mines were closed, were followed
18 from 1970 to 1994. A total of 5,981 individuals were identified from the medical records by a
19 team of medical personnel familiar with the mining technology. A total of 5,536 were eligible for
20 follow-up after 5.5% were excluded due to implausible or incomplete work history and 1.9%
21 were lost to follow-up. A subcohort of 3,258 miners who had worked for at least 10 years
22 underground (80% had held a single job) was also identified. The miners' biannual medical
23 examination records were used to extract the information about personal data, smoking data, and
24 pre-mining occupation, and to reconstruct a chronology of workplaces occupied by the worker
25 since hire for each person.

26 Exposure categories were defined as production, maintenance, and workshop, roughly
27 corresponding to high, medium, and low. Concentrations of total carbon, including elemental and
28 organics, were measured in the airborne fine dust in 1992. A total of 255 samples covering all
29 workplaces was obtained. Most were personal dust samples; some were area dust samples.
30 Cumulative exposure was calculated for each miner, for each year of observation, using the work
31 chronology and the work category. For the workshop category years of employment were
32 considered as exposure time; for production and maintenance years of employment was weighted
33 by a factor of 5/8, since these workers for an 8-hour shift worked for only 5 hours underground.
34 As neither the mining technology nor the type of machinery used had changed substantially from
35 1970 to 1992, the exposure measurements were considered to represent the exposures throughout
36 the study period. Accrued person-years were classified into cumulative exposures and were

1 expressed in intervals of 0.5 ymg/m³. Both the exposure data and the smoking data obtained from
2 the medical files were validated by personal interviews with 1,702 cohort members. Death
3 certificates were obtained from local health centers for 94.4% of deceased members. Autopsy
4 data were available for 13% of the deceased. Internal comparison was done between production
5 and workshop categories. Using East German general male population rates, SMRs were
6 computed for the total cohort as well as the subcohort. Analyses were done using Poisson and
7 Cox regression models.

8 The concentrations of total carbon for production, maintenance, and workshop categories
9 were 0.39 mg/m³, 0.23 mg/m³, and 0.12 mg/m³, respectively. The cumulative exposure ranged
10 from 0.25 ymg/m³ to 6.25 ymg/m³. The regression analysis showed that the cohort's smoking
11 habits were homogenous and that smoking had an even distribution over cumulative exposure.

12 A total of 424 deaths were observed for the entire cohort (SMR = 54). The all-cancer
13 deaths were 133, of which 38 were from lung cancer (SMR = 78). Analysis for the subcohort
14 using the internal comparison group of low exposure (workshop category, mean cumulative
15 exposure = 2.12 ymg/m³) RR of 2.17 (95% CI = 0.79, 5.99) was found for the production
16 category (mean cumulative exposure = 4.38 ymg/m³). The relative risks for lung cancer for 20
17 years of exposure in the production category (highest exposure = cumulative exposure of 4.9
18 ymg/m³) were calculated using Poisson and Cox regression methods. RRs of 1.16 and 1.68 were
19 observed for the total cohort, while RRs of 1.89 and 2.7 were observed for the subcohort by
20 Poisson and Cox regression methods respectively.

21 The main strengths of the study are the information available on diesel exhaust exposure
22 and smoking. Although these potash miners were exposed to salt dust and nitric gases, exposures
23 to other confounders such as heavy metals and radon were absent. Smoking does not seem to be
24 a confounder in this study but cannot be completely ruled out. Unfortunately, the age distribution
25 of the cohort is not available. Since there were only 424 deaths in 25 years of follow-up in this
26 cohort of 5,536, it appears that the cohort is young. Although lung cancer risk was elevated by
27 twofold in the production category of the subcohort of miners who had worked for at least 10
28 years underground at the same job for 80% of their time and did not have more than 3 jobs, it was
29 not statistically significant. The follow-up period for this study was 25 years, but the cohort
30 members could have entered the cohort any time between 1970 and 1990, as long as they worked
31 underground for a year, i.e., they could have worked in the mines for 1 year to 21 years. Thus,
32 the authors may not have had enough follow-up or latency to observe the lung cancer excess.
33 Despite these limitations, the results of this study provide suggestive evidence for the causal
34 association between diesel exhaust and excess lung cancer.

35 Table 7-1 summarizes the above cohort studies.
36

7.2.2. Case-Control Studies of Lung Cancer

7.2.2.1. *Hall and Wynder (1984): A Case-Control Study of Diesel Exhaust Exposure and Lung Cancer*

Hall and Wynder (1984) conducted a case-control study of 502 male lung cancer cases and 502 controls without tobacco-related diseases that examined an association between occupational diesel exhaust exposure and lung cancer. Histologically confirmed primary lung cancer patients who were 20 to 80 years old were ascertained from 18 participating hospitals in 6 U.S. cities 12 months prior to the interview. Eligible controls, patients at the same hospitals without tobacco-related diseases, were matched to cases by age (± 5 years), race, hospital, and hospital room status. The number of male lung cancer cases interviewed totaled 502, which was 64% of those who met the study criteria for eligibility. Of the remaining 36%, 8% refused, 21% were too ill or had died, and 7% were unreliable. Seventy-five percent of eligible controls completed interviews. Of these interviewed controls, 49.9% were from the all-cancers category, whereas 50.1% were from the all-noncancers category. All interviews were obtained in hospitals to gather detailed information on smoking history, coffee consumption, artificial sweetener use, residential history, and abbreviated medical history as well as standard demographic variables. Occupational information was elicited by a question on the usual lifetime occupation and was coded by the abbreviated list of the U.S. Bureau of Census Codes. The odds ratios were calculated to evaluate the association between diesel exhaust exposure and risk of lung cancer incidence. Summary odds ratios were computed by the Mantel-Haenszel method after adjusting for potential confounding by age, smoking, and socioeconomic class. Two-sided, 95% confidence intervals were computed by Woolf's method. Occupational exposure to diesel exhaust was defined by two criteria. First, occupational titles were coded "probably high exposure" as defined by the industrial hygiene standards established for the various jobs. The job titles included under this category were warehousemen, bus and truck drivers, railroad workers, and heavy equipment operators and repairmen. The second method used the National Institute for Occupational Safety and Health (NIOSH) criteria to analyze occupations by diesel exposure. In this method, the estimated proportion of exposed workers was computed for each occupational category by using the NIOSH estimates of the exposed population as the numerator and the estimates of individuals employed in each occupational category from the 1970 census as the denominator. Occupations estimated to have at least 20% of their employees exposed to diesel exhaust were defined as "high exposure," those with 10% to 19% of their employees exposed were defined as "moderate exposure," and those with less than 10% of their employees exposed were defined as "low exposure."

Cases and controls were compared with respect to exposure. The relative risk was 2.0 (95% CI = 1.2, 3.2) for those workers who were exposed to diesel exhaust versus those who

1 were not. The risk, however, decreased to a nonsignificant 1.4 when the data were adjusted for
2 smoking. Analysis by NIOSH criteria found a nonsignificant relative risk of 1.7 in the high-
3 exposure group. There were no significantly increased cancer risks by occupation either by the
4 first method or by the NIOSH method. To assess any possible synergism between diesel exhaust
5 exposure and smoking, the lung cancer risks were calculated for different smoking categories.
6 The relative risks were 1.46 among nonsmokers and ex-smokers, 0.82 among current smokers of
7 <20 cigarettes/day, and 1.3 among current smokers of 20+ cigarettes/day, indicating a lack of
8 synergistic effects.

9 The major strength of this study is the availability of a detailed smoking history for all the
10 study subjects. However, this is offset by lack of diesel exhaust exposure measurements, use of a
11 poor surrogate for exposure, and lack of consideration of latency period. Information was
12 collected on only one major lifetime occupation, and it is likely that those workers who had more
13 than one major job may not have reported the occupation with the heaviest diesel exhaust
14 exposures. Furthermore, the exposure categories based on job titles were broad, and thus would
15 have made a true effect of diesel exhaust difficult to detect.

16 17 **7.2.2.2. *Damber and Larsson (1987): Occupation and Male Lung Cancer, a Case-Control*** 18 ***Study in Northern Sweden***

19 A case-control study of lung cancer was conducted in northern Sweden to determine the
20 occupational risk factors that could explain the large geographic variations of lung cancer
21 incidence in that country. The study region comprised the three northernmost counties of
22 Sweden, with a total male population of about 390,000. The rural municipalities, with 15% to
23 20% of the total population, have forestry and agriculture as dominating industries, and the urban
24 areas have a variety of industrial activities (mines, smelters, steel factories, paper mills, and
25 mechanical workshops). All male cases of lung cancer reported to the Swedish Cancer Registry
26 during the 6-year period between 1972 and 1977 who had died before the start of the study were
27 selected. Of 604 eligible cases, 5 did not have microscopic confirmation, and in another 5 the
28 diagnosis was doubtful, but these cases were included nevertheless. Cases were classified as
29 small-cell carcinomas, squamous cell carcinomas, adenocarcinomas, and other types. For each
30 case a dead control was drawn from the National Death Registry matched by sex, year of death,
31 age, and municipality. Deaths in controls classified as lung cancer and suicides were excluded. A
32 living control matched to the case by sex, year of birth, and municipality was also drawn from the
33 National Population Registry. Postal questionnaires were sent to close relatives of cases and dead
34 controls, and to living controls themselves to collect data on occupation, employment, and
35 smoking habits. Replies were received from 589 cases (98%), 582 surrogates of dead controls
36 (96%), and 453 living controls (97%).

1 Occupational data were collected on occupations or employment held for at least 1 year
2 and included type of industry, company name, task, and duration of employment. Supplementary
3 telephone interviews were performed if occupational data were lacking for any period between
4 age 20 and time of diagnosis. Data analysis involved calculation of the odds ratios by the exact
5 method based on the hypergeometric distribution and the use of a linear logistic regression model
6 to adjust for the potential confounding effects of smoking. Separate analyses were performed
7 with dead and living controls, and on the whole there was good agreement between the two
8 control groups. A person who had been active for at least 1 year in a specific occupation was in
9 the analysis assigned to that occupation.

10 Using dead controls, the odds ratios adjusted for smoking were 1.0 (95% CI = 0.7, 1.5)
11 and 2.7 (95% CI = 1.0, 8.1) for professional drivers (≥ 1 year of employment) and underground
12 miners (≥ 1 year of employment), respectively. For 20 or more years of employment in those
13 occupations, the odds ratios adjusted for smoking were 1.2 (95% CI = 0.9, 2.6) and 9.8 (95% CI
14 = 1.5, 414). These were the only two occupations listed with potential diesel exhaust exposure.
15 An excess significant risk was detected for copper smelter workers, plumbers, electricians, and
16 asbestos workers, as well as concrete and asphalt workers. All the odds ratios were calculated by
17 adjusting for age, smoking, and municipality. A comparison with the live controls resulted in the
18 odds ratios being lower than those observed with dead controls, and none were statistically
19 significant in this comparison.

20 This study did not detect any excess risk of lung cancer for professional drivers, who,
21 among all the occupations listed, had the most potential for exposure to motor vehicle exhaust.
22 However, it is not known whether these drivers were exposed exclusively to gasoline exhaust,
23 diesel exhaust, or varying degrees of both. An excess risk was detected for underground miners,
24 but it is not known if this was due to diesel emissions from engines or from radon daughters in
25 poorly ventilated mines. Although a high response rate (98%) was obtained by the postal
26 questionnaires, the use of surrogate respondents is known to lead to misclassification errors that
27 can bias the results in either direction.

28 29 **7.2.2.3. *Lerchen et al. (1987): Lung Cancer and Occupation in New Mexico***

30 This is a population-based case-control study conducted in New Mexico that examined the
31 association between occupation and occurrence of lung cancer in Hispanic and non-Hispanic
32 whites. Cases involved residents of New Mexico, 25 through 84 years of age, and diagnosed
33 between January 1, 1980, and December 31, 1982, with primary lung cancer, excluding
34 bronchioalveolar carcinoma. Cases were ascertained through the New Mexico Tumor Registry,
35 which is a member of the Surveillance Epidemiology and End Results (SEER) Program of the
36 National Cancer Institute. Controls were chosen by randomly selecting residential telephone

1 numbers and, for those over 65 years of age, from the Health Care Financing Administration's
2 roster of Medicare participants. They were frequency-matched to cases for sex, ethnicity, and 10-
3 year age category with a ratio of 1.5 controls per case. The 506 cases (333 males and 173
4 females) and 771 controls (499 males and 272 females) were interviewed, with a nonresponse rate
5 of 11% for cases. Next of kin provided interviews for 50% and 43% of male and female cases,
6 respectively. Among controls, only 2% of the interviews were provided by next of kin for each
7 sex. Data were collected by personal interviews conducted by bilingual interviewers in the
8 participants' homes. A lifetime occupational history and a self-reported history of exposure to
9 specific agents were obtained for each job held for at least 6 months since age 12. Questions
10 were asked about the title of the position, duties performed, location and nature of industry, and
11 time at each job title. A detailed smoking history was also obtained. The variables on
12 occupational exposures were coded according to the Standard Industrial Classification scheme by
13 a single person and reviewed by another. To test the hypothesis about high-risk jobs for lung
14 cancer, the principal investigator created an a priori listing of suspected occupations and
15 industries by a two-step process involving a literature review for implicated industries and
16 occupations. The principal investigator also determined the appropriate Standard Industrial
17 Classification and Standard Occupational Codes associated with job titles. For four
18 agents—*asbestos*, *wood dust*, *diesel exhaust*, and *formaldehyde*—the industries and occupations
19 determined to have exposure were identified, and linking of specific industries and occupations
20 was based on literature review and consultation with local industrial hygienists.

21 The relative odds were calculated for suspect occupations and industries, classifying
22 individuals as ever employed for at least 1 year in an industry or occupation and defining the
23 reference group as those subjects never employed in that particular industry or occupation.
24 Multiple logistic regression models were used to control simultaneously for age, ethnicity, and
25 smoking status. For occupations with potential diesel exhaust exposure, the analysis showed no
26 excess risks for diesel engine mechanics and auto mechanics. Similarly, when analyzed by
27 exposure to specific agents, the odds ratio (OR) adjusted for age, smoking, and ethnicity was not
28 elevated for diesel exhaust fumes (OR = 0.6, 95% CI = 0.2, 1.6). Significantly elevated ORs were
29 found for uranium miners (OR = 2.8), underground miners (OR = 2.4), construction workers, and
30 welders (OR = 4.3). No excess risks were detected for the following industries: shipbuilding,
31 petroleum refining, printing, blast furnace, and steel mills. No excess risks were detected for the
32 following occupations: construction workers, painters, plumbers, paving equipment operators,
33 roofers, engineers and firemen, woodworkers, and shipyard workers. Females were excluded
34 from detailed analysis because none of the Hispanic female controls had been employed in high-
35 risk jobs; among the non-Hispanic white controls, employment in a high-risk job was recorded for

1 at least five controls for only two industries, construction and painting, for which the OR were not
2 significantly elevated. Therefore, the analyses were presented for males only.

3 Among the many strengths of this study are its population-based design, high participation
4 rate, detailed smoking history, and the separate analysis done for two ethnic groups, southwestern
5 Hispanic and non-Hispanic white males. The major limitations pertain to the occupational
6 exposure data. Job titles obtained from occupational histories were used as proxy for exposure
7 status, but these were not validated. Further, for nearly half the cases, next of kin provided
8 occupational histories. The authors acknowledge the above sources of bias but state without
9 substantiation that these biases would not strongly affect their results. They also did not use a job
10 exposure matrix to link occupations to exposures and did not provide details on the method they
11 used to classify individuals as diesel exhaust exposed based on reported occupations. The
12 observed absence of an association for exposure to asbestos, a well-established lung carcinogen,
13 may be explained by the misclassification errors in exposure status or by sample size constraints
14 (not enough power). Likewise, the association for diesel exhaust reported by only 7 cases and 17
15 controls also may have gone undetected because of low power. In conclusion, there is insufficient
16 evidence from this study to confirm or refute an association between lung cancer and diesel
17 exhaust exposure.

18 19 **7.2.2.4. *Garshick et al. (1987): A Case-Control Study of Lung Cancer and Diesel Exhaust*** 20 ***Exposure in Railroad Workers***

21 An earlier pilot study of the mortality of railroad workers by the same investigators
22 (Schenker et al., 1984) found a moderately high risk of lung cancer among workers exposed to
23 diesel exhaust compared with those who were not. On the basis of these findings the investigators
24 conducted a case-control study of lung cancer in the same population. The population base for
25 this case-control study was approximately 650,000 active and retired male U.S. railroad workers
26 with 10 years or more of railroad service who were born in 1900 or later. The U.S. Railroad
27 Retirement Board (RRB), which operates the retirement system, is separate from the Social
28 Security System, and to qualify for the retirement or survivor benefits the workers had to acquire
29 10 years or more of service. Information on deaths that occurred between March 1, 1981, and
30 February 28, 1982, was obtained from the RRB. For 75% of the deceased population, death
31 certificates were obtained from the RRB, and, for the remaining 25%, they were obtained from
32 the appropriate State departments of health. Cause of death was coded according to the eighth
33 revision of the ICD. The cases were selected from deaths with primary lung cancer, which was
34 the underlying cause of death in most cases. Each case was matched to two deceased controls
35 whose dates of birth were within 2.5 years of the date of birth of the case and whose dates of
36 death were within 31 days of the date of death noted in the case. Controls were selected

1 randomly from workers who did not have cancer noted anywhere on their death certificates and
2 who did not die of suicide or of accidental or unknown causes.

3 Each subject's work history was determined from a yearly job report filed by his employer
4 with the RRB from 1959 until death or retirement. The year 1959 was chosen as the effective
5 start of diesel exhaust exposure for this study since by this time 95% of the locomotives in the
6 United States were diesel powered. Investigators acknowledge that because the transition to
7 diesel-powered engines took place in the early 1950s, some workers had additional exposure prior
8 to 1959; however, if a worker had died or retired prior to 1959, he was considered unexposed.
9 Exposure to diesel exhaust was considered to be dichotomous for this study, which was assigned
10 based on an industrial hygiene evaluation of jobs and work areas. Selected jobs with and without
11 regular diesel exhaust exposure were identified by a review of job title and duties. Personal
12 exposure was assessed in 39 job categories representative of workers with and without diesel
13 exhaust exposure. Those jobs for which no personal sampling was done were considered exposed
14 or unexposed on the basis of similarities in job activities and work locations and by degree of
15 contact with diesel equipment. Asbestos exposure was categorized on the basis of jobs held in
16 1959, or on the last job held if the subject retired before 1959. Asbestos exposure in railroads
17 occurred primarily during the steam engine era and was related mostly to the repair of locomotive
18 steam boilers that were insulated with asbestos. Smoking history information was obtained from
19 the next of kin.

20 Death certificates were obtained for approximately 87% of the 15,059 deaths reported by
21 the RRB, from which 1,374 cases of lung cancer were identified. Fifty-five cases of lung cancer
22 were excluded from the study for either incomplete data (20) or refusal by two States to use
23 information on death certificates to contact the next of kin. Successful matching to at least one
24 control with work histories was achieved for 335 (96%) cases ≤ 64 years of age at death and 921
25 (95%) cases ≥ 65 years of age at death. In both age groups, 90% of the cases were matched with
26 two controls. There were 2,385 controls in the study; 98% were matched within ± 31 days of the
27 date of death, whereas the remaining 2% were matched within 100 days. Deaths from diseases of
28 the circulatory system predominated among controls. Among the younger workers,
29 approximately 60% had exposure to diesel exhaust, whereas among older workers, only 47%
30 were exposed to diesel exhaust.

31 Analysis by a regression model, in which years of diesel exhaust exposure were the sum
32 total of the number of years in diesel-exposed jobs, used as a continuous exposure variable,
33 yielded an odds ratio of lung cancer of 1.39 (95% CI = 1.05, 1.83) for >20 years of diesel exhaust
34 exposure in the ≤ 64 years of age group. After adjustment for asbestos exposure and lifetime
35 smoking (pack-years), the odds ratio was 1.41 (95% CI = 1.06, 1.88). Both crude odds ratio and
36 asbestos exposure as well as lifetime smoking-adjusted odds ratio for the ≥ 65 years of age group

1 were not significant. Increasing years of diesel exhaust exposure, categorized as ≥ 20 diesel years
2 and 5 to 19 diesel years, with 0 to 4 years as the referent group, showed significantly increased
3 risk in the ≤ 64 years of age group after adjusting for asbestos exposure and pack-year category of
4 smoking. For individuals who had ≥ 20 years of diesel exhaust exposure, the odds ratio was 1.64
5 (95% CI = 1.18, 2.29), whereas among individuals who had 5 to 19 years of diesel exhaust
6 exposure, the odds ratio was 1.02 (95% CI = 0.72, 1.45). In the ≥ 65 years of age group, only 3%
7 of the workers were exposed to diesel exhaust for more than 20 years. Relative odds for 5 to 19
8 years and ≥ 20 years of diesel exposure were less than 1 ($p > 0.01$) after adjusting for smoking and
9 asbestos exposure.

10 Alternative models to explain past asbestos exposure were tested. These were variables
11 for regular and intermittent exposure groups and an estimate of years of exposure based on
12 estimated years worked prior to 1959. No differences in results were seen. The interactions
13 between diesel exhaust exposure and the three pack-year categories (< 50 , > 50 , and missing pack-
14 years) were explored. The cross-product terms were not significant. A model was also tested
15 that excluded recent diesel exhaust exposure occurring within the 5 years before death and gave
16 an odds ratio of 1.43 (95% CI = 1.06, 1.94), adjusted for cigarette smoking and asbestos
17 exposure, for workers with 15 years of cumulative exposure. For workers with 5 to 14 years of
18 cumulative exposure, the OR were not significant.

19 The many strengths of the study are consideration of confounding factors such as asbestos
20 exposure and smoking; classification of diesel exhaust exposures by job titles and industrial
21 hygiene sampling; exploration of interactions between smoking, asbestos exposure, and diesel
22 exhaust exposure; and good ascertainment (87%) of death certificates from the 15,059 deaths
23 reported by the RRB.

24 The investigators also recognized and reported the following limitations: overestimation
25 of cigarette consumption by surrogate respondents, which may have exaggerated the contribution
26 of smoking to lung cancer risk, and use of the Interstate Commerce Commission (ICC) job
27 classification as a surrogate for exposure, which may have led to misclassification of diesel
28 exhaust exposure jobs with low intensity and intermittent exposure, such as railroad police and
29 bus drivers, as unexposed. These two limitations would result in underestimation of the lung
30 cancer risk. This source of error could have been avoided if diesel exhaust exposures were
31 categorized by a specific dose range associated with a job title that could have been classified as
32 heavy, medium, low, and zero exposure instead of a dichotomous variable. The use of death
33 certificates to identify cases and controls may have resulted in misclassification. Controls may
34 have had undiagnosed primary lung cancer, and lung cancer cases might have been secondary
35 lesions misdiagnosed as primary lung cancer. However, the investigators quote a third National
36 Cancer Survey report in which the death certificates for lung cancer were coded appropriately in

1 95% of the cases. Last, as in all previous studies, there is a lack of data on the contribution of
2 unknown occupational or environmental exposures and passive smoking. Furthermore, the lung
3 cancer cases were selected between 1981 and 1982, a total of 22 years latency, which is probably
4 short. In conclusion, this study provides strong evidence that occupational diesel exhaust
5 emission exposure increases the risk of lung cancer.
6

7 **7.2.2.5. *Benhamou et al. (1988): Occupational Risk Factors of Lung Cancer in a French*** 8 ***Case-Control Study***

9 This is a case-control study of 1,625 histologically confirmed cases of lung cancer and
10 3,091 matched controls, conducted in France between 1976 and 1980. This study was part of an
11 international study to investigate the role of smoking and lung cancer. Each case was matched
12 with one or two controls, whose diseases were not related, to tobacco use, sex, age at diagnosis
13 (± 5 years), hospital of admission, and interviewer. Information was obtained from both cases and
14 controls on place of residence since birth, educational level, smoking, and drinking habits. A
15 complete lifetime occupational history was obtained by asking participants to give their
16 occupations from the most recent to the first. Women were excluded because most of them had
17 listed no occupation. Men who smoked cigars and pipes were excluded because there were very
18 few in this category. Thus, the study was restricted to nonsmokers and cigarette smokers.
19 Cigarette smoking exposure was defined by age at the first cigarette (nonsmokers, ≤ 20 years, or
20 > 20 years), daily consumption of cigarettes (nonsmokers, < 20 cigarettes a day, and ≥ 20 cigarettes
21 a day), and duration of cigarette smoking (nonsmokers, < 35 years, and ≥ 35 years). The data on
22 occupations were coded by a panel of experts according to their own chemical or physical
23 exposure determinations. Occupations were recorded blindly using the International Standard
24 Classification of Occupations. Data on 1,260 cases and 2,084 controls were available for analysis.
25 The remaining 365 cases and 1,007 controls were excluded because they did not satisfy the
26 required smoking status criteria.

27 A matched logistic regression analysis was performed to estimate the effect of each
28 occupational exposure after adjusting for cigarette status. Matched relative risk ratios were
29 calculated for each occupation with the baseline category, which consisted of patients who had
30 never been engaged in that particular occupation. The matched RR ratios, adjusted for cigarette
31 smoking for the major groups of occupations, showed that the risks were significantly higher for
32 production and related workers, transport equipment operators, and laborers (RR = 1.24, 95% CI
33 = 1.04, 1.47). On further analysis of this group, for occupations with potential diesel emission
34 exposure, significant excess risks were found for motor vehicle drivers (RR = 1.42, 95% CI =
35 1.07, 1.89) and transport equipment operators (RR = 1.35, 95% CI = 1.05, 1.75). No interaction
36 with smoking status was found in any of the occupations. The only other significant excess was

1 observed for miners and quarrymen (RR = 2.14, 95% CI = 1.07, 4.31). None of the significant
2 associations showed a dose-response relationship with duration of exposure.

3 This study was designed primarily to investigate the relationship between smoking (not
4 occupations or environmental exposures) and lung cancer. Although an attempt was made to
5 obtain complete occupational histories, the authors did not clarify whether, in the logistic
6 regression analysis, they used the subjects' first occupation, predominant occupation, last
7 occupation, or ever worked in that occupation as the risk factor of interest. The most important
8 limitation of this study is that the occupations were not coded into exposures for different
9 chemical and physical agents, thus precluding the calculation of relative risks for diesel exposure.
10 Using occupations as surrogate measures of diesel exposure, an excess significant risk was
11 obtained for motor vehicle drivers and transport equipment operators, but not for motor
12 mechanics. However, it is not known if subjects in these occupations worked with diesel engines
13 or nondiesel engines.
14

15 **7.2.2.6. Hayes et al. (1989): Lung Cancer in Motor Exhaust-Related Occupations**

16 This study reports the findings from an analysis of pooled data from three lung cancer
17 case-control studies that examine in detail the association between employment in motor exhaust-
18 related (MER) occupations and lung cancer risk adjusted for confounding by smoking and other
19 risk factors. The three studies were carried out by the National Cancer Institute in Florida (1976
20 to 1979), New Jersey (1980 to 1981), and Louisiana (1979 to 1983). These three studies were
21 selected because the combined group would provide a sufficient sample to detect a risk of lung
22 cancer in excess of 50% among workers in MER occupations. The analyses were restricted to
23 males who had given occupational history. The Florida study was hospital based, with cases
24 ascertained through death certificates. Controls were randomly selected from hospital records
25 and death certificates, excluding psychiatric diseases, matched by age and county. The New
26 Jersey study was population based, with cases ascertained through hospital records, cancer
27 registry, and death certificates. Controls were selected from among the pool of New Jersey
28 licensed drivers and death certificates. The Louisiana study was hospital based (it is not specified
29 how the cases were ascertained), and controls were randomly selected from hospital patients,
30 excluding those with lung diseases and tobacco-related cancers.

31 A total of 2,291 cases of male lung cancers and 2,570 controls were eligible, and the data
32 on occupations were collected by next-of-kin interviews for all jobs held for 6 months or more,
33 including the industry, occupation, and number of years employed. The proportion of next-of-kin
34 interviews varied by site from 50% in Louisiana to 85% in Florida. The coding schemes were
35 reviewed to identify MER occupations, which included truck drivers and heavy equipment
36 operators (cranes, bulldozers, and graders); bus drivers, taxi drivers, chauffeurs, and other motor

1 vehicle drivers; and automobile and truck mechanics. Truck drivers were classified as routemen
2 and delivery men and other truck drivers. All jobs were also classified with respect to potential
3 exposure to known and suspected lung carcinogens. OR were calculated by the maximum
4 likelihood method, adjusting for age by birth year, usual amount smoked, and study area. Logistic
5 regression models were used to examine the interrelationship of multiple variables.

6 A statistically significant excess risk was detected for employment of 10 years or more for
7 all MER occupations (except truck drivers) adjusted for birth cohort, usual daily cigarette use,
8 and study area. The odds ratio for lung cancer using data gathered by direct interviews was 1.4
9 (95% CI = 1.1, 2.0), allowing for multiple MER employment, and 2.0 (95% CI = 1.3, 3.0),
10 excluding individuals with multiple MER employment. OR for all MER employment, except
11 truck drivers who were employed for less than 10 years, were 1.3 (95% CI = 1.0, 1.7) and 1.3
12 (95% CI = 0.9, 1.8) including and excluding multiple MER employment, respectively. OR were
13 then derived for specific MER occupations and, to avoid the confounding effects of multiple MER
14 job classifications, analyses were also done excluding subjects with multiple MER job exposures.
15 Truck drivers employed for more than 10 years had an odds ratio of 1.5 (95% CI = 1.1, 1.9). A
16 similar figure was obtained excluding subjects with multiple MER employment. An excess risk
17 was not detected for truck drivers employed less than 10 years. The only other job category that
18 showed a statistically significant excess for lung cancer included taxi drivers and chauffeurs who
19 worked multiple MER jobs for less than 10 years (OR = 2.5, 95% CI = 1.4, 4.8). For the same
20 category, the risk for individuals working in that job for more than 10 years was 1.2 (95% CI =
21 0.5, 2.6). A statistically significant positive trend ($p < 0.05$) with increasing employment of <2
22 years, 2 to 9 years, 10 to 19 years, and 20+ years was observed for truck drivers but not for other
23 MER occupations. A statistically nonsignificant excess risk was also observed for heavy
24 equipment operators, bus drivers, taxi drivers and chauffeurs, and mechanics employed for 10
25 years or more. All of the above-mentioned OR were derived, adjusted for birth cohort, usual
26 daily cigarette use, and State of residence. Exposure to other occupational suspect lung
27 carcinogens did not account for the excess risks detected.

28 Results of this large study provide evidence that workers in MER jobs are at an excess
29 risk of lung cancer that is not explained by their smoking habits or exposures to other lung
30 carcinogens. Because no information on type of engine had been collected, it was not possible to
31 determine if the excess risk was due to exposure to diesel exhaust or gasoline exhaust or a
32 mixture of the two. Among the study's other limitations are a possible bias due to
33 misclassification of jobs reported by the large proportion of next-of-kin interviews. Such a bias
34 would make the effect of diesel exhaust harder to detect due to broad categorization of jobs and
35 the problems in classifying individuals into uniform occupational groups based on the pooled data
36 in the three studies that used different occupational classification schemes.

1 **7.2.2.7. *Steenland et al. (1990): A Case-Control Study of Lung Cancer and Truck Driving in***
2 ***the Teamsters Union***

3 Steenland et al. conducted a case-control study of lung cancer deaths in the Teamsters
4 Union to determine the risk of lung cancer among different occupations. Death certificates were
5 obtained from the Teamsters Union files in the central States for 10,485 (98%) male decedents
6 who had filed claims for pension benefits and who had died in 1982 and 1983. Individuals were
7 required to have 20 years' tenure in the union to be eligible to claim benefits. Cases comprised all
8 deaths (n = 1,288) from lung cancer, coded as ICD 162 or 163 for underlying or contributory
9 cause on the death certificate. The 1,452 controls comprised every sixth death from the entire
10 file, excluding deaths from lung cancer, bladder cancer, and motor vehicle accidents. Detailed
11 information on work history and potential confounders such as smoking, diet, and asbestos
12 exposure was obtained by questionnaire. Seventy-six percent of the interviews were provided by
13 spouses and the remainder by some other next of kin. The response rate was 82% for cases and
14 80% for controls. Using these interview data and the 1980 census occupation and industry codes,
15 subjects were classified either as nonexposed or as having held other jobs with potential diesel
16 exhaust exposure. Data on job categories were missing for 12% of the study subjects. A second
17 work history file was also created based on the Teamsters Union pension application that lists
18 occupation, employer, and dates of employment. A three-digit U.S. census code for occupation
19 and industry was assigned to each job for each individual. This Teamsters Union work history file
20 did not have information on whether men drove diesel or gasoline trucks, and the four principal
21 occupations were long-haul drivers, short-haul or city drivers, truck mechanics, and dockworkers.
22 Subjects were assigned the job category in which they had worked the longest.

23 The case-control analysis was done using unconditional logistic regression. Separate
24 analyses were conducted for work histories from the Teamsters Union pension file and from next-
25 of-kin interviews. Covariate data were obtained from next-of-kin interviews. Analyses were also
26 performed for two time periods: employment after 1959 and employment after 1964. These two
27 cut-off years reflect years of presumed dieselization: 1960 for most trucking companies and 1965
28 for independent driver and nontrucking firms. Data for analysis could be obtained for 994 cases
29 and 1,085 controls using Teamsters Union work history and for 872 cases and 957 controls using
30 next-of-kin work history. When exposure was considered as a dichotomous variable, for both
31 Teamsters Union and next-of-kin work history, no single job category had an elevated risk. From
32 the next-of-kin data, diesel truck drivers had an odds ratio of 1.42 (95% CI = 0.74, 2.47) and
33 diesel truck mechanics had an odds ratio of 1.35 (95% CI = 0.74, 2.47). OR by duration of
34 employment as a categorical variable were then estimated. For the Teamsters Union work history
35 data, when only employment after 1959 was considered, both long-haul ($p < 0.04$) and short-haul
36 drivers (not significant) showed an increase in risk with increased years of exposure. The length-

1 of-employment categories for which the trends were analyzed were 1 to 11 years, 12 to 17 years,
2 and 18 years or more. Using 1964 as the cutoff date, long-haul drivers continued to show a
3 significant positive trend ($p=0.04$), with an odds ratio of 1.64 (95% CI = 1.05, 2.57) for those
4 who worked for 13+ years, the highest category. Short-haul drivers, however, did not show a
5 positive trend when 1964 was used as the cutoff date. Similar trend analysis was done for most
6 next-of-kin data. A marginal increase in risk with increasing duration of employment as a truck
7 driver ($p=0.12$) was observed. For truck drivers who primarily drove diesel trucks for 35 years or
8 longer, the odds ratio for lung cancer was 1.89 (95% CI = 1.04, 3.42). Similarly, the
9 corresponding odds ratio was 1.34 (95% CI = 0.81, 2.22) for both gasoline truck drivers and
10 drivers who drove both types of trucks, and 1.09 (95% CI = 0.44, 2.66) for truck mechanics.

11 No significant interactions between age and diesel exhaust exposure or smoking and diesel
12 exhaust exposure were observed. All the OR were adjusted for age, smoking, and asbestos in
13 addition to various exposure categories.

14 This is a well-designed and analyzed study. The main strengths of the study are the
15 availability of detailed records from the Teamsters Union, a relatively large sample size,
16 availability of smoking data, and measurements of exposures. The authors acknowledge some
17 limitations of this study, which include possible misclassifications of exposure and smoking habits,
18 as information was provided by next of kin; lack of sufficient latency to observe lung cancer
19 excess; and a small nonexposed group ($n = 120$). Also, they could not evaluate the concordance
20 between Teamsters Union and next-of-kin job categories easily because job categories were
21 defined differently in each data set. No data were available on levels of diesel exposure for the
22 different job categories. Despite these limitations, the positive findings of this study, which are
23 probably underestimated, provide a positive evidence toward causal association between diesel
24 exhaust exposure and excess lung cancer.

25 26 **7.2.2.8. Steenland et al. (1998): Diesel Exhaust and Lung Cancer in the Trucking Industry:** 27 ***Exposure-Response Analyses and Risk Assessment***

28 Steenland et al. (1998) conducted an exposure-response analysis by supplementing the
29 data from their earlier case-control study of lung cancer and truck drivers in the Teamsters Union
30 (Steenland et al., 1990) with exposure estimates based on a 1990 industrial hygiene survey of
31 elemental carbon exposure, a surrogate for diesel exhaust in the trucking industry.

32 Study subjects were long-term Teamsters enrolled in the pension system who died during
33 the period 1982-1983. Using death certificate information, the researchers identified 994 cases of
34 lung cancer for the study period, and 1,085 non-lung-cancer deaths served as controls. Subjects
35 were divided into job categories based on the job each held the longest. Most had held only one
36 type of job. The job categories were short-haul driver, long-haul driver, mechanic, dockworker,

1 other jobs with potential diesel exposure, and jobs outside the trucking industry without
2 occupational diesel exposure. Smoking histories were obtained from next of kin. OR were
3 calculated for work in an exposed job category at any time and after 1959 (an estimated date
4 when the majority of heavy-duty trucks had converted to diesel) compared with work in
5 nonexposed jobs. OR were adjusted for age, smoking, and potential asbestos exposure. Trends
6 in effect estimates for duration of work in an exposed job were also calculated.

7 An industrial hygiene survey by Zaebst et al. (1991) of elemental carbon exposures in the
8 trucking industry provided exposure estimates for each job category in 1990. The elemental
9 carbon measurements were generally consistent with the epidemiologic results, in that mechanics
10 were found to have the highest exposures and relative risk, followed by long-haul and then
11 short-haul drivers, although dockworkers had the highest exposures and the lowest relative risks.

12 Past exposures were estimated assuming that they were a function of (1) the number of
13 heavy-duty trucks on the road, (2) the particulate emissions (grams/mile) of diesel engines over
14 time, and (3) leaks from truck exhaust systems for long-haul drivers. Estimates of past exposure
15 to elemental carbon, as a marker for diesel exhaust exposure, for subjects in the case-control
16 study were made by assuming that average 1990 levels for a job category could be assigned to all
17 subjects in that category, and that levels prior to 1990 were directly proportional to vehicle miles
18 traveled by heavy-duty trucks and the estimated emission levels of diesel engines. A 1975
19 exposure level of elemental carbon in terms of micrograms per cubic meter was estimated by the
20 following equation: 1975 level = 1990 level*(vehicle miles 1975/vehicle miles 1990) (emissions
21 1975/emissions 1990). Once estimates of exposure for each year of work history were derived
22 for each subject, analyses were conducted by cumulative level of estimated carbon exposure.

23 Estimates were made for long-haul drivers (n = 1,237), short-haul drivers (n = 297),
24 dockworkers (n = 164), mechanics (n = 88), and those outside the trucking industry (n = 150).
25 Logistic regression was used to estimate OR adjusted for five categories of age, race, smoking
26 (never, former-quitting before 1963, former-quitting in 1963 or later, current-with <1 pack per
27 day, and current-with 1 or more packs per day), diet, and reported asbestos exposure. A variety
28 of models for cumulative exposure were considered, including a log-linear model with cumulative
29 exposure, a model adding a quadratic term for cumulative exposure, a log transform of
30 cumulative exposure, dummy variables for quartile of cumulative exposure, and smoothing splines
31 of cumulative exposure. The estimates of rate ratios from logistic regression for specific levels of
32 exposure to elemental carbon were then used to derive excess risk estimates for lung cancer after
33 lifetime exposure to elemental carbon.

34 The survey found that mechanics had the highest current levels of diesel exhaust
35 exposures and dockworkers who mainly used propane-powered forklifts had the lowest exposure.
36 ORs of 1.69 and 0.93 were observed for the mechanics and dockworkers, respectively. The

1 finding of the highest lung cancer risk for mechanics and lowest for dockworkers is indicative of
2 causal association between the diesel exhaust exposure and development of lung cancer. The log
3 of cumulative exposure was found to be the best-fitting model and was a significant predictor ($p =$
4 0.01). However, the risk among mechanics did not increase with increasing duration of
5 employment.

6 OR for quartile of cumulative exposure show a pattern of significantly increasing trends in
7 risk with increasing exposure, ranging between 1.08 and 1.72, depending on the exposure level
8 and lag structure used. The lifetime excess risk of lung cancer death (through age 75) for a male
9 truck driver was estimated to be in the range of 1.4%-2.3% (95% confidence limits ranged from
10 0.3% to 4.6%) above the background risk, depending on the emissions scenarios assumed. The
11 authors found that current exposures indicated that truck drivers are exposed to diesel exhaust at
12 levels about the same as ambient levels on the highways, which are about double the background
13 levels in urban air. They conclude that the data suggest a positive and significant increase in lung
14 cancer risk with increasing estimated cumulative exposure to diesel exhaust among workers in the
15 trucking industry. They assert that these estimates suggest that the lifetime excess risk for lung
16 cancer is 10 times higher than the OSHA standards, but caution that the results should be viewed
17 as exploratory.

18 The authors acknowledge that the increasing trend in risk with increasing estimates of
19 cumulative exposure is partly due to the fact that a component of cumulative dose is simple
20 duration of exposure, and that analyses by simple duration also exhibit a positive trend with
21 duration. This analysis essentially weights the duration by contrived estimates of exposure
22 intensity, and the authors acknowledge that this weighting depends on very broad assumptions.

23 This is not an analysis of new data that provides independent estimates of relative risk for
24 diesel exhaust and lung cancer incidence. Instead, it is an attempt to convert the data from
25 Steenland's earlier study of lung cancer for the purpose of estimating a different risk metric,
26 "lifetime excess risk of lung cancer," by augmenting these data with limited industrial hygiene data
27 and rationalizations about plausible models for cumulative exposure.

28 The Health Effects Institute (HEI, 1999) and others have raised some questions about the
29 exposure estimations and control for confounding variables. EPA and NIOSH will address these
30 concerns in the year 2000. It should be noted that these concerns are about the use of these data
31 for quantitative risk assessment. As far as qualitative risk assessment is concerned, this study is
32 still considered to be positive and strong.
33

1 **7.2.2.9. *Boffetta et al. (1990): Case-Control Study on Occupational Exposure to Diesel***
2 ***Exhaust and Lung Cancer Risk***

3 This is an ongoing (since 1969) case-control study of tobacco-related diseases in 18
4 hospitals (six U.S. cities). Cases comprise 2,584 males with histologically confirmed primary lung
5 cancers. Sixty-nine cases were matched to 1 control, whereas 2,515 were matched to 2 controls.
6 Controls were individuals who were diagnosed with non-tobacco-related diseases. The matching
7 was done for sex, age (± 2 years), hospital, and year of interview. The interviews were conducted
8 at the hospitals at the time of diagnosis. In 1985, the occupational section of the questionnaire
9 was modified to include the usual occupation and up to five other jobs as well as duration (in
10 years) worked in those jobs. After 1985, information was also obtained on exposure to 45 groups
11 of chemicals, including diesel exhaust at the workplace or during hobby activities. A priori
12 aggregation of occupations was categorized into low probability of diesel exhaust exposure
13 (reference group), possible exposure (19 occupations), and probable exposure (13 occupations).
14 Analysis was conducted based on “usual occupation” on all study subjects, and any occupation
15 with sufficient cases was eligible for further analysis. In addition, cases enrolled after 1985 for
16 which there were self-reported diesel exhaust exposure and detailed work histories were also
17 analyzed separately.

18 Both matched and unmatched analyses were done by calculating the adjusted (for smoking
19 and education) relative odds using the Mantel-Haenzel method and calculating the test-based
20 95% confidence interval using the Miettinen method. Unconditional logistic regression was used
21 to adjust for potential confounders (the PROC LOGIST of SAS). Linear trends for risk were also
22 tested according to Mantel.

23 Adjusted relative odds for possible and probable exposure groups as well as the truck
24 drivers were slightly below unity, none being statistically significant for the entire study
25 population. Although slight excesses were observed for the self-reported diesel exhaust exposure
26 group and the subset of post-1985 enrollees for highest duration of exposure (for self-reported
27 exposure, occupations with probable exposure, and truck drivers), none was statistically
28 significant. Trend tests for the risk of lung cancer among self-reported diesel exhaust exposure,
29 probable exposure, and truck drivers with increasing exposure (duration of exposure used as
30 surrogate for increasing dose) were nonsignificant too. Statistically significant lung cancer
31 excesses were observed for cigarette smoking only.

32 The major strength of this study is availability of detailed smoking history. Even though
33 detailed information was obtained for the usual and five other occupations (1985), because it was
34 difficult to estimate or verify the actual exposure to diesel exhaust, duration of employment was
35 used as a surrogate for dose instead. The numbers of cases and controls were large; however, the
36 number of individuals exposed to diesel exhaust was relatively few, thus reducing the power of

1 the study. This study did not attempt latency analysis either. Due to these limitations, the
2 findings of this study are unable to provide either positive or negative evidence for a causal
3 association between diesel exhaust and occurrence of lung cancer.
4

5 **7.2.2.10. Emmelin et al. (1993): Diesel Exhaust Exposure and Smoking: A Case-Referent**
6 **Study of Lung Cancer Among Swedish Dock Workers**

7 This case-control study of lung cancer was drawn from a cohort defined as all male
8 workers who had been employed as dockworkers for at least 6 months between 1950 and 1974.
9 In the population of 6,573 from 20 ports, there were 90 lung cancer deaths (cases), identified
10 through Swedish death and cancer registers, during the period 1960 to 1982. Of these 90 deaths,
11 the 54 who were workers at the 15 ports for which exposure surrogate information was available
12 were chosen for the case-control study. Four controls, matched on port and age, were chosen for
13 each case from the remaining cohort who had survived to the time of diagnosis of the case. Both
14 live and deceased controls were included. The final analyses were done on 50 cases and 154
15 controls who had complete information on employment dates and smoking data. The smoking
16 strata were created by classifying ex-smokers as nonsmokers if they had not smoked for at least 5
17 years prior to the date of diagnosis of the case; otherwise they were classified as smokers.

18 Relative odds and regression coefficients were calculated using conditional logistic
19 regression models. Comparisons were made both with and without smoking included as a
20 variable, and the possible interaction between smoking and diesel exhaust was tested. Both the
21 weighted linear regressions of the adjusted relative odds and the regression coefficients were used
22 to test mortality trends with all three exposure variables.

23 Exposure to diesel exhaust was assessed indirectly by initially measuring (1) exposure
24 intensity based on exhaust emission, (2) characteristics of the environment in terms of ventilation,
25 and (3) measures of proportion of time in higher exposed jobs. For exhaust emissions, annual
26 diesel fuel consumption at a port was used as the surrogate. For ventilation, the annual
27 proportion of ships with closed or semiclosed holds was used as the surrogate. The proportion of
28 time spent below decks was used as the surrogate for more exposed jobs. Although data were
29 collected for all three measures, only the annual fuel consumption was used for analysis. Because
30 every man was likely to rotate through the various jobs, the authors thought using annual
31 consumption of diesel fuel was the appropriate measure of exposure. Consequently, in a second
32 analysis, the annual fuel consumption was divided by the number of employees in the same port
33 that year to come up with the fuel-per-person measure, which was further used to create a second
34 measure, “exposed time.” The “annual fuel” and exposed-time data were entered in a calendar
35 time-exposure matrix for each port, from which individual exposure measures were created. A
36 third measure, “machine time” (years of employment from first exposure), was also used to

1 compare the results with other studies. All exposure measures were accumulated from the first
2 year of employment or first year of diesel machine use, whichever came later. The last year of
3 exposure was fixed at 1979. All exposures up to 2 years before the date of lung cancer diagnosis
4 were omitted from both cases and matched controls. A priori classification into three categories
5 of low, medium, and high exposure was done for all three exposure variables: machine time, fuel,
6 and exposed time.

7 Conditional logistic regression models, adjusting for smoking status and using low
8 exposures and/or nonsmokers as a comparison group, yielded positive trends for all exposure
9 measures, but no trend test results were reported, and only the relative odds for the exposed-time
10 exposure measure in the high-exposure group (OR = 6.8, 90% CI = 1.3 to 34.9) was reported as
11 statistically significant. For smokers, adjusting for diesel exhaust exposure level, the relative odds
12 were statistically significant and about equal for all three exposure variables: machine time, OR =
13 5.7 (90% CI = 2.4 to 13.3); fuel, OR = 5.5 (90% CI = 2.4 to 12.7); and exposed time, OR = 6.2
14 (90% CI = 2.6 to 14.6). Interaction between diesel exhaust and smoking was tested by
15 conditional logistic regression in the exposed-time variable. Although there were positive trends
16 for both smokers and nonsmokers, the trend for smokers was much steeper: low, OR = 3.7 (90%
17 CI = 0.9 to 14.6); medium, OR = 10.7 (90% CI = 1.5 to 78.4); and high, OR = 28.9 (90% CI =
18 3.5 to 240), indicating more than additive interaction between these two variables.

19 In the weighted linear regression model with the exposed-time variable, the results were
20 similar to those using the logistic regression model. The authors also explored the smoking
21 variable further in various analyses, some of which suggested a strong interaction between diesel
22 exhaust and smoking. However, with just six nonsmokers and no further categorization of
23 smoking amount or duration, these results are of limited value.

24 The diesel exhaust exposure matrices created using three different variables are intricate.
25 Analyses by any of these variables yield essentially the same positive results and positive trends,
26 providing consistent support for a real effect of diesel exhaust exposure, at least in smokers.
27 However, methodological limitations to this study prevent a more definitive conclusion. The
28 numbers of cases and controls are small. There are very few nonsmokers; thus, testing the effects
29 of diesel exhaust exposure in them is futile. Lack of information on asbestos exposure, to which
30 dockworkers are usually exposed, may also confound the results. Also, no latency analyses are
31 presented. Overall, despite these limitations, this study supports the earlier findings of excess lung
32 cancer mortality among individuals exposed to diesel exhaust.
33

1 **7.2.2.11. Swanson et al. (1993): Diversity in the Association Between Occupation and Lung**
2 **Cancer Among Black and White Men**

3 This population-based case-control study of lung cancer was conducted in metropolitan
4 Detroit. The cases and controls for this study were identified from the Occupational Cancer
5 Incidence Surveillance Study (OCISS). A total of 3,792 incident lung cancer cases and 1,966
6 colon and rectal cancer cases used as controls, diagnosed between 1984 and 1987 among white
7 and black males aged 40 to 84 years, were selected for the study. Information was obtained by
8 telephone interview either with the individual or a surrogate about lifetime work history and
9 smoking history, as well as medical, demographic, and residential history. Occupation and
10 industry data were coded using the 1980 U.S. Census Bureau classification codes. The
11 investigators selected certain occupations and industries as having little or no exposure to
12 carcinogens and defined them as an unexposed group. Analysis was done using logistic
13 regression method and adjusting for age at diagnosis, pack-years of cigarette smoking, and race.

14 The results were presented by various occupations and industries; those with potential
15 exposures to diesel exhaust were drivers of heavy trucks and light trucks, farmers, and railroad
16 workers, respectively. Among white males, increasing lung cancer risks were observed with
17 increasing duration of employment for drivers of heavy trucks, drivers of light trucks, and
18 farmers. Although none of the individual ORs were statistically significant, trend tests were
19 significant for all three occupations ($p \leq 0.5$). On the other hand, among black males increasing
20 lung cancer risks with increasing duration of employment were observed for farmers only, with an
21 OR of 10.4 (95% CI = 1.4, 77.1) reaching significance for employment of 20+ years. As for the
22 railroad industry, increasing lung cancer risks with increasing duration of employment were
23 observed for both white and black males. The trend test was significant for white males only,
24 with an OR of 2.4 (95% CI = 1.1, 5.1) reaching significance for employment of 10+ years.

25 The main strengths of the study are large sample size, availability of lifetime work history
26 and smoking history, and the population-based study format, precluding selection bias. The major
27 limitation, as in other studies, is lack of direct information on specific exposures. The interesting
28 result of this study is lung cancer excesses observed in farmers, mainly among crop farmers, who
29 have potential exposure to diesel exhaust from their tractors in addition to pesticides, herbicides,
30 and other PM₁₀. The authors point out that this is the first study to find excess lung cancer in this
31 occupation.

1 **7.2.2.12. Hansen et al. (1998): Increased Risk of Lung Cancer Among Different Types of**
2 **Professional Drivers in Denmark**

3 This is a population-based case-control study of lung cancer, conducted in professional
4 drivers in Denmark. The cases first diagnosed as primary lung cancer between 1970 and 1989
5 among males born between 1897 and 1966 were identified from the Danish Cancer Registry. The
6 registry provided the information on diagnosis from ICD-7, name, sex, and unique personal
7 identification number (PIDN). Information about past employment was obtained by linkage with
8 the nationwide pension fund. The fund keeps the records by name and PIDN about the date of
9 start and end of each job and unique company number of the employer. The records are kept
10 even after the employee has retired or died. Information about current employment was obtained
11 from the Danish Central Population Registry (CPR) by linkage with the PIDN.

12 Of 37,597 cases identified from the Registry, 8,853 did not have any employment records.
13 Controls (1:1) for 28,744 lung cancer cases with employment histories were selected randomly
14 from CPR, matched with the case by year of birth and sex. Furthermore, these controls had to be
15 alive, cancer free, and employed prior to the diagnosis of lung cancer in the corresponding case.
16 Employment histories were obtained for the controls in the same fashion as cases from the
17 pension fund. The employment record search resulted in a total of 1,640 lorry/bus drivers and
18 426 taxi drivers. They were further divided into subgroups by their duration of employment.
19 Information about smoking in drivers was acquired from two national surveys conducted in 1970-
20 72 and 1983. No direct information on smoking was available in either cases or controls. A
21 separate case-control study of mesothelioma indirectly looked at asbestos exposure among
22 professional drivers. OR, adjusting for socioeconomic status and 95% CI, were computed using
23 conditional logistic regression (PECAN procedure in the statistical package EPICURE).

24 Significant ORs for lung cancer were found for lorry/bus drivers (OR = 1.31, 95% CI =
25 1.17, 1.46), taxi drivers (OR = 1.64, 95% CI = 1.22, 2.19), and unspecified drivers (OR = 1.39,
26 95% CI = 1.30, 1.51). Significant ORs were found for both lorry/bus drivers and taxi drivers by
27 duration of employment in 1-5 years and >5 years categories, with no lag time and with a 10- year
28 lag time. The OR remained the same for lorry/bus drivers in these employment categories for no
29 lag time and 10-year lag time. Among taxi drivers, on the other hand, the OR of 2.2 in >5 year
30 employment in no-lag-time analysis increased to 3.0 in the 10-year lag time analysis. The authors
31 asserted that the higher risk seen in the taxi drivers may be due to higher exposure attributable
32 due to longer time spent in traffic congestion. The trend tests for increasing risk with increasing
33 duration of employment (surrogate for exposure) were statistically significant ($p < 0.001$) for both
34 lorry/bus drivers and taxi drivers in no-lag-time and 10-year lag time analysis. All the ORs were
35 adjusted for socioeconomic status.

1 The main strengths of the study are the large sample size, availability of information on
2 socioeconomic status, and detailed employment records. The main limitation, however, is lack of
3 information on what type of fuel these vehicles used. It is probably safe to assume that the
4 lorry/buses were diesel powered, whereas the taxis could be either diesel or gasoline powered. A
5 personal communication with Dr. Johnni Hansen confirmed that lorries, buses, and taxis have
6 been using diesel fuel since the beginning of the 1960s. Although direct adjustments were not
7 done for smoking and exposure to asbestos, indirect information on both these confounders
8 indicates that they are unlikely to explain the observed excesses and the increasing risk with
9 increasing duration of employment. Thus, the results of this study are strongly supportive of
10 diesel exhaust being associated with increased lung cancer.

11
12 **7.2.2.13. *Brüske-Hohlfeld et al. (1999): Lung Cancer Risk in Male Workers Occupationally***
13 ***Exposed to Diesel Motor Emissions in Germany***

14 This paper presents a pooled analysis of two case-control studies of lung cancer. The first
15 study, by Jöckel et al. (1995, 1998), was conducted between 1988 and 1993 and had 1,004 cases
16 and 1,004 controls matched for sex, age, and region of residence, selected randomly from the
17 compulsory municipal registries. The inclusion criteria for cases were: they should have been
18 born in or after 1913, should have been of German nationality, and should have been diagnosed
19 with lung cancer within 3 months prior to the interview. The second study, by Wichmann et al.
20 (1998), was ongoing when it was included in this study. The study span covered the years 1990
21 to 1996. By 1994 a total of 3,180 cases and 3,249 controls, randomly selected from the
22 compulsory population registries, were frequency matched on sex, age, and region. The cases
23 were less than 76 years old, were residents of the region and living in Germany for more than 25
24 years, and had a diagnosis not more than 3 months old. Of 4,184 pooled cases and 4,253 pooled
25 controls, the analysis was conducted on 3,498 male cases and 3,541 male controls. A personal
26 interview was conducted with each study participant. Data were collected on basic demographic
27 information, detailed smoking history, and lifelong occupational history about jobs held and
28 industries worked in. The job titles and industries were classified into 33 and 21 categories,
29 respectively, using the German Statistical Office codes.

30 Based on job codes with potential exposure to diesel motor emission (DME), four
31 exposure groups were constituted. Group A comprised professional drivers of trucks, buses,
32 taxis, etc. Group B comprised other traffic-related jobs such as switchmen, diesel locomotive
33 drivers, and diesel forklift truck drivers. Group C comprised bulldozer operators, graders, and
34 excavators. Group D comprised full-time farm tractor drivers. Validation of the jobs was done
35 by written evaluation of the job task descriptions, which also avoided misclassification. The
36 following information was acquired for the construction of job task descriptions: (1) What were

1 your usual tasks at work and how often (in % of daily working hours) were they performed? (2)
2 What did you produce, manufacture, or transport? (3) Which material was used? (4) What kind
3 of machine did you operate? Some individuals had more than one job task with DME exposure.
4 The exposure assessment was done without knowing the status of the case/control.

5 For each individual, cumulative exposure was calculated for the complete work history by
6 categorizing the duration of exposure as >0-3, >3-10, >10-20, >20-30, >30 years, and beginning
7 and end of exposure. The first year of exposure was defined as ≤ 1945 , 1946-1955, and ≥ 1956
8 while the last year of exposure was defined as ≤ 1965 , 1966-1975, and ≥ 1976 . For professional
9 drivers, hours driven per day were accumulated and were classified as “driving hours.”

10 A smoker was defined as any individual who had smoked regularly for at least 6 months.
11 Smoking information was acquired in series with the starting time, type of tobacco, amount
12 smoked, duration in years, and calendar year of quitting. Asbestos exposure was estimated by
13 certain job-specific supplementary questions.

14 The cases and controls were post-hoc stratified into 6 age and 17 region categories. OR
15 adjusted for smoking and asbestos exposure were calculated by conditional logistic regression,
16 using “never exposed” workers as the reference group. The adjustment for cigarette smoking was
17 done by using pack-years as a continuous variable; adjustment for other tobacco products was
18 done by considering them as a binary variable. A total of 716 cases and 430 controls were found
19 to be ever exposed to DME. The smoking- and asbestos-adjusted OR of 1.43 (95% CI = 1.23,
20 1.67) for all DME exposed was reduced from the crude OR of 1.91. For the entire group the
21 various analyses yielded statistically significant ORs ranging from 1.25 to 2.31, adjusted for
22 smoking and asbestos exposure (West Germany, >10-20 years and >20-30 years of exposure, first
23 year of exposure in 1946-1955 and 1956+, end of exposure in 1966-1975 and 1976+, and for the
24 job categories of Group A, B, and C). The risk increased with increasing years of exposure, and
25 for both the first year of exposure (≤ 1945 , 1946-1955, and ≥ 1956) and end year of exposure
26 (≤ 1965 , 1966-1975, and ≥ 1976).

27 Separate analyses by four job categories (all the ORs were adjusted for smoking and
28 asbestos exposure) showed that for professional drivers (Group A) the overall OR was 1.25 (95%
29 CI = 1.05, 1.47). Significant ORs were found for various factors in West Germany only. The
30 factors were: >0-3 years and >10-20 years of exposure (OR = 1.69, 95% CI = 1.13, 2.53, and
31 OR = 2.02, 95% CI = 1.32, 3.08, respectively), beginning of exposure in 1956+ and end of
32 exposure in 1976+ (OR = 1.56, 95% CI = 1.21, 2.03, and OR = 1.5, 95% CI = 1.14, 1.98,
33 respectively), and 1,000-49,999 driving hours (OR = 1.54, 95% CI = 1.15, 2.07). None of the
34 ORs were significant in East Germany in this group.

35 For other traffic-related jobs (Group B) the overall OR was 1.53 (95% CI = 1.04, 2.24).
36 The ORs for beginning of exposure in 1956+ and end of exposure in 1976+ were OR = 1.71, 95%

1 CI = 1.05, 2.78, and OR = 2.68, 95% CI = 1.47, 4.90, respectively. The risk increased with
2 increasing duration of exposure and was statistically significant for >10-20 years (OR = 2.49) and
3 more than 20 years (OR = 2.88). No separate analyses for West Germany and East Germany
4 were presented in this category.

5 For heavy equipment operators (Group C) the overall OR of 2.31 (95% CI = 1.44, 3.7)
6 was highest among all the job categories. Significant ORs were observed for beginning exposure
7 in 1946-1955 (OR = 2.83, 95% CI = 1.10, 7.23) and end exposure in 1966-1975 (OR = 3.74,
8 95% CI = 1.20, 11.64). The risk increased with increasing duration of exposure and was
9 statistically significant for more than 20 years of exposure (OR = 4.3). Although no separate
10 analyses for West Germany and East Germany were presented, investigators mentioned that for
11 this job group hardly any difference was seen between West Germany and East Germany.

12 For drivers of the farming tractors (Group D) the overall OR of 1.29 was not significant.
13 Risk increased with increasing duration of exposure and was significant for exposure of more than
14 30 years (OR = 6.81, 95% CI = 1.17, 39.51). No separate analyses for West Germany and East
15 Germany were presented in this category.

16 The professional drivers and the other traffic-related job categories probably have mixed
17 exposures to gasoline exhaust in general traffic. On the other hand, it should be noted that
18 exposure to DME among heavy equipment and farm tractor drivers is much higher and not as
19 mixed as in professional drivers. The heavy equipment drivers usually drive repeatedly through
20 their own equipment's exhaust. Therefore, the observed highest risk for lung cancer in this job
21 category establishes a direct link with the DME. The only other study that found significantly
22 higher risk for heavy equipment operators (RR = 2.6) was conducted by Boffeta et al. (1988).
23 Although the only significant excess was observed for farming tractor operators among
24 individuals with more than 30 years of exposure, a steady increase in risk was observed for this
25 job category with increasing exposure. The investigators stated that the working conditions and
26 the DME of tractors remained fairly constant over the years. This increase may be due mainly to
27 exposure to DME and, in addition, PM₁₀.

28 This is a well-designed, well-conducted, and well-analyzed study. Its main strengths are
29 large sample size, resulting in good statistical power; inclusion of incident cases that were
30 diagnosed not more than 3 months prior to the interview; use of only personal interviews,
31 reducing recall bias; diagnosis ascertained by cytology or histology; and availability of lifelong
32 detailed occupational and smoking history. Exposure estimation for each individual was based on
33 job codes and industry codes, which were validated by written job descriptions to avoid
34 misclassification. The main limitation of the study is lack of data on actual exposure to DME.
35 The cumulative quantitative exposures were calculated based on time spent in each job with
36 potential exposure to DME and the type of equipment used. Thus, this study provides strong

1 evidence for a causal association between exposure to diesel exhaust and occurrence of lung
2 cancer.

3 Table 7-2 summarizes the above lung cancer case-control studies.
4

5 **7.2.3. Summaries of Studies and Meta-Analyses of Lung Cancer**

6 **7.2.3.1. *Cohen and Higgins (1995): Health Effects of Diesel Exhaust: Epidemiology***

7 The Health Effects Institute (HEI) reviewed all published epidemiologic studies on the
8 health effects of exposure to diesel exhaust available through June 1993, identified by a
9 MEDLINE search and by reviewing the reference sections of published research and earlier
10 reviews. HEI identified 35 reports of epidemiologic studies (16 cohort and 19 case-control) of
11 the relation of occupational exposure to diesel emissions and lung cancer published between 1957
12 and 1993.

13 HEI reviewed the 35 reports for epidemiologic evidence of health effects of exposure to
14 diesel exhaust for lung cancer, other cancers, and nonmalignant respiratory disease. They found
15 that the data were strongest for lung cancer. The evidence suggested that occupational exposure
16 to diesel exhaust from diverse sources increases the rate of lung cancer by 20% to 40% in
17 exposed workers generally, and to a greater extent among workers with prolonged exposure.
18 They also found that the results are not explicable by confounding caused by cigarette smoking or
19 other known sources of bias.

20 Control for smoking was identified in 15 studies. Six studies (17%) reported relative risk
21 estimates less than 1; 29 studies (83%) reported at least relative risk indicating positive
22 association. Twelve studies indicating a relative risk greater than 1 had 95% confidence intervals,
23 which excluded unity.

24 The authors conclude that epidemiologic data consistently show weak associations
25 between exposure to diesel exhaust and lung cancer. They find that the evidence suggests that
26 long-term exposure to diesel exhaust in a variety of occupational circumstances is associated with
27 a 1.2- to 1.5-fold increase in the relative risk of lung cancer compared with workers classified as
28 unexposed. Most of the studies that controlled for smoking found that the association between
29 increased risk of lung cancer and exposure to diesel exhaust persisted after such controls were
30 applied, although in some cases the excess risk was lower. None of the studies measured
31 exposure to diesel emissions or characterized the actual emissions from the source of exposure for
32 the time period most relevant to the development of lung cancer. Most investigators classified
33 exposure on the basis of work histories reported by subjects or their next of kin, or by retirement
34 records. Although these data provide relative rankings of exposure, the absence of concurrent
35 exposure information is the key factor that limits interpretation of the epidemiologic findings and
36 subsequently their utility in making quantitative estimates of cancer risks.

1 This is a comprehensive and thorough narrative review of studies of the health effects of
2 diesel exhaust. It does not undertake formal estimation of summary measures of effect or
3 evaluation of heterogeneity in the results. The conclusion drawn about the consistency of the
4 results is based on the author's assessment of the failure of potential biases and alternative
5 explanations for the increase in risk to account for the observed consistency. In many if not most
6 studies, the quality of the data used to control confounding was relatively crude. Although the
7 studies do include qualitative assessment of whether control for smoking is taken into account,
8 careful scrutiny of the quality of the control or adjustment for smoking among the studies is
9 absent. This leaves open the possibility that prevalent residual confounding by inadequate control
10 for smoking in many or most studies may account for the consistent associations seen.

11 12 **7.2.3.2. Bhatia et al. (1998): Diesel Exhaust Exposure and Lung Cancer**

13 Bhatia et al. (1998) report a meta-analysis of 29 published¹ cohort and case-control
14 studies of the relation between occupational exposure to diesel exhaust and lung cancer. A search
15 of the epidemiologic literature was conducted for all studies concerning lung cancer and diesel
16 exhaust exposure. Occupational studies involving mining were excluded because of concern
17 about the possible influence of radon and silica exposures. Studies in which the minimum interval
18 from time of first exposure to end of follow-up was less than 10 years, and studies in which work
19 with diesel equipment or engines could not be confirmed or reliably inferred, were excluded.
20 When studies presented risk estimates for more than one specific occupational category of diesel
21 exhaust-exposed workers, the subgroup risk estimates were used in the meta-analysis.
22 Smoking-adjusted effect measures were used when present.

23 Of 29 studies 23 met the criteria for inclusion in the meta-analysis. The observed relative
24 risk estimates were greater than 1 in 21 of these studies; this result is unlikely to be due to chance.
25 The pooled relative risk weighted by study precision was 1.33 (95% CI = 1.24, 1.44), indicating
26 increased relative risk for lung cancer from occupational exposure to diesel exhaust. Subanalyses
27 by study design (case-control and cohort studies) and by control for smoking produced results
28 that did not differ from those of the overall pooled analysis. Cohort studies using internal
29 comparisons showed higher relative risks than those using external comparisons. (See Figure 7-
30 1.)

31 Bhatia and colleagues conclude that the analysis shows a small but consistent increase in
32 the risk for lung cancer among workers with exposure to diesel exhaust. The authors evaluate the
33 dependence of the relative risk estimate on the presence of control for smoking among studies,

¹Of 35 studies identified in the literature search, 6 pairs of studies represented analyses of the same study population, reducing the number of studies to 29.

1 and provide a table that allows assessment of whether the quality of the data contributing to
2 control for smoking is related to the relative risk estimates (albeit in a limited number of studies).
3 Bhatia et al. assert that residual confounding is not affecting the summary estimates or
4 conclusions for the following reasons: (1) the pooled relative risks for studies adjusted for
5 smoking were the same as those for studies not adjusting for smoking; (2) in those studies giving
6 risk estimates adjusted for smoking and risk estimates not adjusted for smoking, there was only a
7 small reduction in the pooled relative risk from diesel exhaust exposure; and (3) in studies with
8 internal comparison populations, in which confounding is less likely, the pooled relative risk
9 estimate was 1.43.

10 The validity of this assessment depends on the adequacy of control for smoking in the
11 individual studies. If inadequate adjustment for smoking is employed and residual confounding by
12 cigarette smoking pertains in the result of the individual studies, then the comparisons and
13 contrasts of the pooled estimates the authors cite as reasons for dismissing the effect of residual
14 confounding by smoking will remain contaminated by residual confounding in the individual
15 studies. In fact, Bhatia et al. erroneously identify the treatment of the smoking data in the main
16 analysis for the 1987 report by Garshick et al. as a continuous variable representing pack-years of
17 smoking, whereas the analysis actually dichotomized the pack-years data into two crude dose
18 categories (above and below the 50 pack-years level). This clearly reduced the quality of the
19 adjustment for smoking, which already suffered from the fact that information on cumulative
20 cigarette consumption was missing for more than 20% of the lung cancer cases. In this instance,
21 the consistency between the adjusted and unadjusted estimates of the relative risk for diesel
22 exhaust exposure may be attributable to failure of adjustment rather than lack of confounding by
23 cigarette smoking, and pooled estimates of association of diesel exhaust with lung cancer derived
24 in the meta-analysis would remain confounded. A similar problem exists for the Bhatia et al.
25 representation of the control for confounding in the study by Boffetta and Stellman (1988). Such
26 mischaracterizations may indicate an overstatement by Bhatia et al. that the association of DE and
27 lung cancer is insensitive to adjustment.

28 An evaluation of the potential for publication bias is presented that provides reassurance
29 that the magnitude of published effects is not a function of the precision or study power; however,
30 this assessment cannot rule out the possibility of publication bias.

31
32 **7.2.3.3. *Lipsett and Campleman (1999): Occupational Exposure to Diesel Exhaust and Lung***
33 ***Cancer: A Meta-Analysis***

34 Lipsett and Campleman (1999) conducted electronic searches to identify epidemiologic
35 studies published between 1975 and 1995 of the relationship of occupational exposure to diesel
36 exhaust and lung cancer. Studies were selected based on the following criteria: (1) Estimates of

1 relative risks and their standard errors must be reported or derivable from the information
2 presented. (2) Studies must have allowed for a latency period of 10 or more years for
3 development of lung cancer after onset of exposure. (3) No obvious bias resulted from
4 incomplete case ascertainment in follow-up studies. (4) Studies must be independent: that is, a
5 single representative study selected from any set of multiple analyses of data from the same
6 population. Studies focusing on occupations involving mining were excluded because of potential
7 confounding by radon, arsenic, and silica, as well as possible interactions between cigarette
8 smoking and exposure to these substances in lung cancer induction.

9 Thirty of the 47 studies initially identified as relevant met the specified inclusion criteria.
10 Several risk estimates were extracted from six studies reporting results from multiple mutually
11 exclusive diesel-related occupational subgroups. If a study reported effects associated with
12 several levels or durations of exposure, the effect reported for the highest level or longest
13 duration of exposure was used. If estimates for several occupational subsets were reported, the
14 most diesel-specific occupation or exposure was selected. Adjusted risk estimates were used
15 when available.

16 Thirty-nine independent estimates of relative risk and standard errors were extracted.
17 Pooled estimates of relative risk were calculated using a random-effects model. Among study
18 populations most likely to have had substantial exposure to diesel exhaust, the pooled smoking-
19 adjusted relative risk was 1.47 (95% CI = 1.29, 1.67). (See Figure 7-2.)

20 The between-study variance of the relative risks indicated the presence of significant
21 heterogeneity in the individual estimates. The authors evaluated the potential sources of
22 heterogeneity by subset analysis and linear meta-regressions. Major sources of heterogeneity
23 included control for confounding by smoking, selection bias (a healthy worker effect), and
24 exposure patterns characteristic of different occupational categories. A modestly higher, pooled
25 relative risk was derived for the subset of case-control studies, which, unlike the cohort studies,
26 showed little evidence of heterogeneity.

27 An evaluation of the potential for publication bias is presented that provides reassurance
28 that the magnitude of published effects is not a function of the precision or study power; however,
29 this assessment cannot rule out the possibility of publication bias.

30 Although a relatively technical approach was used in deriving summary estimates of
31 relative risk and the evaluation of possible sources of variation in the relative risks in this meta-
32 analysis, this approach should not be confused with rigorous evaluation of the potential
33 weaknesses among the studies included in the analysis. The heterogeneity attributable to
34 statistical adjustment for smoking was evaluated on the basis of a dichotomous assessment of
35 whether control for smoking could be identified in the studies considered. This does not reflect
36 the adequacy of the adjustment for smoking employed in the individual studies considered. The

1 potential for residual confounding by inadequate adjustment for the influence of smoking remains
2 in the summary estimate of the relative risk.

3 4 **7.2.4. Summary and Discussion**

5 Certain extracts of diesel exhaust have been demonstrated as both mutagenic and
6 carcinogenic in animals and in humans. Animal data suggest that diesel exhaust is a pulmonary
7 carcinogen among rodents exposed by inhalation to high doses over long periods of time. While
8 rat lung cancer response to diesel exhaust is not suitable for dose-response extrapolation to
9 humans, the positive lung cancer response doses imply a hazard for humans. Because large
10 working populations are currently exposed to diesel exhaust and because nonoccupational
11 ambient exposures currently are of concern as well, the possibility that exposure to this complex
12 mixture may be carcinogenic to humans has become an important public health issue.

13 Because diesel emissions become diluted in the ambient air, it is difficult to study the
14 health effects in the general population. Nonoccupational exposure to diesel exhaust is worldwide
15 in urban areas. Thus, “unexposed” reference populations used in occupational cohort studies are
16 likely to contain a substantial number of individuals who are nonoccupationally exposed to diesel
17 exhaust. Furthermore, the “exposed” group in these studies is based on job titles, which in most
18 instances are not verified or correlated with environmental hygiene measurement. The issue of
19 health effect measurement is further complicated by the fact that occupational cohorts tend to be
20 healthy and have below-average mortality, usually referred to as the “healthy worker effect.”
21 Hence, the usual standard mortality ratios observed in cohort mortality studies are likely to be
22 underestimations of true risk.

23 A major difficulty with the occupational studies considered here was measurement of
24 actual diesel exhaust exposure. Because all the cohort mortality studies were retrospective,
25 assessment of health effects from exposure to diesel exhaust was naturally indirect. In these
26 occupational settings, no systematic quantitative records of ambient air were available. Most
27 studies compared men in job categories with presumably some exposure to diesel exhaust with
28 either standard populations (presumably no exposure to diesel exhaust) or men in other job
29 categories from industries with little or no potential for diesel exhaust exposure. A few studies
30 have included measurements of diesel fumes, but there is no standard method for the
31 measurement. No attempt is made to correlate these exposures with the cancers observed in any
32 of these studies, nor is it clear exactly which extract should have been measured to assess the
33 occupational exposure to diesel exhaust. All studies have relied on the job categories or self-
34 report of exposure to diesel exhaust. Gustavsson et al. (1990), Emmelin et al. (1993), and
35 Brüske-Hohlfeld et al. (1999) estimated exposure levels by getting detailed histories of job
36 tasks/categories and computing cumulative exposures, which unfortunately were not verifiable

1 due to of the lack of industrial hygiene data. In the studies by Garshick et al. (1987, 1988), the
2 diesel-exhaust-exposed job categories were verified on the basis of an industrial hygiene survey
3 done by Woskie et al. (1988a,b). The investigators found that in most cases the job titles were
4 good surrogates for diesel exhaust exposure. Also, in the railroad industry, where only persons
5 who had at least 10 years of work experience were included in the study, the workers tended not
6 to change job categories over the years. Thus, a job known only at one point in time was a
7 reasonable marker of past diesel exhaust exposure. Unfortunately, the exposure was only
8 qualitatively verified. Quantitative use of this information would have been much more
9 meaningful. Zaebst et al. (1991) conducted an industrial hygiene survey of elemental carbon
10 exposure in the trucking industry by job categories. Using these exposure measurements,
11 Steenland et al. (1998) conducted an exposure-response analysis of their earlier lung cancer case-
12 control study (Steenland et al., 1990). These exposure data are currently being verified and will
13 be used for quantitative risk assessment in the near future.

14 Occupations involving potential exposure to diesel exhaust are miners, truck drivers,
15 transportation workers, railroad workers, and heavy equipment operators. No known studies in
16 metal miners have assessed whether diesel exhaust is associated with lung cancer. Currently,
17 there are about 385 underground metal mines in the United States. Of these, 250 have been
18 permanently operating and 135 have been intermittently operating (Steenland, 1986).
19 Approximately 20,000 miners are employed, but not all of them are currently working in the
20 mines. Diesel engines were introduced in metal mines in the early to mid-1960s. Although all
21 these mines use diesel equipment, it is difficult to estimate how many of these miners were
22 actually exposed to diesel fumes.

23 Diesel engines were introduced in coal mines at an even later date, and their use is still
24 quite limited. In 1983, approximately 1,000 diesel units were in place in underground coal mines,
25 up from about 200 units in 1977 (Daniel, 1984). The number of units per mine varies greatly; 1
26 mine may account for more than 100 units.

27 Even if it were possible to estimate how many miners (metal and coal) were exposed to
28 diesel exhaust, it would be very difficult to separate out the confounding effects of other potential
29 pulmonary carcinogens, such as radon decay products or heavy metals (e.g., arsenic, chromium).
30 Furthermore, the relatively short latency period limits the usefulness of these cohorts of miners.

31 32 **7.2.4.1. Summary of the Cohort Mortality Studies**

33 The cohort studies mainly demonstrated an increase in lung cancer. Studies of bus
34 company workers by Waller (1981), Rushton et al. (1983), and Edling et al. (1987) failed to
35 demonstrate any statistically significant excess risk of lung cancer, but these studies have certain
36 methodological problems, such as small sample sizes, short follow-up periods (just 6 years in the

1 Rushton et al. study), lack of information on confounding variables, and lack of analysis by
2 duration of exposure, duration of employment, or latency that preclude their use in determining
3 the carcinogenicity of diesel exhaust. Although the Waller (1981) study had a 25-year follow-up
4 period, the cohort was restricted to employees (ages 45 to 64) currently in service. Employees
5 who left the job earlier, as well as those who were still employed after age 64 and who may have
6 died from cancer, were excluded.

7 Wong et al. (1985) conducted a mortality study of heavy equipment operators that
8 demonstrated a nonsignificant positive trend for cancer of the lung with length of membership and
9 latency. Analysis of deceased retirees showed a significant excess of lung cancer. Individuals
10 without work histories who started work prior to 1967, when records were not kept, may have
11 been in the same jobs for the longest period of time. Workers without job histories included those
12 who had the same job before and after 1967 and thus may have worked about 12 to 14 years
13 longer; these workers exhibited significant excess risks of lung cancer and stomach cancer. If this
14 assumption about duration of jobs is correct, then these site-specific causes can be linked to diesel
15 exhaust exposure. One of the methodologic limitations of this study is that most of these men
16 worked outdoors; thus, this cohort might have had relatively low exposure to diesel exhaust. The
17 authors did not present any environmental measurement data either. Because of the absence of
18 detailed work histories for 30% of the cohort and the availability of only partial work histories for
19 the remaining 70%, jobs were classified and ranked according to presumed diesel exposure.
20 Information is lacking regarding duration of employment in the job categories (used for surrogate
21 of exposure) and other confounding factors (alcohol consumption, cigarette smoking, etc.). Thus,
22 this study cannot be used to support or refute a causal association between exposure to diesel
23 exhaust and lung cancer.

24 A 2-year mortality analysis by Boffetta and Stellman (1988) of the American Cancer
25 Society's prospective study, after controlling for age and smoking, demonstrated an excess risk of
26 lung cancer in certain occupations with potential exposure to diesel exhaust. These excesses were
27 statistically significant among miners (RR = 2.67, 95% CI = 1.63, 4.37) and heavy equipment
28 operators (RR = 2.6, 95% CI = 1.12, 6.06). Recently Brüske-Hohlfeld et al. (1999) also have
29 observed significantly higher risk for lung cancer, in the range of 2.31 to 4.3, for heavy equipment
30 operators. The elevated risks were nonsignificant in railroad workers (RR = 1.59) and truck
31 drivers (RR = 1.24). A dose response was also observed for truck drivers. With the exception of
32 miners, exposure to diesel exhaust occurred in the three other occupations showing an increase in
33 the risk of lung cancer. Despite methodologic limitations, such as the lack of representiveness of
34 the study population (composed of volunteers only, who were probably healthier than the general
35 population), leading to an underestimation of the risk, and the questionable reliability of exposure

1 data based on self-administered questionnaires that were not validated, this study is suggestive of
2 a causal association between exposure to diesel exhaust and excess risk of lung cancer.

3 Two mortality studies were conducted by Gustavsson et al. (1990) and Hansen (1993)
4 among bus garage workers (Stockholm, Sweden) and truck drivers, respectively. An SMR of 122
5 was found among bus garage workers, based on 17 cases. A nested case-control study was also
6 conducted in this cohort. Detailed exposure matrices based on job tasks were assembled for both
7 diesel exhaust and asbestos exposures. Statistically significant increasing lung cancer relative
8 risks of 1.34, 1.81, and 2.43 were observed for diesel exhaust indices of 10 to 20, 20 to 30, and
9 >30, respectively, using 0 to 10 as a comparison group. Adjustment for asbestos exposure did
10 not change the results. The main strength of this study is the detailed exposure matrices; some of
11 the limitations are low power (small cohort) and lack of smoking histories. But smoking is not
12 likely to be different among study individuals irrespective of their exposure status to diesel
13 exhaust.

14 Hansen (1993), on the other hand, found statistically significant SMR of 160 from cancer
15 of bronchus and lung. No dose response was observed, although the excesses were observed in
16 most of the age groups (30 to 39, 45 to 49, 50 to 54, 55 to 59, 60 to 64, and 65 to 74). There are
17 quite a few methodologic limitations to this study. Exposure to diesel exhaust was assumed in
18 truck drivers for diesel-powered trucks, but no validation of exposure was attempted. Follow-up
19 period was short, no latency analysis was done, and smoking data were lacking. However, a
20 population survey carried out in 1988 showed very little difference in smoking habits of residents
21 of rural area and the total Danish male population, thus, smoking is unlikely to confound the
22 finding of excess lung cancer. The findings of both these studies are consistent with the findings
23 of other truck driver studies and are supportive of causal association.

24 Two mortality studies of railroad workers were conducted by Howe et al. (1983) and
25 Garshick et al. (1988). The Howe et al. study, which was conducted in Canada, found relative
26 risks of 1.2 ($p<0.01$) and 1.35 ($p<0.001$) among “possibly” and “probably” exposed groups,
27 respectively. The trend test showed a highly significant dose-response relationship with exposure
28 to diesel exhaust and the risk of lung cancer. The main limitation of the study was the inability to
29 separate overlapping exposures of coal dust/combustion fumes and diesel fumes. Information on
30 jobs was available at retirement only. There also was insufficient detail on the classification of
31 jobs by diesel exhaust exposure. The exposures could have been nonconcurrent or concurrent,
32 but because the data are lacking, it is possible that the observed excess could be due to the effect
33 of both coal dust/combustion fumes and diesel fumes and not just one or the other. It should be
34 noted that, so far, coal dust has not been demonstrated to be a pulmonary carcinogen in studies of
35 coal miners. However, lack of data on confounders such as asbestos and smoking (though use of
36 the internal comparison group to compute relative risks minimizes confounding by smoking)

1 makes interpretation of this study difficult. When three diesel exhaust exposure categories were
2 examined for smoking-related diseases such as emphysema, laryngeal cancer, esophageal cancer,
3 and buccal cancer, positive trends were observed, raising a possibility that the dose response
4 demonstrated for diesel exposure may have been due to smoking. The findings of this study are at
5 best suggestive of diesel exhaust being a lung carcinogen.

6 The strong evidence for linking diesel exhaust exposure to lung cancer comes from the
7 Garshick et al. (1988) railroad worker study conducted in the United States. Relative risks of
8 1.57 (95% CI = 1.19, 2.06) and 1.34 (95% CI = 1.02, 1.76) were found for ages 40 to 44 and 45
9 to 49, respectively, after the exclusion of workers exposed to asbestos. The investigators
10 reported that the risk of lung cancer increased with increasing duration of employment. As this
11 was a large cohort study with a lengthy follow-up and adequate analysis, including dose response
12 (based on duration of employment as a surrogate) as well as adjustment for other confounding
13 factors such as asbestos, the observed association between increased lung cancer and exposure to
14 diesel exhaust is more meaningful. Even though the reanalysis of these data by Crump et al.
15 (1991) found that the relative risk could be positively or negatively related to duration of
16 exposure depending on how age was controlled, additional analysis by Garshick et al. (1991)
17 found that the relationship between years exposed when adjusted for the attained age and calendar
18 years was flat to negative, depending on the choice of the model. They also found that deaths
19 were underreported by approximately 20% to 70% between 1977 and 1980, and their analysis
20 based on job titles, limited to 1959-1976, showed that the youngest workers still had the highest
21 risk of dying of lung cancer. On the other hand, an analysis of the same data by California EPA
22 (CalEPA, 1998) yielded a positive dose response set using age at 1959 and adding an interaction
23 term of age and calendar year in the model. However, Crump (1999) reported a negative dose
24 response in his latest analysis. The divergent results of these recent analyses do not negate the
25 strong evidence this study provides for the qualitative evaluation. The observance of dose
26 response would have strengthened the causal association, but an absence of a dose response does
27 not negate it.

28 Suggestive evidence is provided by a recent study of potash miners in Germany.
29 The information on the exposure (including elemental carbon and organics), work chronology,
30 and work category was used by the investigators to calculate cumulative exposures for each
31 worker. Furthermore, information on smoking habits indicated homogeneity in the cohort.
32 A statistically nonsignificant twofold increase in lung cancer was observed in the production
33 workers as compared to workshop workers. The lack of significance for this finding could be due
34 to short follow-up, not enough latency, and relatively young age of the cohort.

1 **7.2.4.2. Summary of the Case-Control Studies of Lung Cancer**

2 Among the 11 lung cancer case-control studies reviewed in this chapter, only 2 studies did
3 not find any increased risk of lung cancer. Lerchen et al. (1987) did not find any excess risk of
4 lung cancer, after adjusting for age and smoking, for diesel fume exposure. The major limitation
5 of this study was a lack of adequate exposure data derived from the job titles obtained from
6 occupational histories. Next of kin provided the occupational histories for 50% of the cases that
7 were not validated. The power of the study was small (analysis done on males only, 333 cases).
8 Similarly, Boffeta et al. (1990) did not find any excess of lung cancer after adjusting for smoking
9 and education. This study had a few methodological limitations. The lung cancer cases and
10 controls were drawn from the ongoing study of tobacco-related diseases. It is interesting to note
11 that the leading risk factor for lung cancer is cigarette smoking. The exposure was not measured.
12 Instead, occupations were used as surrogates for exposure. Furthermore, there were very few
13 individuals in the study who were exposed to diesel exhaust. On the other hand, statistically
14 nonsignificant excess risks were observed for diesel exhaust exposure by Hall and Wynder (1984)
15 in workers who were exposed to diesel exhaust versus those who were not (OR = 1.4 and 1.7
16 with two different criteria) and by Damber and Larsson (1987) in professional drivers (OR = 1.2).
17 These rates were adjusted for age and smoking. Hall and Wynder (1984) had a high
18 nonparticipation rate of 36%. Therefore, the positive results found in this study are
19 underestimated at best. In addition, the self-reported exposures used in the study by Hall and
20 Wynder (1984) were not validated. This study also had low power to detect excess risk of lung
21 cancer for specific occupations.

22 The study by Benhamou et al. (1988), after adjusting for smoking, found significantly
23 increased risks of lung cancer among French motor vehicle drivers (RR = 1.42) and transport
24 equipment operators (RR = 1.35). The main limitation of the study was the inability to separate
25 exposures to diesel exhaust from those to gasoline exhaust because both motor vehicle drivers
26 and transport equipment operators probably were exposed to the exhausts of both types of
27 vehicles.

28 Hayes et al. (1989) combined data from three studies (conducted in three different States)
29 to increase the power to detect an association between lung cancer and occupations with a high
30 potential for exposure to diesel exhaust. They found that truck drivers employed for more than
31 10 years had a significantly increased risk of lung cancer (OR = 1.5, 95% CI = 1.1, 1.9). This
32 study also found a significant trend of increasing risk of lung cancer with increasing duration of
33 employment among truck drivers. The relative odds were computed by adjusting for birth cohort,
34 smoking, and State of residence. The main limitation of this study is again the mixed exposures to
35 diesel and gasoline exhausts, because information on type of engine was lacking. Also, potential
36 bias may have been introduced because the way in which the cause of death was ascertained for

1 the selection of cases varied in the three studies. Furthermore, the methods used in these studies
2 to classify occupational categories were different, probably leading to incompatibility of
3 occupational categories.

4 Emmelin et al. (1993), in their Swedish dockworkers from 15 ports, found increased
5 relative odds of 6.8 (90% CI = 1.3 to 34.9). A strong interaction between smoking and diesel
6 exhaust was observed in this study. Of 50 cases and 154 controls, only 6 individuals were
7 nonsmokers. Although intricate exposure matrices were created using three different variables,
8 no direct exposure measurement was done. Despite the limitations of small number of cases and
9 controls; lack of data on asbestos exposure, which is fairly common in dockworkers; and very few
10 nonsmokers; this study provides consistent support for a real effect of diesel exhaust exposure and
11 occurrence of lung cancer, at least in smokers.

12 In a population-based lung cancer case-control study Swanson et al. (1993) found
13 statistically significant excess risks adjusted for age at diagnosis, smoking, and race, among white
14 male drivers of heavy trucks employed for ≥ 20 years and railroad workers employed for ≥ 10
15 years (OR = 2.5, 95% CI = 1.1, 4.4 and OR = 2.4, 95% CI = 1.1, 5.1, respectively), and among
16 black farmers employed for ≥ 20 years (OR = 10.4, 95% CI = 1.4, 77.1). Although individual
17 ORs were not significant for various occupations with potential exposure to diesel exhaust,
18 statistically significant trends were observed for drivers of heavy trucks, light trucks, farmers, and
19 railroad industry workers among whites, and among black farmers ($p \leq 0.5$). The main strengths of
20 the study are availability of data on lifetime work history and smoking history; the main limitation
21 is absence of actual specific exposure data. This is the first study that found increased lung cancer
22 risk for farmers, who are exposed to diesel exhaust of their farm tractors.

23 The most convincing evidence comes from the case-control studies, among railroad
24 workers by Garshick et al. (1987), among truck drivers of the Teamsters Union by Steenland et
25 al. (1990, 1998), among different professional drivers in Denmark by Hansen et al. (1998), and
26 among male workers occupationally exposed to diesel motor emissions in Germany by Brüske-
27 Hohlfeld et al. (1999). Garshick et al. found that after adjustment for asbestos and smoking, the
28 relative odds for continuous exposure were 1.39 (95% CI = 1.05, 1.83). Among the younger
29 workers with longer diesel exhaust exposure, the risk of lung cancer increased with duration of
30 exposure after adjusting for asbestos and smoking. Even after the exclusion of recent diesel
31 exhaust exposure (5 years before death), the relative odds increased to 1.43 (95% CI = 1.06,
32 1.94). This appears to be a well-conducted and well-analyzed study with reasonably good power.
33 Potential confounders were controlled adequately, and interactions between diesel exhaust and
34 other lung cancer risk factors were tested. Some of the limitations of this study are inadequate
35 latency period, misclassification of exposure because ICC job classification was used as surrogate
36 for exposure, and use of death certificates for identification of cases and controls.

1 Steenland et al. (1990), on the other hand, created two separate work history files, one
2 from Teamsters Union pension files and the other from next-of-kin interviews. Using duration of
3 employment as a categorical variable and considering employment after 1959 (when presumed
4 dieselization occurred) for long-haul drivers, the risk of lung cancer increased with increasing
5 years of exposure. Using 1964 as the cutoff, a similar trend was observed for long-haul drivers.
6 For short-haul drivers, the trend was positive with a 1959 cutoff, but not when 1964 was used as
7 the cutoff. For truck drivers who primarily drove diesel trucks and worked for 35 years, the
8 relative odds were 1.89. The main strengths of the study are availability of detailed records from
9 the Teamsters Union, a relatively large sample size, availability of smoking data, and
10 measurements of exposure. The limitations of this study include possible misclassifications of
11 exposure and smoking, lack of levels of diesel exposure, a smaller nonexposed group, and an
12 insufficient latency period. Recently Steenland et al. (1998) conducted an exposure-response
13 analysis on these cases and controls, using the industrial hygiene survey results of Zaebst et al.
14 (1991). The estimates were made for long-haul drivers, short-haul drivers, dockworkers,
15 mechanics, and those outside the trucking industry. The survey found that mechanics had the
16 highest current levels of diesel exhaust exposures and dockworkers who mainly used propane-
17 powered forklifts had the lowest exposure. The finding of the highest lung cancer risk for
18 mechanics and lowest for dock workers is indicative of a causal association between the diesel
19 exhaust exposure and development of lung cancer. However, the risk among mechanics did not
20 increase with increasing duration of employment. The OR for quartile cumulative exposure,
21 computed by using logistic regression adjusted for age, race, smoking, diet, and asbestos
22 exposure, showed a pattern of increasing trends in risk with increasing exposure, between 1.08
23 and 1.72 depending upon exposure level and lag structure used.

24 Hansen et al. (1998), in their study of professional drivers in Denmark, found statistically
25 significant ORs (adjusted for socioeconomic status) of 1.31, 1.64, and 1.39 for lorry/bus drivers,
26 taxi drivers, and unspecified drivers, respectively. The lag time analyses for duration of
27 employment were unchanged for lorry/bus drivers but increased to OR = 3 from 2.2 in taxi drivers
28 with a lag time of 10 years and duration of employment of > 5 years. The authors asserted that the
29 higher risk seen in the taxi drivers may be due to higher exposure to these drivers because of
30 longer time spent in traffic congestion. Furthermore, the trend tests for increasing risk of lung
31 cancer with increasing duration of employment were statistically significant for both lorry/bus
32 drivers and taxi drivers in both 10-year lag time and no lag time. The main strengths of the study
33 are the large sample size, availability of detailed employment records, and information on
34 socioeconomic status. The main limitations are absence of individual data on smoking habits and
35 asbestos exposure, and information about the type of fuel used for the vehicles driven by these
36 professional drivers. A personal communication with the main investigator revealed that the

1 lorries/buses and taxis have been using diesel fuel since the early 1960s. Moreover, indirect
2 information about smoking and asbestos exposure indicated that these two confounders are
3 unlikely to explain the observed excesses or the trends, resulting in strong support of earlier
4 positive studies.

5 Brüske-Hohlfeld et al. (1999) recently conducted a pooled analysis of two case-control
6 studies among male workers occupationally exposed to DME in Germany. The investigators
7 collected data on demographic information, detailed smoking, and occupational history. Job titles
8 and industries were classified in 33 and 21 categories respectively. Job descriptions were written
9 and verified to avoid misclassification. Individual cumulative DME exposures and smoking pack-
10 years were calculated. Asbestos exposures were estimated by certain job-specific supplementary
11 questions. Analysis of 3,498 lung cancer cases and 3,541 controls yielded statistically significant
12 ORs ranging from 1.25 to 2.31 adjusted for smoking and asbestos exposure. The risk increased
13 with increasing years of exposure for both the first year of exposure and the end year of exposure.
14 These investigators presented analyses by various job categories, by years of exposure, first and
15 end years of exposure and, when possible, separately for West and East Germany. Significantly
16 higher risks were found among all four job categories. For professional drivers (of trucks, buses,
17 and taxis) ORs ranged from 1.25 to 2.53. For other traffic-related jobs (switchmen, diesel
18 locomotive drivers, diesel forklift truck drivers), ORs ranged from 1.53 to 2.88. For heavy
19 equipment operators (bulldozers, graders, and excavators), ORs ranged from 2.31 to 4.3, and for
20 drivers of farming equipment the only significant excess (OR = 6.81) was for exposure for < 30
21 years.

22 This study shows increased risk for all the DME-exposed job categories. The professional
23 drivers and the other traffic-related jobs also have some mixed exposures to gasoline exhaust in
24 general traffic. On the other hand, it should be noted that exposure to DME among heavy
25 equipment and farm tractor drivers is much higher and not as mixed as in professional drivers.
26 The heavy equipment drivers usually drive repeatedly through their own equipment's exhaust.
27 Therefore, the observed highest risk for lung cancer in this job category establishes a strong link
28 with the DME. The only other study that found significantly higher risk for heavy equipment
29 operators (RR = 2.6) was conducted by Boffeta et al. (1988). Although the only significant
30 excess in the group was observed for farming tractor operators with more than 30 years of
31 exposure, a steady increase in risk was observed for this job category with increasing exposure.
32 The investigators stated that the working conditions and the DME of tractors remained fairly
33 constant over the years. This increase may be due mainly to exposure to DME and PM₁₀.

34 The main strengths of the study are large sample size, resulting in good statistical power;
35 inclusion of incident cases diagnosed not more than 3 months prior to the interview; use of only
36 personal interviews, reducing recall bias; diagnoses ascertained by cytology or histology; and

1 availability of lifelong detailed occupational and smoking history. Exposure estimation done for
2 each individual was based on job codes and industry codes, which were validated by written job
3 descriptions to avoid misclassification.

4 The main limitation of the study is lack of data on actual exposure to DME. The
5 cumulative quantitative exposures were calculated on the basis of time spent in each job with
6 potential exposure to DME and the type of equipment used. Thus, this study provides strong
7 evidence for causal association between exposure to diesel exhaust and occurrence of lung cancer.
8

9 **7.2.4.3. Summary of the Reviews and Meta-Analyses of Lung Cancer**

10 Three summaries of studies concerned with the relationship of diesel exhaust exposure and
11 lung cancer risk are reviewed. The HEI report is a narrative study of more than 35 epidemiologic
12 studies (16 cohort and 19 case-control) of occupational exposure to diesel emissions published
13 between 1957 and 1993. Control for smoking was identified in 15 studies. Six of the studies
14 (17%) reported relative risk estimates less than 1, whereas 29 (83%) reported at least 1 relative
15 risk, indicating a positive association. Twelve studies indicating a relative risk greater than 1 had
16 95% confidence intervals that excluded unity. These studies found that the evidence suggests that
17 occupational exposure to diesel exhaust from diverse sources increases the rate of lung cancer by
18 20% to 40% in exposed workers generally, and to a greater extent among workers with
19 prolonged exposure. They also found that the results are not explicable by confounding due to
20 cigarette smoking or other known sources of bias.

21 Bhatia et al. (1998) identified 23 studies that met criteria for inclusion in the meta-analysis.
22 The observed relative risk estimates were greater than 1 in 21 of these studies. The pooled
23 relative risk weighted by study precision was 1.33 (95% CI= 1.24, 1.44), which indicated
24 increased relative risk for lung cancer from occupational exposure to diesel exhaust. Subanalyses
25 by study design (case-control and cohort studies) and by control for smoking produced results
26 that did not differ from those of the overall pooled analysis. Cohort studies using internal
27 comparisons showed higher relative risks than those using external comparisons.

28 Lipsett and Campleman (1999) identify 39 independent estimates of relative risk among
29 30 eligible studies of diesel exhaust and lung cancer published between 1975 and 1995. Pooled
30 relative risks for all studies and for study subsets were estimated using a random effect model.
31 Interstudy heterogeneity was also modeled and evaluated. A pooled smoking-adjusted relative
32 risk was 1.47 (95% CI = 1.29, 1.67). Substantial heterogeneity was found in the pooled-risk
33 estimates. Adjustment for confounding by smoking, having a lower likelihood of selection bias,
34 and increased study power were all found to contribute to lower heterogeneity and increased
35 pooled estimates of relative risk.

1 There is some variability in the conclusions of these summaries of the association of diesel
2 exhaust and lung cancer. The three analyses find that smoking is unlikely to account for the
3 observed effects, and all conclude that the data support a causal association between lung cancer
4 and diesel exhaust exposure. On the other hand, Stöber and Abel (1996), Muscat and Wynder
5 (1995), and Cox (1997) call into question the assertions by Cohen and Higgins (1995), Bhatia et
6 al. (1998), and Lipsett and Campleman (1999) that the associations seen for diesel exhaust and
7 lung cancer are unlikely to be due to bias. They argue that methodologic problems are prevalent
8 among the studies, especially in evaluation of diesel engine exposure and control of confounding
9 by cigarette smoking. The conclusions of the two meta-analyses are based on magnitude of
10 pooled relative risk estimates and evaluation of potential sources of heterogeneity in the estimates.
11 Despite the statistical sophistication of the meta-analyses, the statistical models used cannot
12 compensate for deficiencies in the original studies and will remain biased to the extent that bias
13 exists in the original studies.

14 15 **7.2.4.4. Discussion of Relevant Methodologic Issues**

16 A persistent association of risk for lung cancer and diesel exhaust exposure has been
17 observed in more than 30 epidemiologic studies published in the literature over the past 40 years.
18 Evaluation of whether this association can be attributed to a causal relation between diesel
19 exhaust exposure and lung cancer requires careful consideration of whether chance, bias, or
20 confounding might be likely alternative explanations.

21 A total of 10 cohort and 12 case-control studies are reviewed in this chapter. An
22 increased lung cancer risk was observed in 8 cohort and 10 case-control studies, even though the
23 results were not always statistically significant. There is a consistent tendency for point estimates
24 of relative risk to be greater than one in studies that adjusted (either directly or indirectly) for
25 smoking, had a long enough follow-up, and sufficient statistical power among truck drivers,
26 railroad workers, dock workers, and heavy equipment workers. If this elevated risk was due to
27 chance one would expect almost equal distribution of these point estimates to be above and below
28 one. Many of the studies provide confidence intervals for their estimates of excess risk or
29 statistical tests, which indicate that it is unlikely that the individual study findings were due to
30 random variation. The persistence of this association between diesel exhaust and lung cancer risk
31 in so many studies indicates that the possibility is remote that the observed association in
32 aggregate is due to chance. It is unlikely that chance alone accounts for the observed relation
33 between diesel exhaust and lung cancer.

34 The excess risk is observed in both cohort and case-control designs, which contradicts the
35 concern that a methodologic bias specifically characteristic of either design (e.g., recall bias)
36 might account for the observed effect. Selection bias is certainly present in some of the

1 occupational cohort studies that use external population data in estimating relative risks, but this
2 form of selection bias (a healthy worker effect) would only obscure, rather than spuriously
3 produce, an association between diesel exhaust and lung cancer. Several occupational
4 epidemiologic studies that use more appropriate data for their estimates are available. Selection
5 biases may be operating in some case-control studies, but it is not obvious how such a bias could
6 be sufficiently uniform in effect, prevalent, and strong enough to lead to the consistent association
7 seen in the aggregate data. Given the variety of designs used in studying the diesel exhaust and
8 lung cancer association and the number of studies in different populations, it is unlikely that
9 routinely studying noncomparable groups is an explanation for the consistent association seen.
10 Exposure information bias is certainly a problem for almost all of the studies concerned. Detailed
11 and reliable individual-level data on diesel exhaust exposure for the period of time relevant to the
12 induction of lung cancer are not available and are difficult to obtain. Generally, the only
13 information from which diesel exposure can be inferred is occupational data, which is a poor
14 surrogate for the true underlying exposure distribution. Study endpoints are frequently mortality
15 data taken from death certificate information, which is frequently inaccurate and often does not
16 fully characterize the lung cancer incidence experience of the population in question. Using
17 inaccurate surrogates for lung cancer incidence and for diesel exposure can lead to substantial
18 bias, and these shortcomings are endemic in the field. In most cases these shortcomings will lead
19 to misclassification of exposure and of outcome, which is nondifferential. Nondifferential
20 misclassification of exposure and/or outcome can bias estimates of a diesel exhaust–lung cancer
21 association, if one exists, toward the null; but it is unlikely that such misclassification would
22 produce a spurious estimate in any one study. It is even more unlikely that it would bias a
23 sufficient number of studies in a uniform direction to account for the persistent aggregate
24 association observed.

25 Moreover, throughout this chapter, various methodologic limitations of individual studies
26 have been discussed, such as small sample size, short follow-up period, lack of data on
27 confounding variables, use of death certificates to identify the lung cancer cases, and lack of
28 latency analysis. The studies with small sample sizes (i.e., not enough power) and short follow-up
29 periods (i.e., not enough latent period) have been difficult to interpret due to these limitations.

30 The most important confounding variable is smoking which is a strong risk factor for lung
31 cancer. All the studies considered for this report are either cohort retrospective mortality or case-
32 control studies where history of exposures in the past is elicited. Smoking history is usually
33 difficult to obtain in such instances. The smoking histories obtained from surrogates (next of kin,
34 either spouse or offspring) were found to be accurate by Lerchen and Samet (1986) and
35 McLaughlin et al. (1987). Lerchen and Samet did not detect any consistent bias in the report of
36 cigarette consumption. In contrast, overreporting of cigarette smoking by surrogates was

1 observed by Rogot and Reid (1975), Kolonel et al. (1977), and Humble et al. (1984). Kolonel et
2 al. found that the age at which an individual started smoking was reported within 4 years of actual
3 age 84% of the time. These studies indicate that surrogates were able to provide fairly credible
4 information on the smoking habits of the study subjects. If the surrogates of the cases were more
5 likely to overreport cigarette smoking compared with the controls, then it might be harder to find
6 an effect of diesel exhaust because most of the increase in lung cancer would be attributed to
7 smoking rather than to exposure to diesel exhaust.

8 Some studies do not adjust for tobacco smoke exposure. Even though smoking is a
9 strong risk for lung cancer, it is only a confounder if there are differential smoking habits among
10 individuals exposed to diesel exhaust versus individuals who are not exposed. Most of the
11 occupational cohorts include workers from the same socioeconomic background or used an
12 internal comparison group; hence, it is unlikely that confounding by cigarette smoking is
13 substantial in these studies. Some studies have adjusted for socioeconomic status and some
14 studies have compared the cigarette smoking habits by conducting rural and urban general
15 population surveys. Besides, in studies with long enough latency, adjustment for cigarette
16 smoking did not alter substantially the observed higher risk.

17 Another methodologic concern in these studies is use of death certificates to determine
18 cause of death. Death certificates were used by all of the cohort mortality studies and some of the
19 case-control studies of lung cancer to determine cause of death. Use of death certificates could
20 lead to misclassification bias because of overdiagnosis. Studies of autopsies done between 1960
21 and 1971 demonstrated that lung cancer was overdiagnosed when compared with hospital
22 discharge, with no incidental cases found at autopsy (Rosenblatt et al., 1971). Schottenfeld et al.
23 (1982) also found an overdiagnosis of lung cancer among autopsies conducted in 1977 and 1978.
24 On the other hand, Percy et al. (1981) noted 95% concordance when comparing 10,000 lung
25 cancer deaths observed in the Third National Cancer Survey from 1969 to 1971 (more than 90%
26 were confirmed histologically) to death-certificate-coded cause of death. These more recent
27 findings suggest that the diagnosis of lung cancer on death certificates is better than anticipated.
28 In reality, lung cancer is one cause of death that has been found to be generally reliably diagnosed
29 on the death certificate.

30 Finally, several investigators have not conducted latency analysis in their studies. The
31 latent period for lung cancer development is up to 30 years or more. Considering the fact that
32 dieselization was not complete till almost 1959 for locomotives and the 1970s for the trucking
33 industry in the USA, most of the cohort studies do not have a long enough follow-up period to
34 allow for latency of 30+ years. In addition, the study inclusion criteria for most of the studies are
35 individuals who worked in the industry for at least 6 months /1 year from the beginning of the
36 follow-up period to the end of the follow-up period. Hence, the later the individual enters the

1 cohort, the shorter the follow-up period; thus, the latent period is insufficient for the occurrence
2 of lung cancer. Therefore, the observed slight to moderate increase in risk of lung cancer could
3 be due to insufficient latency. On the other hand, in certain case-control studies the elapsed
4 period between the identification of the lung cancer cases and exposure to diesel exhaust is long
5 enough to allow for the 30+ years latency needed for the development of lung cancer (Hansen et
6 al., 1998; Brüske-Hohlfeld et al., 1999). These investigators identified lung cancer cases in the
7 early to mid-1990s and found significant excess risks for lung cancer among the individuals
8 exposed to diesel exhaust. It should be noted that the use of diesel fuel for trucks, buses, and
9 taxis had started in their countries (Denmark and Germany, respectively) in the early 1960s.

11 **7.2.4.5. Evaluation of Causal Association**

12 In most situations, epidemiologic data are used to delineate the causality of certain health
13 effects. Several cancers have been causally associated with exposure to agents for which there is
14 no direct biological evidence. Insufficient knowledge about the biological basis for diseases in
15 humans makes it difficult to identify exposure to an agent as causal, particularly for malignant
16 diseases when the exposure was in the distant past. Consequently, epidemiologists and biologists
17 have provided a set of criteria that define a causal relationship between exposure and the health
18 outcome. A causal interpretation is enhanced for studies that meet these criteria. None of these
19 criteria actually proves causality; actual proof is rarely attainable when dealing with environmental
20 carcinogens. None of these criteria should be considered either necessary (except temporality of
21 exposure) or sufficient in itself. The absence of any one or even several of these criteria does not
22 prevent a causal interpretation. However, if more criteria apply, this provides more credible
23 evidence for causality.

24 Thus, applying the Hill criteria (1965) of causal inference, as modified by Rothman
25 (1986), to the studies reviewed here resulted in the following:

- 27 • *Strength of association.* This phrase refers to the magnitude of the ratio of
28 incidence or mortality (RRs or ORs). Several studies found statistically significant
29 RRs and ORs that ranged from 1.2 to 2.6 (Howe et al., 1983; Rushton et al., 1983;
30 Wong et al., 1985; Gustavsson et al., 1990; Emmlin et al., 1993; Hansen et al.,
31 1993; Hansen et al., 1998) and, after adjustment for smoking and/or asbestos, RRs
32 and ORs remained statistically significant and in the same range in certain studies
33 (Dambar and Larson 1987; Garshick et al., 1987, 1988; Benhamou et al., 1988;
34 Boffetta and Stellman, 1988; Hays et al., 1989; Steenland et al., 1990; Swanson et
35 al., 1993; Brüsk-Hohlfeld et al., 1999). In addition, two meta-analyses
36 demonstrated that not only did excess in lung cancer remain the same after

1 stratification/adjustment for smoking and occupation, but in several instances the
2 pooled RRs showed modest increases, with little evidence of heterogeneity.
3 Overall, the studies in epidemiologic terms show relatively modest to weak
4 association between diesel exhaust and occurrence of lung cancer. Even though
5 strong associations are more likely to be causal than modest-to-weak associations,
6 the fact that association is relatively modest or weak does not rule out the causal
7 link.

- 8 • *Consistency.* Increased lung cancer risk has been observed in several cohort and
9 case-control studies, conducted in several industries and occupations in which
10 workers were potentially exposed to diesel exhaust. However, not all the excesses
11 were statistically significant. Statistically significant lung cancer excesses adjusted
12 for smoking were observed in truck drivers (Hayes et al., 1989; Hansen et al.,
13 1993; Swanson et al., 1993; Brüske-Hohlfeld et al., 1999), professional drivers
14 (Benhamou et al., 1988; Brüske-Hohlfeld et al., 1999), railroad workers (Garshick
15 et al., 1987; Swanson et al., 1993), heavy equipment drivers (Boffetta et al., 1988;
16 Brüske-Hohlfeld et al., 1999), and farm tractor drivers (Swanson et al., 1993;
17 Brüske-Hohlfeld et al., 1999). Furthermore, the two recent meta-analyses by
18 Bhatia et al. (1998) and Lipsett and Campleman (1999) found that even though a
19 substantial heterogeneity existed in their initial pooled estimates, stratification on
20 several factors demonstrated a relationship between exposure to DE and excess
21 lung cancer that remained positive throughout various analyses.
- 22 • *Specificity.* This criterion requires that a single cause lead to a single effect. With
23 respect to exposure to diesel exhaust, excess for lung cancer is the only effect that
24 is found to be consistently elevated and statistically significant in several studies.
25 Quite a few studies have examined diesel exhaust for other effects such as bladder
26 cancer, leukemia, gastrointestinal cancers, prostate cancer etc. The evidence for
27 these effects is inadequate. Rothman (1986), in his discussion about causality
28 criteria, states “Causes of a given effect, however, cannot be expected to be
29 without other effects on any logical grounds. In fact, everyday experience teaches
30 us repeatedly that single events may have many effects. Hill’s discussion of this
31 standard for inference is replete with reservations, but even so, the criterion seems
32 useless and misleading.”
- 33 • *Temporality.* The only necessary, but not sufficient, criterion described by Hill for
34 causality inference is that exposure to a causal agent precedes the effect in time.
35 This criterion is clearly satisfied in the studies reviewed here. Temporality can be
36 explored further in addressing the latency issue. A certain period is necessary for

1 development of an effect after exposure to a causal agent has occurred. For
2 instance, in cancer-causing agents a latent period can vary from 5 years (childhood
3 leukemia) to ≥ 30 years (mesothelioma). Most of the studies reviewed here did not
4 conduct the latency analysis. Some studies had a short follow-up period that did
5 not allow enough time for the latency period (Waller, 1981; Howe et al., 1983;
6 Rushton et al., 1983; Wong et al., 1985, Hansen et al., 1993) while several studies
7 clearly allowed for an adequate latency period (Garshick et al., 1987; Gustavsson
8 et al., 1990; Steenland et al., 1990; Swanson et al., 1993; Brüske-Hohlfeld et al.,
9 1999). Both type of studies showed mixed results.

- 10 • *Biological gradient.* This criterion refers to the dose-response curve. Due to the
11 lack of quantitative data on diesel exhaust exposure in most studies reviewed here,
12 analyzing the dose-response curve directly was not possible. In very few studies
13 was exposure to diesel exhaust addressed specifically. Most investigators have
14 used job titles/categories and duration of employment as surrogates for exposure
15 and thus have presented response in relation to duration of employment.
16 Significant dose-response (using duration of employment as a surrogate) was
17 observed in various studies for railroad workers (Howe et al., 1983; Garshick et
18 al., 1987; Garshick et al., 1988; Swanson et al., 1993), truck drivers (Boffetta and
19 Stellman, 1988; Hayes et al., 1989; Steenland et al., 1990; Swanson et al., 1993;
20 Hansen et al., 1998; Brüske-Hohlfeld et al., 1999), transportation/heavy equipment
21 operators (Wong et al., 1985; Gustavsson et al., 1990; Brüske-Hohlfeld et al.,
22 1999), farmers/farm tractor users (Swanson et al., 1993; Brüske-Hohlfeld et al.,
23 1999), and dockworkers (Emmelin et al., 1993).
- 24 • *Biological plausibility.* This criterion refers to the biologic plausibility of the
25 hypothesis, an important concern that may be difficult to judge. The hypothesis
26 considered for this review is that occupational exposure to diesel exhaust is
27 causally associated with the occurrence of lung cancer and is supported by the
28 following: First, diesel exhaust has been shown to cause lung and other cancers in
29 animals (Heinrich et al., 1986b; Iwai et al., 1986b; Mauderly et al., 1987; Pott et
30 al., 1990; Mauderly et al., 1994). Second, it contains highly mutagenic substances
31 such as polycyclic aromatic hydrocarbons as well as nitroaromatic compounds
32 (Claxton, 1983; Ball et al., 1990; Gallagher et al., 1993; Sera et al., 1994; Nielsen
33 et al., 1996a) that are recognized human pulmonary carcinogens (IARC, 1989).
34 Third, diesel exhaust consists of carbon core particles with surface layers of
35 organics and gases; the tumorigenic activity may reside in one, some, or all of
36 these components. As explained in Chapter 4, there is clear evidence that the

1 organic constituents, both in particles and vapor phases, have the capacity to
2 interact with DNA and give rise to mutations, chromosomal aberrations, and cell
3 transformations, all well- established steps in the process of carcinogenesis.
4 Further, increased levels of peripheral blood cell DNA adducts associated with
5 occupational exposure to diesel exhaust have been observed in humans (Nielsen et
6 al., 1996a,b). Thus, the above evidence makes a convincing case that occupational
7 exposures to diesel exhaust are causally associated with the occurrence of lung
8 cancer—highly plausible biologically.
9

10 In conclusion, the epidemiologic studies of exposure to diesel exhaust and occurrence of
11 lung cancer furnish evidence that is consistent with a causal association. This association
12 observed in several studies is unlikely to be due to chance or bias. Although many studies did not
13 have information on smoking, confounding by smoking is unlikely in these studies because the
14 comparison population was from the same socioeconomic class. The strength of association was
15 weak to modest (RRs/ORs between 1.2 and 2.6), with dose-response relationship observed in
16 several studies. Last, but not least, there is strong evidence for biological plausibility that
17 exposure to diesel exhaust would result in excess risk of lung cancer in humans.
18

19 **7.3. CARCINOGENICITY OF DIESEL EMISSIONS IN LABORATORY ANIMALS**

20 This chapter summarizes studies that assess the carcinogenic potential of diesel exhaust in
21 laboratory animals. The first portion of this chapter summarizes results of inhalation studies.
22 Experimental protocols for the inhalation studies typically consisted of exposure (usually chronic)
23 to diluted exhaust in whole-body exposure chambers using rats, mice, and hamsters as model
24 species. Some of these studies used both filtered (free of particulate matter) diesel exhaust and
25 unfiltered (whole) diesel exhaust to differentiate gaseous-phase effects from effects induced by
26 diesel PM (DPM) and its adsorbed components. Other studies were designed to evaluate the
27 relative importance of the carbon core of the diesel particle versus that of particle-adsorbed
28 compounds. Finally, a number of exposures were carried out to determine the combined effect of
29 inhaled diesel exhaust and tumor initiators, tumor promoters, or cocarcinogens.

30 Particulate matter concentrations in the diesel exhaust used in these studies ranged from
31 0.1 to 12 mg/m³. In this chapter, any indication of statistical significance implies that $p \leq 0.05$ was
32 reported in the reviewed publications. A summary of the animal inhalation carcinogenicity studies
33 and their results is presented in Table 7-3.

34 Results of lung implantation and intratracheal instillation studies of whole diesel particles,
35 extracted diesel particles, and particle extracts are reported in Section 7.3.3 and in Tables 7-4 and
36 7-5. Studies destined to assess the carcinogenic effects of DPM as well as solvent extracts of

1 DPM following subcutaneous (s.c.) injection, intraperitoneal (i.p.) injection, or intratracheal (itr.)
2 instillation in rodents are summarized in Section 7.3.5. Individual chemicals present in the
3 gaseous phase or adsorbed to the particle surface were not included in this review because
4 assessments of those of likely concern (i.e., formaldehyde, acetaldehyde, benzene, polycyclic
5 aromatic hydrocarbons [PAHs]) have been published elsewhere (U.S. EPA, 1993).

7 **7.3.1. Inhalation Studies (Whole Diesel Exhaust)**

8 **7.3.1.1. Rat Studies**

9 The potential carcinogenicity of inhaled diesel exhaust was first evaluated by Karagianes et
10 al. (1981). Male Wistar rats (40 per group) were exposed to room air or diesel engine exhaust
11 diluted to a DPM concentration of 8.3 (\pm 2.0) mg/m³, 6 hr/day, 5 days/week for up to 20 months.
12 The animals were exposed in 3,000 L plexiglass chambers. Airflow was equal to 50 liters per
13 minute. Chamber temperatures were maintained between 25° and 26.5 °C. Relative humidity
14 ranged from 45% to 80%. Exposures were carried out during the daytime. The connected to an
15 electric generator and operated at varying loads and speeds to simulate operating conditions in an
16 occupational situation. To control the CO concentration at 50 ppm, the exhaust was diluted 35:1
17 with clean air. Six rats per group were sacrificed after 4, 8, 16, and 20 months exposure for gross
18 necropsy and histopathological examination.

19 The only tumor detected was a bronchiolar adenoma in the group exposed over 16 months
20 to diesel exhaust. No lung tumors were reported in controls. The equivocal response may have
21 been caused by the relatively short exposure durations (20 months) and small numbers of animals
22 examined. In more recent studies, for example, Mauderly et al. (1987), most of the tumors were
23 detected in rats exposed for more than 24 months.

24 General Motors Research Laboratories sponsored chronic inhalation studies at the
25 Southwest Research Institute using male Fischer 344 rats, 30 per group, exposed to DPM
26 concentrations of 0.25, 0.75, or 1.5 mg/m³ (Kaplan et al., 1983; White et al., 1983). The animals
27 were exposed in 12.6 m³ exposure chambers. Airflow was adjusted to provide 13 changes per
28 hour. Temperature was maintained at 22 \pm 2 °C. The exposure protocol was 20 hr/day, 7
29 days/week for 9 to 15 months. Exposures were halted during normal working hours for servicing.
30 Some animals were sacrificed following completion of exposure, while others were returned to
31 clean air atmospheres for an additional 8 months. Control animals received clean air. Exhaust
32 was generated by 5.7-L Oldsmobile engines (four different engines used throughout the
33 experiment) operated at a steady speed and load simulating a 40-mph driving speed of a full-size
34 passenger car.

35 Although five instances of bronchoalveolar carcinoma were observed in 90 rats exposed to
36 diesel exhaust for 15 months and held an additional 8 months in clean air, compared with none

1 among controls, statistical significance was not achieved in any of the exposure groups. These
2 included one tumor in the 0.25 mg/m³ group, three in the 0.75 mg/m³ group, and one in the 1.5
3 mg/m³ group. Rats kept in clean-air chambers for 23 months did not exhibit any carcinomas. No
4 tumors were observed in any of the 180 rats exposed to diesel exhaust for 9 or 15 months without
5 a recovery period, or in the respective controls for these groups. Equivocal results may again
6 have been due to less-than-lifetime duration of the study as well as insufficient exposure
7 concentrations. Although the increases in tumor incidences in the groups exposed for 15 months
8 and held an additional 8 months in clean air were not statistically significant, relative to controls,
9 they were slightly greater than the historic background incidence of 3.7% for this specific lesion in
10 this strain of rat (Ward, 1983). The first definitive studies linking inhaled diesel exhaust to
11 induction of lung cancer in rats were reported by researchers in Germany, Switzerland, Japan, and
12 the United States in the mid-to-late 1980s. In a study conducted at the Fraunhofer Institute
13 exhaust-generating system and exposure atmosphere characteristics are presented in Appendix A.
14 The type of engine used (3-cylinder, 43 bhp diesel) is normally used in mining situations and was
15 of Toxicology and Aerosol Research, female Wistar rats were exposed for 19 hr/day, 5 days/week
16 to both filtered and unfiltered (total) diesel exhaust at an average particulate matter concentration
17 of 4.24 mg/m³. Animals were exposed for a maximum of 2.5 years. The exposure system as
18 described by Heinrich et al. (1986a) used a 40 kilowatt 1.6-L diesel engine operated continuously
19 under the U.S. 72 FTP driving cycle. The engines used European Reference Fuel with a sulfur
20 content of 0.36%. Filtered exhaust was obtained by passing engine exhaust through a Luwa FP-
21 65 HT 610 particle filter heated to 80 °C and a secondary series of filters (Luwa FP-85, Luwa
22 NS-30, and Drager CH 63302) at room temperature. The filtered and unfiltered exhausts were
23 diluted 1:17 with filtered air and passed through respective 12 m³ exposure chambers. Mass
24 median aerodynamic diameter of DPM was 0.35 ± 0.10 µm (mean ± SD). The gas-phase
25 components of the diesel exhaust atmospheres are presented in Appendix A.

26 The effects of exposure to either filtered or unfiltered exhaust were described by Heinrich
27 et al. (1986b) and Stöber (1986). Exposure to unfiltered exhaust resulted in 8 bronchoalveolar
28 adenomas and 9 squamous cell tumors in 15 of 95 female Wistar rats examined, for a 15.8%
29 tumor incidence. Although statistical analysis was not provided, the increase appears to be highly
30 significant. In addition to the bronchioalveolar adenomas and squamous cell tumors, there was a
31 high incidence of bronchioalveolar hyperplasia (99%) and metaplasia of the bronchioalveolar
32 epithelium (65%). No tumors were reported among rats exposed to filtered exhaust (n = 92) or
33 clean air (n = 96).

34 Mohr et al. (1986) provided a more detailed description of the lung lesions and tumors
35 identified by Heinrich et al. (1986a,b) and Stöber (1986). Substantial alveolar deposition of
36 carbonaceous particles was noted for rats exposed to unfiltered diesel exhaust. Squamous

1 metaplasia was observed in 65.3% of the rats breathing unfiltered diesel exhaust, but not in the
2 control rats. Of nine squamous cell tumors, one was characterized as a Grade I carcinoma
3 (borderline atypia, few to moderate mitoses, and slight evidence of stromal invasion), and the
4 remaining eight were classified as benign keratinizing cystic tumors.

5 Iwai et al. (1986) examined the long-term effects of diesel exhaust inhalation on female
6 F344 rats. The exhaust was generated by a 2.4-L displacement truck engine. The exhaust was
7 diluted 10:1 with clean air at 20 °C to 25 °C and 50% relative humidity. The engines were
8 operated at 1,000 rpm with an 80% engine load. These operating conditions were found to
9 produce exhaust with the highest particle concentration and lowest NO₂ and SO₂ content. For
10 those chambers using filtered exhaust, proximally installed high-efficiency particulate air (HEPA)
11 filters were used. Three groups of 24 rats each were exposed to unfiltered diesel exhaust, filtered
12 diesel exhaust, or filtered room air for 8 hr/day, 7 days/week for 24 months. Particle
13 concentration was 4.9 mg/m³ for unfiltered exhaust. Concentrations of gas-phase exhaust
14 components were 30.9 ppm NO_x, 1.8 ppm NO₂, 13.1 ppm SO₂, and 7.0 ppm CO.

15 No lung tumors were found in the 2-year control (filtered room air) rats, although one
16 adenoma was noted in a 30-months control rat, providing a spontaneous tumor incidence of
17 4.5%. No lung tumors were observed in rats exposed to filtered diesel exhaust. Nineteen of the
18 24 exposed to unfiltered exhaust survived for 2 years. Of these, 14 were randomly selected for
19 sacrifice at this time. Four of the rats developed lung tumors; two of these were malignant. Five
20 rats of this 2-year exposure group were subsequently placed in clean room air for 3 to 6 months
21 and four eventually (time not specified) exhibited lung tumors (three malignancies). Thus, the
22 lung tumor incidence for total tumors was 42.1% (8/19) and 26.3% (5/19) for malignant tumors
23 in rats exposed to whole diesel exhaust. The tumor types identified were adenoma (3/19),
24 adenocarcinoma (1/19), adenosquamous carcinoma (2/19), squamous carcinoma (1/19), and
25 large-cell carcinoma (1/19). The lung tumor incidence in rats exposed to whole diesel exhaust
26 was significantly greater than that of controls ($p \leq 0.01$). Tumor data are summarized in Table
27 7-3. Malignant splenic lymphomas were detected in 37.5% of the rats in the filtered exhaust
28 group and in 25.0% of the rats in the unfiltered exhaust group; these values were significantly
29 ($p \leq 0.05$) greater than the 8.2% incidence noted in the control rats. The study demonstrates
30 production of lung cancer in rats following 2-year exposure to unfiltered diesel exhaust. In
31 addition, splenic malignant lymphomas occurred during exposure to both filtered and unfiltered
32 diesel exhaust. This is the only report to date of tumor induction at an extrarespiratory site by
33 inhaled diesel exhaust in animals.

34 A chronic (up to 24 months) inhalation exposure study was conducted by Takemoto et al.
35 (1986), in which female Fischer 344 rats were exposed to diesel exhaust generated by a 269-cc
36 YANMAR-40CE NSA engine operated at an idle state (1,600 rpm). Exposures were 4

1 hours/day, 4 days/week. The animals were exposed in a 376-L exposure chamber. Air flow was
2 maintained at 120 L/min. Exhaust was diluted to produce a particle concentration of 2-4 mg/m³.
3 When not exposed the animals were maintained in an air-conditioned room at a temperature of 24
4 ± 2°C and a relative humidity of 55 ± 5% with 12 hr of light and darkness. Temperature and
5 humidity in the exposure chambers was not noted. The particle concentration of the diesel
6 exhaust in the exposure chamber was 2 to 4 mg/m³. B[a]P and 1-nitropyrene concentrations were
7 0.85 and 93 µg/g of particles, respectively. No lung tumors were reported in the diesel-exposed
8 animals. It was also noted that the diesel engine employed in this study was originally used as an
9 electrical generator and that its operating characteristics (not specified) were different from those
10 of a diesel-powered automobile. However, the investigators deemed it suitable for assessing the
11 effects of diesel emissions.

12 Mauderly et al. (1987) provided data affirming the carcinogenicity of automotive diesel
13 engine exhaust in F344/Crl rats following chronic inhalation exposure. Male and female rats were
14 exposed to diesel engine exhaust at nominal DPM concentrations of 0.35 (n = 366), 3.5
15 (n = 367), or 7.1 (n = 364) mg/m³ for 7 hr/day, 5 days/week for up to 30 mo. Sham-exposed
16 (n = 365) controls breathed filtered room air. A total of 230, 223, 221, and 227 of these rats
17 (sham-exposed, low-, medium-, and high-exposure groups, respectively) were examined for lung
18 tumors. These numbers include those animals that died or were euthanized during exposure and
19 those that were terminated following 30 months of exposure. The exhaust was generated by 1980
20 model 5.7-L Oldsmobile V-8 engines operated through continuously repeating U.S. Federal Test
21 Procedure (FTP) urban certification cycles. The engines were equipped with automatic
22 transmissions connected to eddy-current dynamometers and flywheels simulating resistive and
23 inertial loads of a midsize passenger car. The D-2 diesel control fuel (Phillips Chemical Co.) met
24 U.S. EPA certification standards and contained approximately 30% aromatic hydrocarbons and
25 0.3% sulfur. Following passage through a standard automotive muffler and tailpipe, the exhaust
26 was diluted 10:1 with filtered air in a dilution tunnel and serially diluted to the final
27 concentrations. The primary dilution process was such that particle coagulation was retarded.
28 Mokler et al. (1984) provided a detailed description of the exposure system. No exposure-related
29 changes in body weight or lifespan were noted for any of the exposed animals, nor were there any
30 signs of overt toxicity. Collective lung tumor incidence was greater (z statistic,
31 $p \leq 0.05$) in the high (7.1 mg/m³) and medium (3.5 mg/m³) exposure groups (12.8% and 3.6%,
32 respectively) versus the control and low (0.35 mg/m³) exposure groups (0.9% and 1.3%,
33 respectively). In the high-dose group the incidences of tumor types reported were adenoma
34 (0.4%), adenocarcinomas plus squamous cell carcinomas (7.5%), and squamous cysts (4.9%). In
35 the medium-dose group adenomas were reported in 2.3% of animals, adenocarcinomas plus
36 squamous cell carcinomas in 0.5%, and squamous cysts in 0.9%. In the low-exposure group

1 adenocarcinomas plus squamous cell carcinomas were detected in 1.3% of the rats. Using the
2 same statistical analysis of specific tumor types, adenocarcinoma plus squamous cell carcinoma
3 and squamous cyst incidence was significantly greater in the high-exposure group, and the
4 incidence of adenomas was significantly greater in the medium-exposure group. A significant
5 ($p < 0.001$) exposure-response relationship was obtained for tumor incidence relative to exposure
6 concentration and lung burden of DPM. These data are summarized in Table 7-3. A logistic
7 regression model estimating tumor prevalence as a function of time, dose (lung burden of DPM),
8 and sex indicated a sharp increase in tumor prevalence for the high dose level at about 800 days
9 after the commencement of exposure. A less pronounced, but definite, increase in prevalence
10 with time was predicted for the medium-dose level. Significant effects were not detected at the
11 low concentration. DPM (mg per lung) of rats exposed to 0.35, 3.5, or 7.1 mg of DPM/m³ for 24
12 months were 0.6, 11.5, and 20.8, respectively, and affirmed the greater-than-predicted
13 accumulation that was the result of decreased particle clearance following high-exposure
14 conditions.

15 In summary, this study demonstrated the pulmonary carcinogenicity of high concentrations
16 of whole, diluted diesel exhaust in rats following chronic inhalation exposure. In addition,
17 increasing lung particle burden resulting from this high-level exposure and decreased clearance
18 was demonstrated. A logistic regression model presented by Mauderly et al. (1987) indicated that
19 both lung DPM burden and exposure concentration may be useful for expressing exposure-effect
20 relationships.

21 A long-term inhalation study (Ishinishi et al., 1988a; Takaki et al., 1989) examined the
22 effects of emissions from a light-duty (LD) and a heavy-duty (HD) diesel engine on male and
23 female Fischer 344/Jcl rats. The LD engines were 1.8-L, 4-cylinder, swirl-chamber-type power
24 plants, and the HD engines were 11-L, 6-cylinder, direct-injection-type power plants. The
25 engines were connected to eddy-current dynamometers and operated at 1,200 rpm (LD engines)
26 and 1,700 rpm (HD engines). Nippon Oil Co. JIS No. 1 or No. 2 diesel fuel was used. The 30-
27 months whole-body exposure protocol (16 h/day, 6 days/week) used DPM concentrations of 0,
28 0.5, 1, 1.8, or 3.7 mg/m³ from HD engines and 0, 0.1, 0.4, 1.1, or 2.3 mg/m³ from LD engines.
29 The animals inhaled the exhaust emissions from 1700 to 0900 h. Sixty-four male rats and 59 to
30 61 female rats from each exposure group were evaluated for carcinogenicity.

31 For the experiments using the LD series engines, the highest incidence of hyperplastic
32 lesions plus tumors (72.6%) was seen in the highest exposure (2.3 mg/m³) group. However, this
33 high value was the result of the 70% incidence of hyperplastic lesions; the incidence of adenomas
34 was only 0.8% and that of carcinomas 1.6%. Hyperplastic lesion incidence was considerably
35 lower for the lower exposure groups (9.7%, 4.8%, 3.3%, and 3.3% for the 1.1, 0.4, and 0.1
36 mg/m³ and control groups, respectively). The incidence of adenomas and carcinomas, combining

72 males and females, was not significantly different among exposure groups (2.4%, 4.0%, 0.8%, 2.4%, and 3.3% for the 2.3, 1.1, 0.4, and 0.1 mg/m³ groups and the controls, respectively).

For the experiments using the HD series engines, the total incidence of hyperplastic lesions, adenomas, and carcinomas was highest (26.6%) in the 3.7 mg/m³ exposure group. The incidence of adenomas plus carcinomas for males and females combined equaled 6.5%, 3.3%, 0%, 0.8%, and 0.8% at 3.7, 1.8, 1, and 0.4 mg/m³ and for controls, respectively. A statistically significant difference was reported between the 3.7 mg/m³ and the control groups for the HD series engines. The carcinomas were identified as adenomas, adenosquamous carcinomas, and squamous cell carcinomas. Although the number of each was not reported, it was noted that the majority were squamous cell carcinomas. A progressive dose-response relationship was not demonstrated. Tumor incidence data for this experiment are presented in Table 7-3.

The Ishinishi et al. (1988a) study also included recovery tests in which rats exposed to whole diesel exhaust (DPM concentration of 0.1 or 1.1 mg/m³ for the LD engine and 0.5 or 1.8 mg/m³ for the HD engine) for 12 months were examined for lung tumors following 6-, 12-, or 18-months recovery periods in clean air. The incidences of neoplastic lesions were low, and pulmonary DPM burden was lower than for animals continuously exposed to whole diesel exhaust and not provided a recovery period. The only carcinoma observed was in a rat examined 12 months following exposure to exhaust (1.8 mg/m³) from the HD engine.

Brightwell et al. (1986, 1989) studied the effects of diesel exhaust on male and female F344 rats. The diesel exhaust was generated by a 1.5-L Volkswagen engine that was computer-operated according to the U.S. 72 FTP driving cycle. The engine was replaced after 15 mo. The engine emissions were diluted by conditioned air delivered at 800 m³/h to produce the high-exposure (6.6 mg/m³) diesel exhaust atmosphere. Further dilutions of 1:3 and 1:9 produced the medium- (2.2 mg/m³) and low- (0.7 mg/m³) exposure atmospheres. The CO and NO_x concentrations (mean ± SD) were 32 ± 11 ppm and 8 ± 1 ppm in the high-exposure concentration chamber. The inhalation exposures were conducted overnight to provide five 16-h periods per week for 2 years; surviving animals were maintained for an additional 6 mo.

For males and females combined, a 1.2% (3/260), 0.7% (1/144), 9.7% (14/144), and 38.5% (55/143) incidence of primary lung tumors occurred in F344 rats following exposure to clean air or 0.7, 2.2, and 6.6 mg of DPM/m³, respectively (Table 7-3). Diesel exhaust-induced tumor incidence in rats was dose-related and higher in females than in males (Table 7-3). These data included animals sacrificed at the interim periods (6, 12, 18, and 24 mo); therefore, the tumor incidence does not accurately reflect the effects of long-term exposure to the diesel exhaust atmospheres. When tumor incidence is expressed relative to the specific intervals, a lung tumor incidence of 96% (24/25), 76% (19/25) of which were malignant, was reported for female rats in the high-dose group exposed for 24 months and held in clean air for the remainder of their lives.

For male rats in the same group, the tumor incidence equaled 44% (12/27), of which 37% (10/27) were malignant. It was also noted that many of the animals exhibiting tumors had more than one tumor, often representing multiple histological types. The numbers and types of tumors identified in the rats exposed to diesel exhaust included adenomas (40), squamous cell carcinomas (35), adenocarcinomas (19), mixed adenoma/adenocarcinomas (9), and mesothelioma (1). It should be noted that exposure during darkness (when increased activity would result in greater respiratory exchange and greater inhaled dose) could account, in part, for the high response reported for the rats.

Lewis et al. (1989) also examined the effects of inhalation exposure of diesel exhaust and/or coal dust on tumorigenesis on F344 rats. Groups of 216 male and 72 female rats were exposed to clean air, whole diesel exhaust (2 mg soot/m³), coal dust (2 mg/m³ respirable concentration; 5 to 6 mg/m³ total concentration), or diesel exhaust plus coal dust (1 mg/m³ of each respirable concentration; 3.2 mg/m³ total concentration) for 7 h/day, 5 days/week during daylight hours for up to 24 mo. Groups of 10 or more males were sacrificed at intermediate intervals (3, 6, and 12 mo). The diesel exhaust was produced by a 7.0-L, 4-cycle, water-cooled Caterpillar Model 3304 engine using No. 2 diesel fuel (<0.5% sulfur by mass). The exhaust was passed through a Wagner water scrubber, which lowered the exhaust temperature and quenched engine backfire. The animals were exposed in 100-cubic-foot chambers. Temperature was controlled at 22±2 °C and relative humidity at 50%±10%. The exhaust was diluted 27-fold with chemically and biologically filtered clean air to achieve the desired particle concentration.

Histological examination was performed on 120 to 121 male and 71 to 72 female rats terminated after 24 months of exposure. The exhaust exposure did not significantly affect the tumor incidence beyond what would be expected for aging F344 rats. There was no postexposure period, which may explain, in part, the lack of significant tumor induction. The particulate matter concentration was also less than the effective dose in several other studies.

In a more recent study reported by Heinrich et al. (1995), female Wistar rats were exposed to whole diesel exhaust (0.8, 2.5, or 7.0 mg/m³) 18 h/day, 5 days/week for up to 24 mo, then held in clean air an additional 6 mo. The animals were exposed in either 6 or 12 m³ exposure chambers. Temperature and relative humidity were maintained at 23-25 °C and 50%-70%, respectively. Diesel exhaust was generated by two 40-kw 1.6-L diesel engines (Volkswagen). One of them was operated according to the U.S. 72 cycle. The other was operated under constant load conditions. The first engine did not supply sufficient exhaust, which was filled by the second engine. Cumulative exposures for the rats in the various treatment groups were 61.7, 21.8, and 7.4 g/m³ × h for the high, medium, and low whole-exhaust exposures. Significant increases in tumor incidences were observed in the high (22/100; *p*<0.001) and mid (11/200; *p*<0.01) exposure groups relative to clean-air controls (Table 7-3). Only one tumor (1/217), an

adenocarcinoma, was observed in clean-air controls. Relative to clean-air controls, significantly increased incidences were observed in the high-exposure rats for benign squamous cell tumors (14/100; $p < 0.001$), adenomas (4/100; $p < 0.01$), and adenocarcinomas (5/100; $p < 0.05$). Only the incidence of benign squamous cell tumors (7/200; $p < 0.01$) was significantly increased in the mid-exposure group relative to the clean-air controls.

Particle lung burden and alveolar clearance also were determined in the Heinrich et al. (1995) study. Relative to clean air controls, alveolar clearance was significantly compromised by exposure to mid and high diesel exhaust. For the high-diesel-exhaust group, 3-mo recovery time in clean air failed to reverse the compromised alveolar clearance.

In a study conducted at the Inhalation Toxicology Research Institute (Nikula et al., 1995) F344 rats (114-115 per sex per group) were exposed 16 hr/day, 5 days/week during daylight hours to diesel exhaust diluted to achieve particle concentrations of 2.5 or 6.5 mg/m³ for up to 24 mo. Controls (118 males, 114 females) were exposed to clean air. Surviving rats were maintained an additional 6 weeks in clean air, at which time mortality reached 90%. Diesel exhaust was generated with two 1988 Model LH6 General Motors 6.2-L V-8 engines burning D-2 fuel that met EPA certification standards. Chamber air flow was sufficient to provide about 15 exchanges per hour. Relative humidity was 40% to 70% and temperature ranged from 23 to 25 °C.

Following low and high diesel exhaust exposure, the lung burdens were 36.7 and 80.7 mg, respectively, for females and 45.1 and 90.1 mg, respectively, for males. The percentages of susceptible rats (males and females combined) with malignant neoplasms were 0.9 (control), 3.3 (low diesel exhaust), and 12.3 (high diesel exhaust). The percentages of rats (males and females combined) with malignant or benign neoplasms were 1.4 (control), 6.2 (low diesel exhaust), and 17.9 (high diesel exhaust). All primary neoplasms were associated with the parenchyma rather than the conducting airways of the lungs. The first lung neoplasm was observed at 15 mo. Among 212 males and females examined in the high-dose group, adenomas were detected in 23 animals, adenocarcinomas in 22 animals, squamous cell carcinomas in 3 animals, and an adenosquamous carcinoma in 1 animal. For further details see Table 7-3. Analysis of the histopathologic data suggested a progressive process from alveolar epithelial hyperplasia to adenomas and adenocarcinomas.

Iwai et al. (1997) carried out a series of exposures to both filtered and whole exhaust using a light-duty (2,369 mL) diesel engine. The protocol for engine operation was not stated. Groups of female SPF F344 Fischer rats were exposed for 2 years for 8 hr/day, 7 days/week, 8 hr/day, 6 days/week, or 18 hr/day, 3 days/week to either filtered exhaust or exhaust diluted to a particle concentration of 9.4, 3.2, and 5.1 mg/m³, respectively. Cumulative exposure (mg/m³ × hrs of exposure) equaled 274.4, 153.6, and 258.1 mg/m³. The animals were then held for an

additional 6 months in clean air. Lung tumors were reported in 5/121 (4%) of controls, 4/108 (4%) of those exposed to filtered exhaust, and 50/153 (35%) among those exposed to whole exhaust. Among rats exposed to whole diesel exhaust the following number of tumors were detected; 57 adenomas, 24 adenocarcinomas, 2 benign squamous cell tumors, 7 squamous cell carcinomas, and 3 adenosquamous carcinomas. The authors stated that benign squamous cell tumors probably corresponded to squamous cysts in another classification.

7.3.1.2. Mouse Studies

A series of inhalation studies using strain A mice was conducted by Orthoefer et al. (1981). Strain A mice are usually given a series of intraperitoneal injections with the test agent; they are then sacrificed at about 9 months and examined for lung tumors. In the present series, inhalation exposure was substituted. Diesel exhaust was provided by one of two Nissan CN6-33 diesel engines having a displacement of 3244 cc and run on a Federal Short Cycle. Flow through the exposure chambers was sufficient to provide 15 air changes per hour. Temperature was maintained at 24 °C and relative humidity at 75%. In the first study, groups of 25 male Strong A strain (A/S) mice were exposed to irradiated diesel exhaust (to simulate chemical reactions induced by sunlight) or nonirradiated diesel exhaust (6 mg/m³) for 20 h/day, 7 days/week. Additional groups of 40 Jackson A strain (S/J) mice (20 of each sex) were exposed similarly to either clean air or diesel exhaust, then held in clean air until sacrificed at 9 months of age. No tumorigenic effects were detected at 9 months of age. Further studies were conducted in which male A/S mice were exposed 8 hr/day, 7 days/week until sacrifice (approximately 300 at 9 months of age and approximately 100 at 12 months of age). With the exception of those treated with urethan, the number of tumors per mouse did not exceed historical control levels in any of the studies. Exposure to diesel exhaust, however, significantly inhibited the tumorigenic effects of the 5-mg urethan treatment. Results are listed in Table 7-3.

Kaplan et al. (1982) also reported the effects of diesel exposure in strain A mice. Groups of male strain A/J mice were exposed for 20 h/day, 7 days/week for 90 days and held until 9 months of age. Briefly, the animals were exposed in inhalation chambers to diesel exhaust generated by a 5.7-L Oldsmobile engine operated continuously at 40 mph at DPM concentrations of 0, 0.25, 0.75, or 1.5 mg/m³. Controls were exposed to clean air. Temperature was maintained at 22 ± 2 °C and relative humidity at 50% ± 10% within the chambers. Among 458 controls and 485 exposed animals, tumors were detected in 31.4% of those breathing clean air versus 34.2% of those exposed to diesel exhaust. The mean number of tumors per mouse also failed to show significant differences.

In a follow-up study, strain A mice were exposed to diesel exhaust for 8 months (Kaplan et al., 1983; White et al., 1983). After exposure to the highest exhaust concentration (1.5

mg/m³), the percentage of mice with pulmonary adenomas and the mean number of tumors per mouse were significantly less ($p < 0.05$) than those for controls (25.0% vs. 33.5% and 0.30 ± 0.02 [S.E.] vs. 0.42 ± 0.03 [S.E.]) (Table 7-3).

Pepelko and Peirano (1983) summarized a series of studies on the health effects of diesel emissions in mice. Exhaust was provided by two Nissan CN 6-33, 6-cylinder, 3.24-L diesel engines coupled to a Chrysler A-272 automatic transmission and Eaton model 758-DG dynamometer. Sixty-day pilot studies were conducted at a 1:14 dilution, providing DPM concentrations of 6 mg/m³. The engines were operated using the Modified California Cycle. These 20-hr/day, 7-days/week pilot studies using rats, cats, guinea pigs, and mice produced decreases in weight gain and food consumption. Therefore, at the beginning of the long-term studies, exposure time was reduced to 8 h/day, 7 days/week at an exhaust DPM concentration of 6 mg/m³. During the final 12 months of exposure, however, the DPM concentration was increased to 12 mg/m³. For the chronic studies, the engines were operated using the Federal Short Cycle. Chamber temperature was maintained at 24 °C and relative humidity at 50%. Airflow was sufficient for 15 changes per hour.

Pepelko and Peirano (1983) described a two-generation study using Sencar mice exposed to diesel exhaust. Male and female parent-generation mice were exposed to diesel exhaust at a DPM concentration of 6 mg/m³ prior to (from weaning to sexual maturity) and throughout mating. The dams continued exposure through gestation, birth, and weaning. Groups of offspring (130 males and 130 females) were exposed to either diesel exhaust or clean air. The exhaust exposure was increased to a DPM concentration of 12 mg/m³ when the offspring were 12 weeks of age and was maintained until termination of the experiment when the mice were 15 months old.

The incidence of pulmonary adenomas (16.3%) was significantly increased in the mice exposed to diesel exhaust compared with 6.3% in clean-air controls. The incidence in males and females combined was 10.2% in 205 animals examined compared with 5.1% in 205 clean-air controls. This difference was also significant. The incidence of carcinomas was not affected by exhaust exposure in either sex. These results provided the earliest evidence for cancer induction following inhalation exposure to diesel exhaust. The increase in the sensitivity of the study, allowing detection of tumors at 15 mo, may have been the result of exposure from conception. It is likely that Sencar mice are sensitive to induction of lung tumors because they are also sensitive to induction of skin tumors. These data are summarized in Table 7-3.

Takemoto et al. (1986) reported the effects of inhaled diesel exhaust (2 to 4 mg/m³, 4 h/day, 4 days/week, for up to 28 mo) in ICR and C57BL mice exposed from birth. Details of the exposure conditions are presented in Section 7.3.2.1. All numbers reported are for males and females combined. Four adenomas and 1 adenocarcinoma were detected in 34 diesel exhaust-

exposed ICR mice autopsied at 13 to 18 mo, compared with 3 adenomas among 38 controls. Six adenomas and 3 adenocarcinomas were reported in 22 diesel-exposed ICR mice autopsied at 19 to 28 mo, compared with 3 adenomas and 1 adenocarcinoma in 22 controls. Four adenomas and 2 adenocarcinomas were detected in 79 C57BL mice autopsied at 13 to 18 mo, compared with none in 19 unexposed animals. Among males and females autopsied at 19 to 28 mo, 8 adenomas and 3 adenocarcinomas were detected in 71 exposed animals, compared with 1 adenoma among 32 controls. No significant increases in adenoma or adenocarcinoma were reported for either strain of exposed mice. However, the significance of the increase in the combined incidence of adenomas and carcinomas was not evaluated statistically. A statistical analysis by Pott and Heinrich (1990) indicated that the difference in combined benign and malignant tumors between whole diesel exhaust-exposed C57BL/6N mice and corresponding controls was significant at $p < .05$. See Table 7-3 for details of tumor incidence.

Heinrich et al. (1986b) and Stöber (1986), as part of a larger study, also evaluated the effects of diesel exhaust in mice. Details of the exposure conditions reported by Heinrich et al. (1986a) are given in Section 7.3.1.1 and Appendix A. Following lifetime (19 h/day, 5 days/week, for a maximum of 120 weeks) exposure to diesel exhaust diluted to achieve a particle concentration of 4.2 mg/m^3 , 76 female NMRI mice exhibited a total lung tumor incidence of adenomas and adenocarcinomas combined of 32%. Tumor incidences reported for control mice ($n = 84$) equaled 11% for adenomas and adenocarcinomas combined. While the incidence of adenomas showed little change, adenocarcinomas increased significantly from 2.4% for controls to 17% for exhaust-exposed mice. In a follow-up study, however, Heinrich et al. (1995) reported a lack of tumorigenic response in either female NMRI or C57BL/6N mice exposed 17 h/day, 5 days/week for 13.5 to 23 months to whole diesel exhaust diluted to produce a particle concentration of 4.5 mg/m^3 . These data are summarized in Table 7-3.

The lack of a carcinogenic response in mice was reported by Mauderly et al. (1996). In this study, groups of 540 to 600 CD-1 male and female mice were exposed to whole diesel exhaust (7.1 , 3.5 , or 0.35 mg DPM/m^3) for 7 hr/day, 5 days/week for up to 24 mo. Controls were exposed to filtered air. Diesel exhaust was provided by 5.7-L Oldsmobile V-8 engines operated continuously on the U.S. Federal Test Procedure urban certification cycle. The chambers were maintained at 25-28 °C, relative humidity at 40%-60%, and a flow rate sufficient for 15 air exchanges per hour. Animals were exposed during the light cycle, which ran from 6:00 AM to 6:00 PM. DPM accumulation in the lungs of exposed mice was assessed at 6, 12, and 18 months of exposure and was shown to be progressive; DPM burdens were 0.2 ± 0.02 , 3.7 ± 0.16 , and $5.6 \pm 0.39 \text{ mg}$ for the low-, medium-, and high-exposure groups, respectively. The lung burdens in both the medium- and high-exposure groups exceeded that predicted by exposure concentration ratio for the low-exposure group. Contrary to what was observed in rats (Heinrich et al., 1986b;

Stöber, 1986; Nikula et al., 1995; Mauderly et al., 1987), an exposure-related increase in primary lung neoplasms was not observed in the CD-1 mice, supporting the contention of a species difference in the pulmonary carcinogenic response to poorly soluble particles. The percentage incidence of mice (males and females combined) with one or more malignant or benign neoplasms was 13.4, 14.6, 9.7, and 7.5 for controls and low-, medium-, and high-exposure groups, respectively.

Although earlier studies provided some evidence for tumorigenic responses in diesel-exposed mice, no increases were reported in the two most recent studies by Mauderly et al. (1996) and Heinrich et al. (1995), which utilized large group sizes and were well designed and conducted. Overall, the results in mice must therefore be considered to be equivocal.

7.3.1.3. Hamster Studies

Heinrich et al. (1982) examined the effects of diesel exhaust exposure on tumor frequency in female Syrian golden hamsters. Groups of 48 to 72 animals were exposed to clean air or whole diesel exhaust at a mean DPM concentration of 3.9 mg/m³. Inhalation exposures were conducted 7 to 8 hr/day, 5 days/week for 2 years. The exhaust was produced by a 2.4-L Daimler-Benz engine operated under a constant load and a constant speed of 2,400 rpm. Flow rate was sufficient for about 20 exchanges per hour in the 250-L chambers. No lung tumors were reported in either exposure group.

In a subsequent study, Syrian hamsters were exposed 19 hr/day, 5 days/week for a lifetime to diesel exhaust diluted to a DPM concentration of 4.24 mg/m³ (Heinrich et al., 1986b; Stöber, 1986). Details of the exposure conditions are reported in Appendix A. Ninety-six animals per group were exposed to clean air or exhaust. No lung tumors were seen in either the clean-air group or in the diesel exhaust-exposed group.

In a third study (Heinrich et al., 1989b), hamsters were exposed to exhaust from a Daimler-Benz 2.4-L engine operated at a constant load of about 15 kW and at a uniform speed of 2,000 rpm. The exhaust was diluted to an exhaust-clean air ratio of about 1:13, resulting in a mean particle concentration of 3.75 mg/m³. Exposures were conducted in chambers maintained at 22 to 24 °C and 40% to 60% relative humidity for up to 18 mo. Surviving hamsters were maintained in clean air for up to an additional 6 mo. The animals were exposed 19 hr/day, 5 days/week beginning at noon each day, under a 12-hr light cycle starting at 7 AM. Forty animals per group were exposed to whole diesel exhaust or clean air. No lung tumors were detected in either the clean-air or diesel-exposed hamsters.

Brightwell et al. (1986, 1989) studied the effects of diesel exhaust on male and female Syrian golden hamsters. Groups of 52 males and 52 females, 6 to 8 weeks old, were exposed to diesel exhaust at DPM concentrations of 0.7, 2.2, or 6.6 mg/m³. They were exposed 16 hr/day, 5

days/week for a total of 2 years and then sacrificed. Exposure conditions are described in Section 7.3.1.1. No statistically significant (*t* test) relationship between tumor incidence and exhaust exposure was reported.

In summary, diesel exhaust alone did not induce an increase in lung tumors in hamsters of either sex in several studies of chronic duration at high exposure concentrations.

7.3.1.4. Monkey Studies

Fifteen male cynomolgus monkeys were exposed to diesel exhaust (2 mg/m³) for 7 hr/day, 5 days/week for 24 months (Lewis et al., 1989). The same numbers of animals were also exposed to coal dust (2 mg/m³ respirable concentration; 5 to 6 mg/m³ total concentration), diesel exhaust plus coal dust (1 mg/m³ respirable concentration for each component; 3.2 mg/m³ total concentration), or filtered air. Details of exposure conditions were listed previously in the description of the Lewis et al. (1989) study with rats (Section 7.3.1.1) and are listed in Appendix A.

None of the monkeys exposed to diesel exhaust exhibited a significantly increased incidence of preneoplastic or neoplastic lesions. It should be noted, however, that the 24-mo time frame employed in this study may not have allowed the manifestation of tumors in primates, because this duration is only a small fraction of the monkeys' expected lifespan. In fact, there have been no near-lifetime exposure studies in nonrodent species.

7.3.2. Inhalation Studies (Filtered Diesel Exhaust)

Several studies have been conducted in which animals were exposed to diesel exhaust filtered to remove PM. As these studies also included groups exposed to whole exhaust, details can be found in Sections 7.3.1.1 for rats, 7.3.1.2 for mice, and 7.3.1.3 for hamsters. Heinrich et al. (1986b) and Stöber (1986) reported negative results for lung tumor induction in female Wistar rats exposed to filtered exhaust diluted to produce an unfiltered particle concentration of 4.24 mg/m³. Negative results were also reported in female Fischer 344 rats exposed to filtered exhaust diluted to produce an unfiltered particle concentration of 4.9 mg/m³ (Iwai et al., 1986), in Fischer 344 rats of either sex exposed to filtered exhaust diluted to produce an unfiltered particle concentration of 6.6 mg/m³ (Brightwell et al., 1989), in female Wistar rats exposed to filtered exhaust diluted to produce an unfiltered particle concentration of 7.0 mg/m³ (Heinrich et al., 1995), and in female Fischer 344 rats exposed to filtered exhaust diluted to produce unfiltered particle concentrations of 5.1, 3.2, or 9.4 mg/m³ (Iwai et al., 1997). In the Iwai et al. (1986) study, splenic lymphomas were detected in 37.5% of the exposed rats compared with 8.2% in controls.

In the study reported by Heinrich et al. (1986a) and Stober (1986), primary lung tumors were seen in 29/93 NMRI mice (males and females combined) exposed to filtered exhaust, compared with 11/84 in clean-air controls, a statistically significant increase. In a repeat study by Heinrich et al. (1995), however, significant lung tumor increases were not detected in either female NMRI or C57BL/6N mice exposed to filtered exhaust diluted to produce an unfiltered particle concentration of 4.5 mg/m³.

Filtered exhaust also failed to induce lung tumor induction in Syrian Golden hamsters (Heinrich et al., 1986a; Brightwell et al., 1989).

Although lung tumor increases were reported in one study and lymphomas in another, these results could not be confirmed in subsequent investigations. It is therefore concluded that little direct evidence exists for carcinogenicity of the vapor phase of diesel exhaust in laboratory animals at concentrations tested.

7.3.3. Inhalation Studies (Diesel Exhaust Plus Cocarcinogens)

Details of the studies reported here have been described earlier and in Table 7-3. Tumor initiation with urethan (1 mg/kg body weight i.p. at the start of exposure) or promotion with butylated hydroxytolulene (300 mg/kg body weight i.p. week 1, 83 mg/kg week 2, and 150 mg/kg for weeks 3-52) did not influence tumorigenic responses in Sencar mice of both sexes exposed to concentrations of diesel exhaust up to 12 mg/m³ (Pepelko and Peirano, 1983).

Heinrich et al. (1986b) exposed Syrian hamsters of both sexes to diesel exhaust diluted to a particle concentration of 4 mg/m³. See Section 7.3.1.1 for details of the exposure conditions. At the start of exposure the hamsters received either one dose of 4.5 mg diethylnitrosamine (DEN) subcutaneously per kg body weight or 20 weekly intratracheal instillations of 250 µg BaP. Female NMRI mice received weekly intratracheal instillations of 50 or 100 µgBaP for 10 or 20 weeks, respectively, or 50 µg dibenz[ah]anthracene (DBA) for 10 weeks. Additional groups of 96 newborn mice received one s.c. injection of 5 or 10 µg DBA between 24 and 48 hr after birth. Female Wistar rats received weekly subcutaneous injections of dipentyl nitrosamine (DPN) at doses of 500 and 250 mg/kg body weight, respectively, during the first 25 weeks of exhaust inhalation exposure. Neither DEN, DBA, or DPN treatment enhanced any tumorigenic responses to diesel exhaust. Response to BaP did not differ from that of BaP alone in hamsters, but results were inconsistent in mice. Although 20 BaP instillations induced a 71% tumor incidence in mice, concomitant diesel exposure resulted in only a 41% incidence. However, neither 10 BaP instillations nor DBA instillations induced significant effects.

Takemoto et al. (1986) exposed Fischer 344 rats for 2 years to diesel exhaust at particle concentrations of 2 to 4 mg/m³. One month after start of inhalation exposure one group of rats received di-isopropyl-nitrosamine (DIPN) administered i.p. at 1 mg/kg weekly for 3 weeks.

Among injected animals autopsied at 18 to 24 mo, 10 adenomas and 4 adenocarcinomas were reported in 21 animals exposed to clean air, compared with 12 adenomas and 7 adenocarcinomas in 18 diesel-exposed rats. According to the authors, the incidence of adenocarcinomas was not significantly increased by exposure to diesel exhaust.

Brightwell et al. (1989) investigated the concomitant effects of diesel exhaust and DEN in Syrian hamsters exposed to diesel exhaust diluted to produce particle concentrations of 0.7, 2.2, or 6.6 mg/m³ for 2 years. The animals received a single dose of 4.5 mg DEN s.c. 3 days prior to start of inhalation exposure. DEN did not affect the lack of responsiveness to diesel exhaust alone. Heinrich et al. (1989b) also exposed Syrian hamsters of both sexes to diesel exhaust diluted to a particle concentration of 3.75 mg/m³ for up to 18 mo. After 2 weeks of exposure, groups were treated with either 3 or 6 mg DEN/kg body weight, respectively. Again, DEN did not significantly influence the lack of tumorigenic responses to diesel exhaust.

Heinrich et al. (1989a) investigated the effects of DPN in female Wistar rats exposed to diesel exhaust diluted to achieve a particle concentration of 4.24 mg/m³ for 2-2.5 years. DPN at doses of 250 and 500 mg/kg body weight was injected subcutaneously once a week for the first 25 weeks of exposure. The tumorigenic responses to DPN were not affected by exposure to diesel exhaust. For details of exposure conditions of the hamster studies see Section 7.3.1.3.

Heinrich et al. (1986a) and Mohr et al. (1986) compared the effects of exposure to particles having only a minimal carbon core but a much greater concentration of PAHs than DPM does. The desired exposure conditions were achieved by mixing coal oven flue gas with pyrolyzed pitch. The concentration of B[a]P and other PAHs per milligram of DPM was about three orders of magnitude greater than that of diesel exhaust. Female rats were exposed to the flue gas-pyrolyzed pitch for 16 hr/day, 5 days/week at particle concentrations of 3 to 7 mg/m³ for 22 mo, then held in clean air for up to an additional 12 mo. Among 116 animals exposed, 22 tumors were reported in 21 animals, for an incidence of 18.1%. One was a bronchioloalveolar adenoma, one was a bronchioloalveolar carcinoma, and 20 were squamous cell tumors. Among the latter, 16 were classified as benign keratinizing cystic tumors and 4 were classified as carcinomas. No tumors were reported in 115 controls. The tumor incidence in this study was comparable to that reported previously for the diesel exhaust-exposed animals.

In analyzing the studies of Heinrich et al. (1986a,b), Heinrich (1990), Mohr et al. (1986), and Stöber (1986), it must be noted that the incidence of lung tumors occurring following exposure to whole diesel exhaust, coal oven flue gas, or carbon black (15.8%, 18.1%, and 8% to 17%, respectively) was very similar. This occurred despite the fact that the PAH content of the PAH-enriched pyrolyzed pitch was more than three orders of magnitude greater than that of diesel exhaust; carbon black, on the other hand, had only traces of PAHs. Based on these

findings, particle-associated effects appear to be the primary cause of diesel-exhaust-induced lung cancer in rats exposed at high concentrations. This issue is discussed further in Chapter 7.

7.3.4. Lung Implantation or Intratracheal Instillation Studies

7.3.4.1. Rat Studies

Grimmer et al. (1987), using female Osborne Mendel rats (35 per treatment group), provided evidence that PAHs in diesel exhaust that consist of four or more rings have carcinogenic potential. Condensate was obtained from the whole exhaust of a 3.0-L passenger-car diesel engine connected to a dynamometer operated under simulated city traffic driving conditions. This condensate was separated by liquid-liquid distribution into hydrophilic and hydrophobic fractions representing 25% and 75% of the total condensate, respectively. The hydrophilic, hydrophobic, or reconstituted hydrophobic fractions were surgically implanted into the lungs of the rats. Untreated controls, vehicle (beeswax/trioctanoin) controls, and positive (B[a]P) controls were also included in the protocol (Table 7-6). Fraction IIb (made up of PAHs with four to seven rings), which accounted for only 0.8% of the total weight of DPM condensate, produced the highest incidence of carcinomas following implantation into rat lungs. A carcinoma incidence of 17.1% was observed following implantation of 0.21 mg IIb/rat, whereas the nitro-PAH fraction (IIId) at 0.18 mg/rat accounted for only a 2.8% carcinoma incidence. Hydrophilic fractions of the DPM extracts, vehicle (beeswax/trioctanoin) controls, and untreated controls failed to exhibit carcinoma formation. Administration of all hydrophobic fractions (IIa-d) produced a carcinoma incidence (20%) similar to the summed incidence of fraction IIb (17.1%) and IIId (2.8%). The B[a]P positive controls (0.03, 0.1, 0.3 mg/rat) yielded a carcinoma incidence of 8.6%, 31.4%, and 77.1%, respectively. The study showed that the tumorigenic agents were primarily four- to seven-ring PAHs and, to a lesser extent, nitroaromatics. However, these studies demonstrated that simultaneous administration of various PAH compounds resulted in a varying of the tumorigenic effect, thereby implying that the tumorigenic potency of PAH mixtures may not depend on any one individual PAH. This study did not provide any information regarding the bioavailability of the particle-associated PAHs that might be responsible for carcinogenicity.

Kawabata et al. (1986) compared the effects of activated carbon and diesel exhaust on lung tumor formation. One group of 59 F344 rats was intratracheally instilled with DPM (1 mg/week for 10 weeks). A second group of 31 rats was instilled with activated carbon using the same dosing regime. Twenty-seven rats received only the solvent (buffered saline with 0.05% Tween 80), and 53 rats were uninjected. Rats dying after 18 months were autopsied. All animals surviving 30 months or more postinstillation were sacrificed and evaluated for histopathology. Among 42 animals exposed to DPM surviving 18 months or more, tumors were reported in 31,

including 20 malignancies. In the subgroup surviving for 30 mo, tumors were detected in 19 of 20 animals, including 10 malignancies. Among the rats exposed to activated carbon, the incidence of lung tumors equaled 11 of 23 autopsied, with 7 cases of malignancy. Data for those dying between 18 and 30 months and those sacrificed at 30 months were not reported separately. Statistical analysis indicated that activated carbon induced a significant increase in lung tumor incidence compared with no tumors in 50 uninjected controls and 1 tumor in 23 solvent-injected controls. The tumor incidence was significantly greater in the DPM-instilled group and was significantly greater than the increase in the carbon-instilled group.

A study reported by Rittinghausen et al. (1997) suggested that organic constituents of diesel particles play a role in the induction of lung tumors in rats. An incidence of 16.7% pulmonary cystic keratinizing squamous cell lesions was noted in rats intratracheally instilled with 15 mg whole diesel exhaust particles, compared with 2.1% in rats instilled with 15 mg particles extracted to remove all organic constituents, and none among controls. Instillation of 30 mg of extracted particles induced a 14.6% incidence of squamous lesions, indicating the greater effectiveness of particles alone as lung particle overload increased.

Iwai et al. (1997) instilled 2, 4, 8, and 10 mg of whole diesel particles over a 2- to 10-week period into female F/344 rats, 50 or more per group. Tumors were reported in 6%, 20%, 43%, and 74% of the rats, with incidence of malignant tumors equal to 2%, 13%, 34%, and 48%, respectively. In a second experiment comparing whole with extracted diesel particles, tumor incidence equaled 1/48 (2%) in uninjected controls, 3/55 (5%) in solvent controls, 12/56 (21%) in extracted diesel particles, and 13/106 (12%) in animals injected with unextracted particles. Although the extracted particles appeared to be more potent, when converted to a lung burden basis (mg/100 mg dry lung) the incidence was only 14% among those exposed to extracted exhaust compared with 31% in those exposed to whole particles.

Dasenbrock et al. (1996) conducted a study to determine the relative importance of the organic constituents of diesel particles and particle surface area in the induction of lung cancer in rats. Fifty-two female Wistar rats were intratracheally instilled with 16-17 doses of DPM, extracted DPM, printex carbon black (PR), lampblack (LB), benzo[*a*]pyrene (BaP), DPM + BaP, or PR + BaP. The animals were held for a lifetime or sacrificed when moribund. The lungs were necropsied and examined for tumors. Diesel particles were collected from a Volkswagen 1.6-L engine operating on a US FTP-72 driving cycle. The mass median aerodynamic diameter (MMAD) of the diesel particles was 0.25 μm and the specific surface area was 12 m^2/gm . Following extraction with toluene, specific surface area increased to 138 m^2/gm . The MMAD for extracted PR was equal to 14 nm, while the specific surface area equaled 271 m^2/gm . The MMAD for extracted lampblack was equal to 95 nm, with a specific surface area equal to 20 m^2/gm . The BaP content of the treated particles was 11.3 mg per gm diesel particles and 29.5 mg

1 BaP per gm PR. Significant increases in lung tumors were detected in rats instilled with 15 mg
2 unextracted DPM and 30 mg extracted DPM, but not 15 mg extracted DPM. Printex CB was
3 more potent than lampblack CB for induction of lung tumors, whereas BaP was effective only at
4 high doses. Total dose and tumor responses are shown in Table 7-4.

5 A number of conclusions can be drawn from these results. First of all, particles devoid of
6 organics are capable of inducing lung tumor formation, as indicated by positive results in the
7 groups treated with high-dose extracted diesel particles and printex. Nevertheless, toluene
8 extraction of organics from diesel particles results in a decrease in potency, indicating that the
9 organic fraction does play a role in cancer induction. A relationship between cancer potency and
10 particle surface area was also suggested by the finding that printex with a large specific surface
11 area was more potent than either extracted DPM or lampblack, which have smaller specific areas.
12 Finally, while very large doses of BaP are very effective in the induction of lung tumors, smaller
13 doses adsorbed to particle surfaces had little detectable effect, suggesting that other organic
14 components of diesel exhaust may be of greater importance in the induction of lung tumors at low
15 doses of BaP (0.2-0.4 mg).

16 17 **7.3.4.2. Syrian Hamster Studies**

18 Kunitake et al. (1986) and Ishinishi et al. (1988b) conducted a study in which total doses
19 of 1.5, 7.5, or 15 mg of a dichloromethane extract of DPM were instilled intratracheally over 15
20 weeks into male Syrian hamsters that were then held for their lifetimes. The tumor incidences of
21 2.3% (1/44), 0% (0/56), and 1.7% (1/59) for the high-, medium-, and low-dose groups,
22 respectively, did not differ significantly from the 1.7% (1/56) reported for controls. Addition of
23 7.5 mg of B[a]P to a DPM extract dose of 1.5 mg resulted in a total tumor incidence of 91.2%
24 and malignant tumor incidence of 88%. B[a]P (7.5 mg over 15 weeks) alone produced a tumor
25 incidence rate of 88.2% (85% of these being malignant), which was not significantly different
26 from the DPM extract + B[a]P group. Intratracheal administration of 0.03 µg B[a]P, the
27 equivalent content in 15 mg of DPM extract, failed to cause a significant increase in tumors in
28 rats. This study demonstrated a lack of detectable interaction between DPM extract and B[a]P,
29 the failure of DPM extract to induce carcinogenesis, and the propensity for respiratory tract
30 carcinogenesis following intratracheal instillation of high doses of B[a]P. For studies using the
31 DPM extract, some concern must be registered regarding the known differences in chemical
32 composition between DPM extract and DPM. As with all intratracheal instillation protocols,
33 DPM extract lacks the complement of volatile chemicals found in whole diesel exhaust.

34 The effects on hamsters of intratracheally instilled DPM suspension, DPM with Fe₂O₃, or
35 DPM extract with Fe₂O₃ as the carrier were studied by Shefner et al. (1982). The DPM
36 component in each of the treatments was administered at concentrations of 1.25, 2.5, or 5.0

1 mg/week for 15 weeks to groups of 50 male Syrian golden hamsters. The total volume instilled
2 was 3.0 mL (0.2 mL/week for 15 weeks). The DPM and dichloromethane extracts were
3 suspended in physiological saline with gelatin (0.5% w/v), gum arabic (0.5% w/v), and propylene
4 glycol (10% by volume). The Fe₂O₃ concentration, when used, was 1.25 mg/0.2 mL of
5 suspension. Controls received vehicle and, where appropriate, carrier particles (Fe₂O₃) without
6 the DPM component. Two replicates of the experiments were performed. Adenomatous
7 hyperplasia was reported to be most severe in those animals treated with DPM or DPM plus
8 Fe₂O₃ particles and least severe in those animals receiving DPM plus Fe₂O₃. Of the two lung
9 adenomas detected microscopically, one was in an animal treated with a high dose of DPM and
10 the other was in an animal receiving a high dose of DPM extract. Although lung damage was
11 increased by instillation of DPM, there was no evidence of tumorigenicity.

12 13 **7.3.4.3. Mouse Studies**

14 Ichinose et al. (1997a) intratracheally instilled 36 four-week-old male ICR mice per group
15 weekly for 10 weeks with sterile saline or 0.05, 0.1, or 0.2 mg DPM. Particles were collected
16 from a 2.74-L four-cylinder Isuzu engine run at a steady speed of 1,500 rpm under a load of 10
17 torque (kg/m). Twenty-four hours after the last instillation, six animals per group were sacrificed
18 for measurement of lung 8-hydroxydeoxyguanosine (8-OHdG). The remaining animals were
19 sacrificed after 12 months for histopathological analysis. Lung tumor incidence varied from 4/30
20 (13.3%) for controls to 9/30 (30%), 9/29 (31%), and 7/29 (24.1%) for mice instilled with 0.05,
21 0.1, and 0.2 mg/week, respectively. The increase in animals with lung tumors compared with
22 controls was statistically significant for the 0.1 mg dose group, the only group analyzed
23 statistically. Increases in 8-OHdG, an indicator of oxidative DNA damage, correlated well with
24 the increase in tumor incidence in the 0.05 mg dose group, although less so with the other two.
25 The correlation coefficients $r = 0.916, 0.765, \text{ and } 0.677$ for the 0.05, 0.10, and 0.20 mg DPM
26 groups, respectively.

27 In a similar study, 33 four-week-old male ICR mice per group were intratracheally instilled
28 weekly for 10 weeks with sterile saline, 0.1 mg DPM, or 0.1 mg DPM from which the organic
29 constituents were extracted with hexane (Ichinose et al., 1997b). Exhaust was collected from a
30 2.74-L four-cylinder Isuzu engine run at a steady speed of 2,000 rpm under a load of 6 torque
31 (kg/m). Twenty-four hours after the last instillation, six animals per group were sacrificed for
32 measurement of 8-OHdG. Surviving animals were sacrificed after 12 mo. The incidence of lung
33 tumors increased from 3/27 (11.1%) among controls to 7/27 (25.9%) among those instilled with
34 extracted diesel particles and 9/26 (34.6%) among those instilled with unextracted particles. The
35 increase in number of tumor-bearing animals was statistically significant compared with controls

1 ($p < 0.05$) for the group treated with unextracted particles. The increase in 8-OHdG was highly
2 correlated with lung tumor incidence, $r = 0.99$.

4 **7.3.5. Subcutaneous and Intraperitoneal Injection Studies**

5 **7.3.5.1. Mouse Studies**

6 In addition to inhalation studies, Orthoefer et al. (1981) also tested the effects of i.p.
7 injections of DPM on male (A/S) strain mice. Three groups of 30 mice were injected with 0.1 mL
8 of a suspension (particles in distilled water) containing 47, 117, or 235 μg of DPM collected from
9 Fluoropore filters in the inhalation exposure chambers. The exposure system and exposure
10 atmosphere are described in Appendix A. Vehicle controls received injections of particle
11 suspension made up of particulate matter from control exposure filters, positive controls received
12 20 mg of urethan, and negative controls received no injections. Injections were made three times
13 weekly for 8 weeks, resulting in a total DPM dose of 1.1, 2.8, and 5.6 mg for the low-, medium-,
14 and high-dose groups and 20 mg of urethan for the positive control group. These animals were
15 sacrificed after 26 weeks and examined for lung tumors. For the low-, medium-, and high-dose
16 DPM groups, the tumor incidence was 2/30, 10/30, and 8/30, respectively. The incidence among
17 urethan-treated animals (positive controls) was 100% (29/29), with multiple tumors per animal.
18 The tumor incidence for the DPM-treated animals did not differ significantly from that of vehicle
19 controls (8/30) or negative controls (7/28). The number of tumors per mouse was also unaffected
20 by treatment.

21 In further studies conducted by Orthoefer et al. (1981), an attempt was made to compare
22 the potency of DPM with that of other environmental pollutants. Male and female Strain A mice
23 were injected i.p. three times weekly for 8 weeks with DPM, DPM extracts, or various
24 environmental mixtures of known carcinogenicity, including cigarette smoke condensate, coke
25 oven emissions, and roofing tar emissions. Injection of urethan or dimethylsulfoxide (DMSO)
26 served as positive or vehicle controls, respectively. In addition to DPM from the Nissan diesel
27 previously described, an eight-cylinder Oldsmobile engine operated at the equivalent of 40 mph
28 was also used to compare emission effects from different makes and models of diesel engine. The
29 mice were sacrificed at 9 months of age and their lungs examined for histopathological changes.
30 The only significant findings, other than for positive controls, were small increases in numbers of
31 lung adenomas per mouse in male mice injected with Nissan DPM and in female mice injected
32 with coke oven extract. Furthermore, the increase in the extract-treated mice was significant only
33 in comparison with uninjected controls (not injected ones) and did not occur when the experiment
34 was repeated. Despite the use of a strain of mouse known to be sensitive to tumor induction, the
35 overall findings of this study were negative. The authors provided several possible explanations
36 for these findings, the most likely of which were (1) the carcinogens that were present were very

1 weak, or (2) the concentrations of the active components reaching the lungs were insufficient to
2 produce positive results.

3 Kunitake et al. (1986) conducted studies using DPM extract obtained from a 1983 HD
4 MMC—6D22P 11-L V-6 engine. Five s.c. injections of DPM extract (500 mg/kg per injection)
5 resulted in a significant ($p<0.01$) increase in subcutaneous tumors for female C57BL mice (5/22
6 [22.7%] vs. 0/38 among controls). Five s.c. doses of DPM extract of 10, 25, 30, 100, or 200
7 mg/kg failed to produce a significant increase in tumor incidence. One of 12 female ICR mice
8 (8.3%) and 4 of 12 male ICR mice (33.3%) developed malignant lymphomas following neonatal
9 s.c. administration of 10 mg of DPM extract per mouse. The increase in malignant lymphoma
10 incidence for the male mice was statistically significant at $p<0.05$ compared with an incidence of
11 2/14 (14.3%) among controls. Treatment of either sex with 2.5 or 5 mg of DPM extract per
12 mouse did not result in statistically significant increases in tumor incidence.

13 Additional studies using DPM extract from LD (1.8-L, 4-cylinder) as well as HD engines
14 with female ICR and nude mice (BALB/c/cA/JCL-nu) were also reported (Kunitake et al., 1988).
15 Groups of 30 ICR and nude mice each were given a single s.c. injection of 10 mg HD extract, 10
16 mg HD + 50 μ g 12-O-tetradecanoylphorbol 13-acetate (TPA), 10 mg LD extract + 50 μ g TPA,
17 or 50 μ g TPA. No malignant tumors or papillomas were observed. One papillomatous lesion
18 was observed in an ICR mouse receiving LD extract + TPA, and acanthosis was observed in one
19 nude mouse receiving only TPA.

20 In what appears to be an extension of the Kunitake et al. (1986) s.c. injection studies,
21 Takemoto et al. (1988) presented additional data for subcutaneously administered DPM extract
22 from HD and LD diesel engines. In this report, the extracts were administered to 5-week-old and
23 neonatal (<24 hr old) C57BL mice of both sexes. DPM extract from HD or LD engines was
24 administered weekly to the 5-week-old mice for 5 weeks at doses of 10, 25, 50, 100, 200, or 500
25 mg/kg, with group sizes ranging from 15 to 54 animals. After 20 weeks, comparison with a
26 control group indicated a significant increase in the incidence of subcutaneous tumors for the 500
27 mg/kg HD group (5 of 22 mice [22.7%], $p<0.01$), the 100 mg/kg LD group (6 of 32 [18.8%],
28 $p<0.01$), and the 500 mg/kg LD group (7 of 32 [21.9%], $p<0.01$) in the adult mouse experiments.
29 The tumors were characterized as malignant fibrous histiocytomas. No tumors were observed in
30 other organs. The neonates were given single doses of 2.5, 5, or 10 mg DPM extract
31 subcutaneously within 24 hr of birth. There was a significantly higher incidence of malignant
32 lymphomas in males receiving 10 mg of HD extract and of lung tumors for males given 2.5 mg
33 HD extract and for males given 5 mg and females given 10 mg LD extract. A dose-related trend
34 that was not significant was observed for the incidences of liver tumors for both the HD extract-
35 and LD extract-treated neonatal mice. The incidence of mammary tumors in female mice and
36 multiple-organ tumors in male mice was also greater for some extract-treated mice, but was not

1 dose related. The report concluded that LD DPM extract showed greater carcinogenicity than did
2 HD DPM extract.

3 4 **7.3.6. Dermal Studies**

5 **7.3.6.1. Mouse Studies**

6 In one of the earliest studies of diesel emissions, the effects of dermal application of
7 extract from DPM were examined by Kotin et al. (1955). Acetone extracts were prepared from
8 the DPM of a diesel engine (type and size not provided) operated at warmup mode and under
9 load. These extracts were applied dermally three times weekly to male and female C57BL and
10 strain A mice. Results of these experiments are summarized in Table 7-5. In the initial
11 experiments using 52 (12 male, 40 female) C57BL mice treated with DPM extract from an engine
12 operated in warmup mode, two papillomas were detected after 13 mo. Four tumors were
13 detected 16 months after the start of treatment in 8 surviving of 50 exposed male strain A mice
14 treated with DPM extract from an engine operated under full load. Among female strain A mice
15 treated with DPM extract from an engine operated under full load, 17 tumors were detected in 20
16 of 25 mice surviving longer than 13 mo. This provided a significantly increased tumor incidence
17 of 85%. Carcinomas as well as papillomas were seen, but the numbers were not reported.

18 Depass et al. (1982) examined the potential of DPM and dichloromethane extracts of
19 DPM to act as complete carcinogens, carcinogen initiators, or carcinogen promoters. In skin-
20 painting studies, the DPM was obtained from an Oldsmobile 5.7-L diesel engine operated under
21 constant load at 65 km/h. The DPM was collected at a temperature of 100°C. Groups of 40
22 C3H/HeJ mice were used because of their low spontaneous tumor incidence. For the complete
23 carcinogenesis experiments, DPM was applied as a 5% or 10% suspension in acetone.
24 Dichloromethane extract was applied as 5%, 10%, 25%, or 50% suspensions. Negative controls
25 received acetone, and positive controls received 0.2% B[a]P. For tumor-promotion experiments,
26 a single application of 1.5% B[a]P was followed by repeated applications of 10% DPM
27 suspension, 50% DPM extract, acetone only (vehicle control), 0.0001% phorbol 12-myristate 13-
28 acetate (PMA) as a positive promoter control, or no treatment (negative control). For the tumor-
29 initiation studies, a single initiating dose of 10% diesel particle suspension, 50% diesel particle
30 extract, acetone, or PMA was followed by repeated applications of 0.0001% PMA. Following 8
31 months of treatment, the PMA dose in the initiation and promotion studies was increased to
32 0.01%. Animals were treated three times per week in the complete carcinogenesis and initiation
33 experiments and five times per week in promotion experiments. All test compounds were applied
34 to a shaved area on the back of the mouse.

35 In the complete carcinogenesis experiments, one mouse receiving the high-dose (50%)
36 suspension of extract developed a squamous cell carcinoma after 714 days of treatment. Tumor

1 incidence in the B[a]P group was 100%, and no tumors were observed in any of the other groups.
2 For the promotion studies, squamous cell carcinomas with pulmonary metastases were identified
3 in one mouse of the 50% DPM extract group and in one in the 25% extract group. Another
4 mouse in the 25% extract group developed a grossly diagnosed papilloma. Nineteen positive
5 control mice had tumors (11 papillomas, 8 carcinomas). No tumors were observed for any of the
6 other treatment groups. For the initiation studies, three tumors (two papillomas and one
7 carcinoma) were identified in the group receiving DPM suspension and three tumors (two
8 papillomas and one fibrosarcoma) were found in the DPM extract group. These findings were
9 reported to be statistically insignificant using the Breslow and Mantel-Cox tests.

10 Although these findings were not consistent with those of Kotin et al. (1955), the
11 occurrence of a single carcinoma in a strain known to have an extremely low spontaneous tumor
12 incidence may be of importance. Furthermore, a comparison between studies employing different
13 strains of mice with varying spontaneous tumor incidences may result in erroneous assumptions.

14 Nesnow et al. (1982) studied the formation of dermal papillomas and carcinomas
15 following dermal application of dichloromethane extracts from coke oven emissions, roofing tar,
16 DPM, and gasoline engine exhaust. DPM from five different engines, including a preproduction
17 Nissan 220C, a 5.7-L Oldsmobile, a prototype Volkswagen Turbo Rabbit, a Mercedes 300D, and
18 a HD Caterpillar 3304, was used for various phases of the study. Male and female Sencar mice
19 (40 per group) were used for tumor initiation, tumor promotion, and complete carcinogenesis
20 studies. For the tumor-initiation experiments, the DPM extracts were topically applied in single
21 doses of 100, 500, 1,000, or 2,000 µg/mouse. The high dose (10,000 µg/mouse) was applied in
22 five daily doses of 2,000 µg. One week later, 2 µg of the tumor promoter TPA was applied
23 topically twice weekly. The tumor-promotion experiments used mice treated with 50.5 µg of
24 B[a]P followed by weekly (twice weekly for high dose) topical applications (at the
25 aforementioned doses) of the extracts. For the complete carcinogenesis experiments, the test
26 extracts were applied weekly (twice weekly for the high doses) for 50 to 52 weeks. Only extracts
27 from the Nissan, Oldsmobile, and Caterpillar engines were used in the complete carcinogenesis
28 experiments.

29 In the tumor-initiation studies, both B[a]P alone and the Nissan engine DPM extract
30 followed by TPA treatment produced a significant increase in tumor (dermal papillomas)
31 incidence at 7 to 8 weeks postapplication. By 15 weeks, the tumor incidence was greater than
32 90% for both groups. No significant carcinoma formation was noted for mice in the tumor-
33 initiation experiments following exposure to DPM extracts of the other diesel engines, although
34 the Oldsmobile engine DPM extract at 2.0 mg/mouse did produce a 40% papilloma incidence in
35 male mice at 6 mo. This effect, however, was not dose dependent.

1 B[a]P (50.5 µg/week), coke oven extract (at 1.0, 2.0, or 4.0 mg/week), and the highest
2 dose of roofing tar extract (4.0 mg/week) all tested positive for complete carcinogenesis activity.
3 DPM extracts from only the Nissan, Oldsmobile, and Caterpillar engines were tested for complete
4 carcinogenic potential, and all three proved to be negative using the Sencar mouse assay.

5 The results of the dermal application experiments by Nesnow et al. (1982) are presented in
6 Table 7-7. The tumor initiation-promotion assay was considered positive if a dose-dependent
7 response was obtained and if at least two doses provided a papilloma-per-mouse value that was
8 three times or greater than that of the background value. Based on these criteria, only emissions
9 from the Nissan were considered positive. Tumor initiation and complete carcinogenesis assays
10 required that at least one dose produce a tumor incidence of at least 20%. None of the DPM
11 samples yielded positive results based on this criterion.

12 Kunitake et al. (1986, 1988) evaluated the effects of a dichloromethane extract of DPM
13 obtained from a 1983 MMC M-6D22P 11-L V-6 engine. An acetone solution was applied in 10
14 doses every other day, followed by promotion with 2.5 µg of TPA three times weekly for 25
15 weeks. Exposure groups received a total dose of 0.5, 5, 15, or 45 mg of extract. Papillomas
16 were reported in 2 of 50 animals examined in the 45 mg exposure group and in 1 of 48 in the 15
17 mg group compared with 0 of 50 among controls. Differences, however, were not statistically
18 significant.

20 **7.3.7. Summary and Conclusions of Laboratory Animal Carcinogenicity Studies**

21 As early as 1955, Kotin et al. (1955) provided evidence for tumorigenicity and
22 carcinogenicity of acetone extracts of DPM following dermal application and also provided data
23 suggesting a difference in this potential depending on engine operating mode. Until the early
24 1980s, no chronic studies assessing inhalation of diesel exhaust, the relevant mode for human
25 exposure, had been reported. Since then long-term inhalation bioassays with diesel exhaust have
26 been carried out in the United States, Germany, Switzerland, and Japan, testing responses of rats,
27 mice, and Syrian hamsters, and to a limited extent cats and monkeys.

28 It can be reasonably concluded that with adequate exposure, inhalation of diesel exhaust is
29 capable of inducing lung cancer in rats. Responses best fit cumulative exposure (concentration ×
30 daily exposure duration × days of exposure). Examination of rat data shown in Table 7-8
31 indicates a trend of increasing tumor incidence at exposures exceeding 1×10^4 mg·hr/m³.
32 Exposures greater than approximately this value result in lung particle overload, characterized by
33 slowed particle clearance and lung pathology, as discussed in Chapters 3 and 5, respectively.
34 Tumor induction at high doses may therefore be primarily the result of lung particle overload with
35 associated inflammatory responses. Although tumorigenic responses could not be detected under
36 non-particle-overload conditions, the animal experiments lack sensitivity to determine if a

1 threshold exists. However, studies such as those reported by Driscoll et al. (1996) support the
2 existence of a threshold if it is assumed that inflammation is a prerequisite for lung tumor
3 induction. If low-dose effects do occur, it can be hypothesized that the organic constituents are
4 playing a role. See Chapter 7 for a discussion of this issue.

5 Although rats develop adenomas, adenocarcinomas, and adenosquamous cell carcinomas,
6 they also develop squamous keratinizing lesions. This latter spectrum appears for the most part to
7 be peculiar to the rat. In a recent workshop aimed at classifying these tumors (Boorman et al.,
8 1996), it was concluded that when these lesions occur in rats as part of a carcinogenicity study,
9 they must be evaluated on a case-by-case basis and regarded as a part of the total biologic profile
10 of the test article. If the only evidence of tumorigenicity is the presence of cystic keratinizing
11 epitheliomas, it may not have relevance to human safety evaluation of a substance or particle.
12 Their use in quantifying cancer potency is even more questionable.

13 The evidence for response of common strains of laboratory mice exposed under standard
14 inhalation protocols is equivocal. Inhalation of diesel exhaust induced significant increases in lung
15 tumors in female NMRI mice (Heinrich et al., 1986b; Stöber, 1986) and in female Sencar mice
16 (Pepelko and Peirano, 1983). An apparent increase was also seen in female C57BL mice
17 (Takemoto et al., 1986). However, in a repeat of their earlier study, Heinrich et al. (1995) failed
18 to detect lung tumor induction in either NMRI or C57BL/6N mice. No increases in lung tumor
19 rates were reported in a series of inhalation studies using strain A mice (Orthofer et al., 1981;
20 Kaplan et al., 1982, 1983; White et al., 1983). Finally, Mauderly et al. (1996) reported no
21 tumorigenic responses in CD-1 mice exposed under conditions resulting in positive responses in
22 rats. The successful induction of lung tumors in mice by Ichinose et al. (1997a,b) via intratracheal
23 instillation may have been the result of focal deposition of larger doses. Positive effects in Sencar
24 mice may be due to use of a strain sensitive to tumor induction in epidermal tissue by organic
25 agents, as well as exposure from conception, although proof for such a hypothesis is lacking.

26 Attempts to induce significant increases in lung tumors in Syrian hamsters by inhalation of
27 whole diesel exhaust were unsuccessful (Heinrich et al., 1982, 1986b, 1989b; Brightwell et al.,
28 1986). However, hamsters are considered to be relatively insensitive to lung tumor induction. For
29 example, while cigarette smoke, a known human carcinogen, was shown to induce laryngeal
30 cancer in hamsters, the lungs were relatively unaffected (Dontenwill et al., 1973).

31 Neither cats (Pepelko and Peirano, 1983 [see Chapter 7]) nor monkeys (Lewis et al.,
32 1986) developed tumors following 2-year exposure to diesel exhaust. The duration of these
33 exposures, however, was likely to be inadequate for these two longer-lived species, and group
34 sizes were quite small. Exposure levels were also below the maximum tolerated dose (MTD) in
35 the monkey studies and, in fact, only borderline for detection of lung tumor increases in rats.

1 Long-term exposure to diesel exhaust filtered to remove particulate matter failed to induce
2 lung tumors in rats (Heinrich et al., 1986b; Iwai et al., 1986; Brightwell et al., 1989), or in Syrian
3 hamsters (Heinrich et al., 1986b; Brightwell, 1989). A significant increase in lung carcinomas was
4 reported by Heinrich et al. (1986b) in NMRI mice exposed to filtered exhaust. However, in a
5 more recent study the authors were unable to confirm earlier results in either NMRI or C57BL/6N
6 mice (Heinrich et al., 1995). Although filtered exhaust appeared to potentiate the carcinogenic
7 effects of DEN (Heinrich et al., 1982), because of the lack of positive data in rats and equivocal
8 or negative data in mice it can be concluded that filtered exhaust is either not carcinogenic or has
9 a low cancer potency.

10 Kawabata et al. (1986) demonstrated the induction of lung tumors in Fischer 344 rats
11 following intratracheal instillation of DPM. Rittinghausen et al. (1997) reported an increase in
12 cystic keratinizing epitheliomas following intratracheal instillation of rats with either original DPM
13 or DPM extracted to remove the organic fraction, with the unextracted particles inducing a
14 slightly greater effect. Grimmer et al. (1987) showed not only that an extract of DPM was
15 carcinogenic when instilled in the lungs of rats, but also that most of the carcinogenicity resided in
16 the portion containing PAHs with four to seven rings. Intratracheal instillation did not induce
17 lung tumors in Syrian hamsters (Kunitake et al., 1986; Ishinishi et al., 1988b).

18 Dermal exposure and s.c. injection in mice provided additional evidence for tumorigenic
19 effects of DPM. Particle extracts applied dermally to mice have been shown to induce significant
20 skin tumor increases in two studies (Kotin et al., 1955; Nesnow et al., 1982). Kunitake et al.
21 (1986) also reported a marginally significant increase in skin papillomas in ICR mice treated with
22 an organic extract from an HD diesel engine. Negative results were reported by Depass et al.
23 (1982) for skin-painting studies using mice and acetone extracts of DPM suspensions. However,
24 in this study the exhaust particles were collected at temperatures of 100 °C, which would
25 minimize the condensation of vapor-phase organics and, therefore, reduce the availability of
26 potentially carcinogenic compounds that might normally be present on diesel exhaust particles. A
27 significant increase in the incidence of sarcomas in female C57Bl mice was reported by Kunitake
28 et al. (1986) following s.c. administration of LD DPM extract at doses of 500 mg/kg. Takemoto
29 et al. (1988) provided additional data for this study and reported an increased tumor incidence in
30 the mice following injection of LD engine DPM extract at doses of 100 and 500 mg/kg. Results
31 of i.p. injection of DPM or DPM extracts in strain A mice were generally negative (Orthofer et
32 al., 1981; Pepelko and Peirano, 1983), suggesting that the strain A mouse may not be a good
33 model for testing diesel emissions.

34 Results of experiments using tumor initiators such as DEN, B[a]P, DPN, or DBA
35 (Brightwell et al., 1986; Heinrich et al., 1986b; Takemoto et al., 1986) were generally
36 inconclusive regarding the tumor-promoting potential of either filtered or whole diesel exhaust. A

1 report by Heinrich et al. (1982), however, indicated that filtered exhaust may promote the tumor-
2 initiating effects of DEN in hamsters.

3 Several reports (Wong et al., 1985; Bond et al., 1990) affirm observations of the potential
4 carcinogenicity of diesel exhaust by providing evidence for DNA damage in rats. These findings
5 are discussed in more detail in Section 3.6. Evidence for the mutagenicity of organic agents
6 present in diesel engine emissions is also provided in Chapter 4.

7 Evidence for the importance of the carbon core was initially provided by studies of
8 Kawabata et al. (1986), which showed induction of lung tumors following intratracheal instillation
9 of carbon black that contained no more than traces of organics, and studies of Heinrich (1990)
10 that indicated that exposure via inhalation to carbon black (Printex 90) particles induced lung
11 tumors at concentrations similar to those effective in DPM studies. Additional studies by Heinrich
12 et al. (1995) and Nikula et al. (1995) confirmed the capability of carbon particles to induce lung
13 tumors. Induction of lung tumors by other particles of low solubility, such as titanium dioxide
14 (Lee et al., 1986), confirmed the capability of particles to induce lung tumors. Pyrolyzed pitch,
15 on the other hand, essentially lacking a carbon core but having much higher PAH concentrations
16 than DPM, also was effective in tumor induction (Heinrich et al., 1986a, 1994).

17 The relative importance of the adsorbed organics, however, remains to be elucidated and
18 is of some concern because of the known carcinogenic capacity of some of these chemicals.
19 These include polycyclic aromatics as well as nitroaromatics, as described in Chapter 2. Organic
20 extracts of particles also have been shown to induce tumors in a variety of injection, intratracheal
21 instillation, and skin-painting studies, and Grimmer et al. (1987) have, in fact, shown that the
22 great majority of the carcinogenic potential following instillation resided in the fraction containing
23 four- to seven-ring PAHs.

24 In summary, based on positive inhalation studies in rats exposed to high concentrations,
25 intratracheal instillation studies in rats and mice exposed to high doses, and supported by positive
26 mutagenicity studies, the evidence for carcinogenicity of diesel exhaust is considered to be
27 adequate in animals. The contribution of the various fractions of diesel exhaust to the
28 carcinogenic response is less certain. Exposure to filtered exhaust generally failed to induce lung
29 tumors. The presence of known carcinogens adsorbed to diesel particles and the demonstrated
30 tumorigenicity of particle extracts in a variety of injection, instillation, and skin-painting studies
31 indicate a carcinogenic potential for the organic fraction. Studies showing that long-term
32 exposure at high concentrations of poorly soluble particles (e.g., carbon black, TiO₂) can also
33 induce tumors, on the other hand, have provided definitive evidence that the carbon core of the
34 diesel particle is primarily instrumental in the carcinogenic response observed in rats under
35 sufficient exposure conditions. The ability of diesel exhaust to induce lung tumors at non-particle-

1 overload conditions, and the relative contribution of the particles' core versus the particle-
2 associated organics (if effects do occur at low doses) remains to be determined.

3 4 **7.4. MODE OF ACTION OF DIESEL EMISSION-INDUCED CARCINOGENESIS**

5 As noted in Chapter 2, diesel exhaust is a complex mixture that includes a vapor phase and
6 a particle phase. The particle phase consists of an insoluble carbon core with a large number of
7 organic compounds, as well as inorganic compounds such as sulfates, adsorbed to the particle
8 surface. Some of the semivolatile and particle-associated compounds, in particular PAHs, nitro-
9 PAHs, oxy-PAHs, and oxy-nitro-PAHs (Scheepers and Bos, 1992), are considered likely to be
10 carcinogenic in humans. The vapor phase also contains a large number of organic compounds,
11 including several known or probable carcinogens such as benzene and 1,3-butadiene. Because
12 exposure to the vapor phase alone, even at high concentrations, failed to induce lung cancer in
13 laboratory animals (Heinrich et al., 1986), discussion will focus on the particulate matter phase.
14 Additive or synergistic effects of vapor-phase components, however, cannot be totally discounted,
15 as chronic inhalation bioassays involving exposure to diesel particles alone have not been carried
16 out.

17 Several hypotheses regarding the primary mode of action of diesel exhaust have been
18 proposed. Initially it was generally believed that cancer was induced by particle-associated
19 organics acting via a genotoxic mechanism. By the late 1980s, however, studies indicated that
20 carbon particles virtually devoid of organics could also induce lung cancer at sufficient inhaled
21 concentrations (Heinrich, 1990). This finding provided support for a hypothesis originally
22 proposed by Vostal (1986) that induction of lung tumors arising in rats exposed to high
23 concentrations of diesel exhaust is related to overloading of normal lung clearance mechanisms,
24 accumulation of particles, and cell damage followed by regenerative cell proliferation. The action
25 of particles is therefore mediated by epigenetic mechanisms that can be characterized more by
26 promotional than initiation stages of the carcinogenic process. More recently several studies have
27 focused upon the production of reactive oxygen species generated from particle-associated
28 organics, which may induce oxidative DNA damage at exposure concentrations lower than those
29 required to produce lung particle overload. Because it is likely that more than one of these
30 factors is involved in the carcinogenic process, a key consideration is their likely relative
31 contribution at different exposure levels. The following discussion will therefore consider the
32 possible relationship of the organic components of exhaust, inflammatory responses associated
33 with lung particle overload, reactive oxygen species, and physical characteristics of diesel particles
34 to cancer induction, followed by a hypothesized mode of action, taking into account the likely
35 contribution of the factors discussed.

7.4.1. Potential Role of Organic Exhaust Components in Lung Cancer Induction

More than 100 carcinogenic or potentially carcinogenic components have been specifically identified in diesel emissions, including various PAHs and nitroarenes such as 1-nitropyrene (1-NP) and dinitropyrenes (DNPs). The majority of these compounds are adsorbed to the carbon core of the particulate phase of the exhaust and, if desorbed, may become available for biological processes such as metabolic activation to mutagens. Among such compounds identified from diesel exhaust are benzo(*a*)pyrene (B[*a*]P), dibenz[*a,h*]anthracene, pyrene, chrysene, and nitroarenes such as 1-NP, 1,3-DNP, 1,6-DNP, and 1,8-DNP, all of which are mutagenic, carcinogenic, or implicated as procarcinogens or cocarcinogens (Stenback et al., 1976; Weinstein and Troll, 1977; Thyssen et al., 1981; Pott and Stöber, 1983; Howard et al., 1983; Hirose et al., 1984; Nesnow et al., 1984; El-Bayoumy et al., 1988). More recently Enya et al. (1997) reported isolation of 3-nitrobenzanthrone, one of the most powerful direct-acting mutagens known to date, from the organic extracts of diesel exhaust.

Grimmer et al. (1987) separated diesel exhaust particle extract into a water- and a lipid-soluble fraction, and the latter was further separated into a PAH-free, a PAH-containing, and a polar fraction by column chromatography. These fractions were then tested in Osborne-Mendel rats by pulmonary implantation at doses corresponding to the composition of the original diesel exhaust. The water-soluble fraction did not induce tumors; the incidences induced by the lipid-soluble fractions were 0% with the PAH-free fraction, 25% with the PAH and nitro-PAH-containing fractions, and 0% with the polar fraction. The PAH and nitro-PAH-containing fraction, comprising only 1% by weight of the total extract, was thus shown to be responsible for most, if not all, of the carcinogenic activity.

Exposure of rats by inhalation to 2.6 mg/m³ of an aerosol of tar-pitch condensate with no carbon core but containing 50 µg/m³ benzo[*a*]pyrene along with other PAHs for 10 months induced lung tumors in 39% of the animals. The same amount of tar-pitch vapor condensed onto the surface of carbon black particles at 2 and 6 mg/m³ resulted in tumor rates that were roughly two times higher (89% and 72%). Because exposure to 6 mg/m³ carbon black almost devoid of extractable organic material induced a lung tumor rate of 18%, the combination of PAHs and particles increases their effectiveness (Heinrich et al., 1994). Although this study shows the tumor-inducing capability of PAHs resulting from combustion, it should be noted that the benzo[*a*]pyrene content in the coal-tar pitch was about three orders of magnitude greater than in diesel soot. Moreover, because organics are present on diesel particles in a thinner layer and the particles are quite convoluted, they may be more tightly bound and less bioavailable. Nevertheless, these studies provide evidence supporting the involvement of organic constituents of diesel particles in the carcinogenic process.

1 Exposure of humans to related combustion emissions provides some evidence for the
2 involvement of organic components. Mumford et al. (1989) reported greatly increased human
3 lung cancer mortality in Chinese communes burning so-called smoky coal, but not wood, in
4 unvented open-pit fires used for heating and cooking. Although particle concentrations were
5 similar, PAH levels were five to six times greater in the air of communes burning smoky coal.
6 Coke oven emissions, containing high concentrations of PAHs but lacking an insoluble carbon
7 core, have also been shown to be carcinogenic in humans (Lloyd, 1971).

8 Adsorption of PAHs to a carrier particle such as hematite, CB, aluminum, or titanium
9 dioxide enhances their carcinogenic potency (Farrell and Davis, 1974). As already noted,
10 adsorption to carbon particles greatly enhanced the tumorigenicity of pyrolyzed pitch condensate
11 containing B[a]P and other aromatic carcinogens (Heinrich et al., 1995). The increased
12 effectiveness can be partly explained by more efficient transport to the deep lung. Slow release
13 also enhances residence time in the lungs and prevents overwhelming of activating pathways. As
14 discussed in Chapter 3, free organics are likely to be rapidly absorbed into the bloodstream, which
15 may explain why the vapor-phase component of exhaust is relatively ineffective in the induction of
16 pathologic or carcinogenic effects.

17 Even though the organic constituents may be tightly bound to the particle surface,
18 significant elution is still likely because particle clearance half-times are nearly 1 year in humans
19 (Bohning et al., 1982). Furthermore, Gerde et al. (1991a) presented a model demonstrating that
20 large aggregates of inert dust containing crystalline PAHs are unlikely to form at doses typical of
21 human exposure. This allows the particles to deposit and react with the surrounding lung
22 medium, without interference from other particles. Particle-associated PAHs can then be
23 expected to be released more rapidly from the particles. Bond et al. (1984) provided evidence
24 that alveolar macrophages from beagle dogs metabolized B[a]P coated on diesel particles to
25 proximate carcinogenic forms. Unless present on the particle surface, B[a]P is more likely to pass
26 directly into the bloodstream and escape activation by phagocytic cells.

27 The importance of DE-associated PAHs in the induction of lung cancer in humans may be
28 enhanced because of the possibility that the human lung is more sensitive to these compounds
29 than are rat lungs. Rosenkranz (1996) summarized information indicating that in humans and
30 mice, large proportions of lung cancers contain both mutated *p53* suppressor genes and *K-ras*
31 genes. Induction of mutations in these genes by genotoxins, however, is much lower in rats than
32 in humans or mice.

33 B[a]P, although only one of many PAHs present in diesel exhaust, is the one most
34 extensively studied. Bond et al. (1983, 1984) demonstrated metabolism of particle-associated
35 B[a]P and free B[a]P by alveolar macrophages (AM) and by type II alveolar cells. The
36 respiratory tract cytochrome P-450 systems have an even greater concentration in the nonciliated

1 bronchiolar cells (Boyd, 1984). It is worth noting that bronchiolar adenomas that develop
2 following diesel exposure have been found to resemble both Type II and nonciliated bronchiolar
3 cells. It should also be noted that any metabolism of procarcinogens by these latter two cell types
4 probably involves the preextraction of carcinogens in the extracellular lining fluid and/or other
5 endocytotic cells, as they are not especially important in phagocytosis of particles. Thus,
6 bioavailability is an important issue in assessing the relative importance of PAHs.

7 Additionally, a report by Borm et al. (1997) indicates that incubating rat lung epithelial-
8 derived cells with human polymorphonucleocytes (PMNs) (either unactivated or activated by
9 preexposure to phorbol myristate acetate) increases DNA adduct formation caused by exposure
10 to benzo[*a*] pyrene; at 0.05 to 0.5 micromolar concentration, addition of more activated PMN in
11 relation to the number of lung cells further increased adduct formation in a dose-dependent
12 manner. The authors suggest that “an inflammatory response in the lung may increase the
13 biologically effective dose of PAHs, and may be relevant to data interpretation and risk
14 assessment of PAH-containing particles.” These data raise the possibility that diesel exhaust
15 exposure at low concentrations may result in levels of neutrophil influx that would not necessarily
16 be detectable via histopathological examination as acute inflammation, but that might be effective
17 at amplifying any potential diesel exhaust genotoxic effect.

18 Nitro-PAHs have also been implicated as potentially involved in diesel-exhaust-induced
19 lung cancer. Although the nitro-PAH fraction of diesel was less effective than PAHs in the
20 induction of lung cancer when implanted into the lungs of rats (Grimmer et al., 1987), in a study
21 of various extracts of diesel exhaust particles, 30%-40% of the total mutagenicity could be
22 attributed to a group of six nitroarenes (Salmeen et al., 1984). Moreover, Gallagher et al. (1994)
23 reported results suggesting that DNA adducts are formed from nitro-PAHs present in DNA and
24 may play a role in the carcinogenic process. Nitroarenes, however, quantitatively represent a very
25 small percentage of diesel particle extract (Grimmer et al., 1987), making their role in the
26 tumorigenic response uncertain.

27 The induction of DNA adducts in humans occupationally exposed to diesel exhaust
28 indicates the likelihood that PAHs are participating in the tumorigenic response, and that these
29 effects can occur at exposure levels less than those required to induce lung particle overload.
30 Distinct adduct patterns were found among garage workers occupationally exposed to diesel
31 exhaust when compared with nonexposed controls (Nielsen and Autrup, 1994). Furthermore, the
32 findings were concordant with the adduct patterns observed in groups exposed to low
33 concentrations of PAHs from combustion processes. Hemminki et al. (1994) also reported
34 significantly elevated levels of DNA adducts in lymphocytes from garage workers with known
35 diesel exhaust exposure compared with unexposed mechanics. Hou et al. (1995) found elevated
36 adduct levels in bus maintenance workers exposed to diesel exhaust. Although no difference in

1 mutant frequency was observed between the groups, the adduct levels were significantly different
2 (3.2 vs. 2.3×10^{-8}). Nielsen et al. (1996) measured three biomarkers in DE-exposed bus garage
3 workers: lymphocyte DNA adducts, hydroxyethylvaline adducts in hemoglobin, and
4 1-hydroxypyrene in urine. Significantly increased levels were reported for all three. Qu et al.
5 (1996) detected increased adduct levels, as well as increases in some individual adducts, in the
6 blood of underground coal miners exposed to DE.

7 8 **7.4.2. Role of Inflammatory Cytokines and Proteolytic Enzymes in the Induction of Lung** 9 **Cancer in Rats by Diesel Exhaust**

10 It is well recognized that the deposition of particles in the lung can result in the efflux of
11 PMNs from the vascular compartment into the alveolar space compartment in addition to
12 expanding the AM population size. Following acute exposures, the influx of the PMNs is
13 transient, lasting only a few days (Adamson and Bowden, 1978; Bowden and Adamson, 1978;
14 Lehnert et al., 1988). During chronic exposure the numbers of PMNs lavaged from the lungs of
15 diesel-exposed rats generally increased with increasing exposure duration and inhaled DPM
16 concentration (Strom, 1984). Strom (1984) also found that PMNs in diesel-exposed lungs
17 remained persistently elevated for at least 4 months after cessation of exposure, a potential
18 mechanism that may be related to an ongoing release of phagocytized particles. Evidence in
19 support of this possibility was reported by Lehnert et al. (1989) in a study in which rats were
20 intratracheally instilled with 0.85, 1.06, or 3.6 mg of polystyrene particles. The PMNs were not
21 found to be abnormally abundant during the clearance of the two lower lung burdens, but they
22 became progressively elevated in the lungs of the animals in which alveolar-phase clearance was
23 inhibited. Moreover, the particle burdens in the PMNs became progressively greater over time.
24 Such findings are consistent with an ongoing particle relapse process, in which particles released
25 by dying phagocytes are ingested by new ones.

26 The inflammatory response, characterized by efflux of PMNs from the vascular
27 compartment, is mediated by inflammatory chemokines. Driscoll et al. (1996) reported that
28 inhalation of high concentrations of carbon black stimulated the release of macrophage
29 inflammatory protein 2 (MIP-2) and monocyte chemotactic protein 1 (MCP-1). They also
30 reported a concomitant increase in hprt mutants. In a following study it was shown that particle
31 exposure stimulates production of tumor necrosis factor TNF- α , an agent capable of activating
32 expression of several proteins that promote both adhesion of leucocytes and chemotaxis (Driscoll
33 et al., 1997a). In addition, alveolar macrophages also have the ability to release several other
34 effector molecules or cytokines that can regulate numerous functions of other lung cells, including
35 their rates of proliferation (Bitterman et al., 1983; Jordana et al., 1988; Driscoll et al., 1996).

1 Another characteristic of AMs and PMNs under particle overload conditions is the release
2 of a variety of potentially destructive hydrolytic enzymes, a process known to occur
3 simultaneously with the phagocytosis of particles (Sandusky et al., 1977). The essentially
4 continual release of such enzymes during chronic particle deposition and phagocytosis in the lung
5 may be detrimental to the alveolar epithelium, especially to Type I cells. Evans et al. (1986)
6 showed that injury to Type I cells is followed shortly thereafter by a proliferation of Type II cells.
7 Type II cell hyperplasia is a common feature observed in animals that have received high lung
8 burdens of various types of particles, including unreactive polystyrene microspheres. Exaggerated
9 proliferation as a repair or defensive response to DPM deposition may have the effect of
10 amplifying the likelihood of neoplastic transformation in the presence of carcinogens beyond that
11 which would normally occur with lower rates of proliferation, assuming an increase in the cycling
12 of target cells and the probability of a neoplastic-associated genomic disturbance.

14 **7.4.3. Role of Reactive Oxygen Species in Lung Cancer Induction by Diesel Exhaust**

15 Phagocytes from a variety of rodent species produce elevated levels of oxidant reactants in
16 response to challenges, with the physiochemical characteristics of a phagocytized particle being a
17 major factor in determining the magnitude of the oxidant-producing response. Active oxygen
18 species released by the macrophages and lymphatic cells can cause lipid peroxidation in the
19 membrane of lung epithelial cells. These lipid peroxidation products can initiate a cascade of
20 oxygen free radicals that progress through the cell to the nucleus, where they damage DNA. If
21 this damage occurs during the epithelial cell's period of DNA synthesis, there is some probability
22 that the DNA will be replicated unrepaired (Lechner and Mauderly, 1994). The generation of
23 reactive oxygen species by both AMs and PMNs should therefore be considered as one potential
24 factor of what probably is a multistep process that culminates in the development of lung tumors
25 in response to chronic deposition of DPM.

26 Even though products of phagocytic oxidative metabolism, including superoxide anions,
27 hydrogen peroxide, and hydroxyl radicals, can kill tumor cells (Klebanoff and Clark, 1978), and
28 the reactive oxygen species can peroxidize lipids to produce cytotoxic metabolites such as
29 malonyldialdehyde, some products of oxidative metabolism apparently can also interact with DNA
30 to produce mutations. Cellular DNA is damaged by oxygen free radicals generated from a variety
31 of sources (Ames, 1983; Trotter, 1980). Along this line, Weitzman and Stossel (1981) found that
32 human peripheral leukocytes are mutagenic in the Ames assay. This mutagenic activity was
33 related to PMNs and blood monocytes; blood lymphocytes alone were not mutagenic. These
34 investigators speculated that the mutagenic activity of the phagocytes was a result of their ability
35 to produce reactive oxygen metabolites, inasmuch as blood leukocytes from a patient with chronic
36 granulomatous diseases, in which neutrophils have a defect in the NADPH oxidase generating

1 system (Klebanoff and Clark, 1978), were less effective in producing mutations than were normal
2 leukocytes. Of related significance, Phillips et al. (1984) demonstrated that the incubation of
3 Chinese hamster ovary cells with xanthine plus xanthine oxidase (a system for enzymatically
4 generating active oxygen species) resulted in genetic damage hallmarked by extensive
5 chromosomal breakage and sister chromatid exchange and produced an increase in the frequency
6 of thioguanidine-resistant cells (HGPRT test). Aside from interactions of oxygen species with
7 DNA, increasing evidence also points to an important role of phagocyte-derived oxidants and/or
8 oxidant products in the metabolic activation of procarcinogens to their ultimate carcinogenic form
9 (Kensler et al., 1987).

10 Driscoll et al. (1997b) have demonstrated that exposure to doses of particles producing
11 significant neutrophilic inflammation are associated with increased mutation in rat alveolar type II
12 cells. The ability of particle-elicited macrophages and neutrophils to exert a mutagenic effect on
13 epithelial cells in vitro supports a role for these inflammatory cells for the in vivo mutagenic
14 effects of particle exposure. The inhibition of bronchoalveolar lavage cell-induced mutations by
15 catalase implies a role for cell-derived oxidants in this response.

16 Hatch and co-workers (1980) have demonstrated that interactions of guinea pig AMs with
17 a wide variety of particles, such as silica, metal oxide-coated fly ash, polymethylmethacrylate
18 beads, chrysotile asbestos, fugitive dusts, polybead carboxylate microspheres, glass and latex
19 beads, uncoated fly ash, and fiberglass increase the production of reactive oxygen species. Similar
20 findings have been reported by numerous investigators for human, rabbit, mouse, and guinea pig
21 AMs (Drath and Karnovsky, 1975; Allen and Loose, 1976; Beall et al., 1977; Lowrie and Aber,
22 1977; Miles et al., 1977; Rister and Baehner, 1977; Hoidal et al., 1978). PMNs are also known to
23 increase production of superoxide radicals, hydrogen peroxide, and hydroxyl radicals in response
24 to membrane-reactive agents and particles (Goldstein et al., 1975; Weiss et al., 1978; Root and
25 Metcalf, 1977). Although these responses may occur at any concentration, they are likely to be
26 greatly enhanced at high exposure concentrations with slowed clearance and lung particle
27 overload.

28 Reactive oxygen species can also be generated from particle-associated organics. Sagai et
29 al. (1993) reported that DPM can nonenzymatically generate active oxygen species (e.g.,
30 superoxide [O_2^-] and hydroxyl radical [$\cdot OH$] in vitro without any biologically activating systems)
31 such as microsomes, macrophages, hydrogen peroxide, or cysteine. Because DPM washed with
32 methanol could no longer produce these radicals, it was concluded that the active components
33 were compounds extractable with organic solvents. However, the nonenzymatic contribution to
34 the DPM-promoted active oxygen production was negligible compared with that generated via an
35 enzymatic route (Ichinose et al., 1997a). They reported that O_2^- and $\cdot OH$ can be enzymatically
36 generated from DPM by the following process. Soot-associated quinone-like compounds are

1 reduced to the semiquinone radical by cytochrome P-450 reductase. These semiquinone radicals
2 then reduce O_2 to O_2^- , and the produced superoxide reduces ferric ions to ferrous ions, which
3 catalyzes the homobiotic cleavage of H_2O_2 dismutated from O_2 by superoxide dismutase or
4 spontaneous reactions to produce $\cdot OH$. According to Kumagai et al. (1997), while quinones are
5 likely to be the favored substrates for this reaction, the participation of nitroaromatics cannot be
6 ruled out.

7 One of the critical lesions to DNA bases generated by oxygen free radicals is 8-
8 hydroxydeoxyguanosine (8-OHdG). The accumulation of 8-OHdG as a marker of oxidative DNA
9 damage could be an important factor in enhancing the mutation rate leading to lung cancer
10 (Ichinose et al., 1997a). For example, formation of 8-OHdG adducts leads to G:C to T:A
11 transversions unless repaired prior to replication. Nagashima et al. (1995) demonstrated that the
12 production of (8-OHdG) is induced in mouse lungs by intratracheal instillation of DPM. Ichinose
13 et al. (1997b) reported further that although intratracheal instillation of DPM in mice induced a
14 significant increase in lung tumor incidence, comparable increases were not reported when mice
15 were instilled with extracted DPM (to remove organics). Lung injury was also less in the mice
16 instilled with extracted DPM. Moreover, increases in 8-OHdG in the mice instilled with
17 unextracted DPM correlated very well with increases in tumor rates. In a related study, Ichinose
18 et al. (1997a) intratracheally instilled small doses of DPM, 0.05, 0.1, or 0.2 mg weekly for 3
19 weeks, in mice fed standard or high-fat diets either with or without β -carotene. High dietary fat
20 enhanced DPM-induced lung tumor incidence, whereas β -carotene, which may act as a free
21 radical scavenger, partially reduced the tumorigenic response. Formation of 8-OHdG was again
22 significantly correlated with lung tumor incidence in these studies, except at the highest dose.
23 Dasenbrock et al. (1996) reported that extracted DPM, intratracheally instilled into rats (15 mg
24 total dose) induced only marginal increases in lung tumor induction, while unextracted DPM was
25 considerably more effective. Although adducts were not measured in this study, it nevertheless
26 provides support for the likelihood that activation of organic metabolites and/or generation of
27 oxygen free radicals from organics are involved in the carcinogenic process. Additional
28 support for the involvement of particle-associated radicals in tissue damage was provided by the
29 finding that pretreatment with superoxide dismutase (SOD), an antioxidant, markedly reduced
30 lung injury and death due to instillation of DPM. Similarly, Hirafuji et al. (1995) found that the
31 antioxidants catalase, deferoxamine, and MK-447 inhibited the toxic effects of DPM on guinea
32 pig tracheal cells and tissues in vitro.

33 Although the data presented supported the hypothesis that generation of reactive oxygen
34 species resulting from exposure to DPM is involved in the carcinogenic process, it should be
35 noted that 8-OHdG is efficiently repaired and that definitive proof of a causal relationship in
36 humans is still lacking. It is also uncertain whether superoxide or hydroxyl radicals chemically

1 generated by DPM alone promote 8-OHdG production in vivo and induce lung toxicity, because
2 SOD is extensively located in mammalian tissues. Nevertheless, demonstration that oxygen free
3 radicals can be generated from particle-associated organics, that their presence will induce adduct
4 formation and DNA damage unless repaired, that tumor induction in experimental animals
5 correlates with OhdG adducts, and that treatment with antioxidant limits lung damage, provides
6 strong support for the involvement of oxygen free radicals in the toxicologic and carcinogenic
7 response to diesel exhaust.

8 9 **7.4.4. Relationship of Physical Characteristics of Particles to Cancer Induction**

10 The biological potential of inhaled particles is strongly influenced by surface chemistry and
11 character. For example, the presence of trace metal compounds such as aluminum and iron, as
12 well as ionized or protonated sites, is important in this regard (Langer and Nolan, 1994). A major
13 factor is specific surface area (surface area/mg). PMNs characteristically are increased abnormally
14 in the lung by diesel exhaust exposure, but their presence in the lungs does not appear to be
15 excessive following the pulmonary deposition of even high lung burdens of spherical TiO₂
16 particles in the 1-2 μm diameter range (Strom, 1984). In these studies lung tumors were detected
17 only at an inhaled concentration of 250 μg/m³. In a more recent study in which rats were exposed
18 to TiO₂ in the 15-40 nm size range, inhibition of particle clearance and tumorigenesis were
19 induced at concentrations of 10 mg/m³ (Heinrich et al., 1995). Comparison of several chronic
20 inhalation studies correlating particle mass and particle surface area retained in the lung with
21 tumor incidence indicated that particle surface area is a much better dosimeter than particle mass
22 (Oberdörster and Yu, 1990; Driscoll et al., 1996). Heinrich et al. (1995) also found that lung
23 tumor rates increased with specific particle surface area following exposure to diesel exhaust,
24 carbon black, or titanium dioxide, irrespective of particle type. Langer and Nolan (1994) reported
25 that the hemolytic potential of Min-U-Sil15, a silica flour, increased in direct relationship to
26 specific surface area at nominal particle diameters ranging from 0.5 to 20 μm.

27 Ultrafine particles appear to be more likely to be taken up by lung epithelial cells. Riebe-
28 Imre et al. (1994) reported that CB is taken up by lung epithelial cells in vitro, inducing
29 chromosomal damage and disruption of the cytoskeleton, lesions that closely resemble those
30 present in tumor cells. Johnson et al. (1993) reported that 20-nm polytetrafluoroethylene particles
31 are taken up by pulmonary epithelial cells as well as polymorphonuclear leucocytes, inducing an
32 approximate 4-, 8-, and 40-fold increase in the release of interleukin-1 alpha and beta, inducible
33 nitric oxide synthetase, and macrophage inflammatory protein, respectively.

34 The carcinogenic potency of diesel particles, therefore, appears to be related, at least to
35 some extent, to their small size and convoluted shape, which results in a large specific particle
36 surface area. Toxicity and carcinogenicity increased with increasing particle size into the

1 submicron range. For example, Heinrich et al. (1995) have shown that ultrafine titanium dioxide
2 (approximately 0.2 μm diameter) is much more toxic than particles with a 10-fold greater
3 diameter of the same composition used in an earlier study by Lee et al. (1986). This increase in
4 toxicity has been noted with even smaller particles. For example, carbon black particles 20 nm in
5 diameter were shown to be significantly more toxic than 50 nm particles (Murphy et al., 1999).
6 The relationship between particle size and toxicity is of concern because, as noted in Chapter 2,
7 approximately 50%-90% of the number of particles in diesel exhaust are in the size range from 5
8 to 50 nm. Other than disruption of the cytoskeleton of epithelial cells, there is little information
9 regarding the means by which particle size influences carcinogenicity as well as noncancer
10 toxicity.

11 12 **7.4.5. Integrative Hypothesis for Diesel-Induced Lung Cancer**

13 The induction of lung cancer by large doses of carbon black via inhalation (Heinrich et al.,
14 1995; Mauderly et al., 1991; Nikula et al., 1995) or intratracheal instillation (Kawabata et al.,
15 1994; Pott et al., 1994; Dasenbrock et al., 1996) led to the development of the lung particle
16 overload hypothesis. According to this hypothesis the induction of neoplasia by insoluble low-
17 toxicity particles is associated with an inhibition of lung particle clearance and the involvement of
18 persistent alveolar epithelial hyperplasia. Driscoll (1995), Driscoll et al. (1996), and Oberdörster
19 and Yu (1990) outlined a proposed mechanism for the carcinogenicity of diesel exhaust at high
20 doses that emphasizes the role of phagocytic cells. Following exposure, phagocytosis of particles
21 acts as a stimulant for oxidant production and inflammatory cytokine release by lung phagocytes.
22 It was hypothesized that at high particle exposure concentrations the quantity of mediators
23 released by particle-stimulated phagocytes exceeds the inflammatory defenses of the lung (e.g.,
24 antioxidants, oxidant-metabolizing enzymes, protease inhibitors, cytokine inhibitors), resulting in
25 tissue injury and inflammation. With continued particle exposure and/or the persistence of
26 excessive particle burdens, there then develops an environment of phagocytic activation, excessive
27 mediator release-tissue injury and, consequently, more tissue injury, inflammation, and tissue
28 release. This is accompanied by cell proliferation. As discussed in a review by Cohen and Ellwein
29 (1991), conceptually, cell proliferation can increase the likelihood that any oxidant-induced or
30 spontaneously occurring genetic damage becomes fixed in a dividing cell and is clonally expanded.
31 The net result of chronic particle exposures sufficient to elicit inflammation and cell proliferation
32 in the rat lung is an increased probability that the genetic changes necessary for neoplastic
33 transformation will occur. A schematic of this hypothesis has been outlined by McClellan (1997)
34 (see Figure 7-3). In support of this hypothesis, it was reported that concentrations of inhaled CB
35 resulted in increased cytokine expression and inflammatory influx of neutrophils (Oberdörster et
36 al., 1995), increased formation of 8-OhdG (Ichinose et al., 1997b), and increase in the yield of

1 hprt mutants, an effect ameliorated by treatment with antioxidants (Driscoll, 1995; Driscoll et al.,
2 1996). Metabolism of carcinogenic organics to active forms as well as the generation of reactive
3 oxygen species from certain organic species are likely to contribute to the toxic and carcinogenic
4 process.

5 At low concentrations, inflammatory effects associated with lung particle overload are
6 generally absent. However, activation of organic carcinogens and generation of oxidants from the
7 organic fraction can still be expected. Actual contribution depends upon elution and the
8 effectiveness of antioxidants. Direct effects of ultrafine diesel particles taken up by epithelial cells
9 are also likely to play a role.

10 Although high-dose induction of cancer is logically explained by this hypothesis, particle
11 overload has not been clearly shown to induce lung cancer in other species. As noted in the
12 quantitative chapter, the relevance of the rat pulmonary response is therefore problematic. The
13 rat pulmonary noncancer responses to DPM, however, have fairly clear interspecies and human
14 parallels. In response to poorly soluble particles such as DPM, humans and rats both develop an
15 alveolar macrophage response, accumulate particles in the interstitium, and show mild interstitial
16 fibrosis (ILSI, 2000). Other species (mice, hamsters) also have shown similar noncancer
17 pulmonary responses to DPM, but without accompanying cancer response. The rat response for
18 noncancer pulmonary histopathology, however, seems to be more pronounced compared with
19 humans or other species, i.e., rats appear to be more sensitive. Although many critical elements of
20 interspecies comparison, such as the role of airway geometry and patterns of particle deposition,
21 need further elucidation, this basic interspecies similarity and greater sensitivity of pulmonary
22 response seen after longer exposures at high doses make pulmonary histopathology in rats a valid
23 basis for noncancer dose-response assessment.

24 25 **7.4.6. Summary**

26 Recent studies have shown tumor rates resulting from exposures to nearly organic-free CB
27 particles at high concentrations to be similar to those observed for diesel exhaust exposures, thus
28 providing strong evidence for a particle overload mechanism for DE-induced pulmonary
29 carcinogenesis in rats. Such a mechanism is also supported by the fact that carbon particles per se
30 cause inflammatory responses and increased epithelial cell proliferation and that AM function may
31 be compromised under conditions of particle overload.

32 The particle overload hypothesis appears sufficient to account for DE-induced lung cancer
33 in rats. However, there is increasing evidence for lung cancer induction in humans at
34 concentrations insufficient to induce lung particle overload as seen in rats (Section 3.7 and ILSI
35 2000). Uptake of particles by epithelial cells at ambient or occupational exposure levels, DNA
36 damage resulting from oxygen-free radicals generated from organic molecules, and the gradual in

1 situ extraction and activation of procarcinogens associated with the diesel particles are likely to
2 play a role in this response. The slower particle clearance rates in humans (up to a year or more)
3 may result in greater extraction of organics. This is supported by reports of increased DNA
4 adducts in humans occupationally exposed to diesel exhaust at concentrations unlikely to induce
5 lung particle overload. Although these modes of action can be expected to function at lung
6 overload conditions also, they are likely to be overwhelmed by inflammatory associated effects.

7 The evidence to date indicates that caution must be exercised in extrapolating observations
8 made in animal models to humans when assessing the potential for DE-induced
9 pulmonary carcinogenesis. The carcinogenic response and the formation of DNA adducts in rats
10 exposed to diesel exhaust and other particles at high exposure concentrations may be species-
11 specific and not particle-specific. The likelihood that different modes of action predominate at
12 high and low doses also renders low-dose extrapolation to ambient concentrations uncertain.

14 **7.5. WEIGHT-OF-EVIDENCE EVALUATION FOR POTENTIAL HUMAN** 15 **CARCINOGENICITY**

16 A weight-of-evidence evaluation is a synthesis of all pertinent information addressing the
17 question of how likely an agent is to be a human carcinogen. EPA's 1986 Guidelines for
18 Carcinogen Risk Assessment (U.S. EPA, 1986) provide a classification system for the
19 characterization of the overall weight of evidence for potential human carcinogenicity based on
20 human evidence, animal evidence, and other supportive data. This system includes Group A:
21 *Human Carcinogen*; Group B: *Probable Human Carcinogen*; Group C: *Possible Human*
22 *Carcinogen*; Group D: *Not Classifiable as to Human Carcinogenicity*; and Group E: *Evidence*
23 *for Noncarcinogenicity to Humans*.

24 As part of the guidelines development and updating process, the Agency has developed
25 revisions to the 1986 guidelines to take into account knowledge gained in recent years about the
26 carcinogenic processes. With regard to the weight-of-evidence evaluation for potential human
27 carcinogenicity, EPA's 1996 Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA,
28 1996b) and the subsequent revised external review draft (U.S. EPA, 1999) emphasize the need for
29 characterizing cancer hazard, in addition to hazard identification. Accordingly, the question to be
30 addressed in hazard characterization is expanded to how likely an agent is to be a human
31 carcinogen, and under what exposure conditions a cancer hazard may be expressed. The revised
32 guidelines also stress the importance of considering the mode(s) of action information for making
33 an inference about potential cancer hazard beyond the range of observation, typically encountered
34 at levels of exposure in the general environment. "Mode of action" refers to a series of key
35 biological events and processes that are critical to the development of cancer. This is contrasted
36 with "mechanisms of action," which is defined as a more detailed description of the complete

1 sequence of biological events at the molecular level that must occur to produce a carcinogenic
2 response.

3 To express the weight of evidence for potential human carcinogenicity, EPA's proposed
4 guidelines utilize a hazard narrative in place of the classification system. However, in order to
5 provide some measure of consistency, standard hazard descriptors are used as part of the hazard
6 narrative to express the conclusion regarding the weight of evidence for potential human
7 carcinogenicity.

8 The sections to follow evaluate and weigh the individual lines of evidence and combine all
9 evidence to make an informed judgement about the potential human carcinogenicity of DE. A
10 conclusion in accordance with EPA's 1986 classification system (U.S. EPA, 1986) is provided, as
11 well as a hazard narrative along with appropriate hazard descriptors according to EPA's Proposed
12 Revised Guidelines (U.S. EPA, 1996b, 1999). These sections draw on information reviewed in
13 Chapters 2, 3, 4, and 7.

14 15 **7.5.1. Human Evidence**

16 Twenty-two epidemiologic studies about the carcinogenicity of workers exposed to DE in
17 various occupations are reviewed in Section 7.2. Exposure to DE has typically been inferred
18 based on job classification within an industry. Increased lung cancer risk, although not always
19 statistically significant, has been observed in 8 out of 10 cohort and 10 of 12 case-control studies
20 within several industries, including railroad workers, truck drivers, heavy equipment operators,
21 and professional drivers. The increased lung cancer relative risks generally range from 1.2 to 1.5,
22 though a few studies show relative risks as high as 2.6. Statistically significant increases in pooled
23 relative risk estimates (1.33 to 1.47) from two independent meta-analyses further support a
24 positive relationship between DE exposure and lung cancer in a variety of DE-exposed
25 occupations.

26 The generally small increased lung cancer relative risk (less than 2) observed in these
27 analyses potentially weakens the evidence of causality. When a relative risk is less than 2, if
28 confounders (e.g., smoking, asbestos exposure) are having an effect on the observed risk
29 increases, it could be enough to account for the increased risk. With the strongest risk factor for
30 lung cancer being smoking, there is a concern that smoking effects may be influencing the
31 magnitude of the observed increased relative risks. However, in studies for which the effects of
32 smoking were accounted for, increased relative risks for lung cancer prevailed. Though some
33 studies did not have information on smoking, confounding by smoking is unlikely in these studies
34 because the comparison population was from the same socioeconomic class. Moreover, when the
35 meta-analysis focused only on the smoking-controlled studies, the relative risks tended to
36 increase.

1 As evaluated in Chapter 7 (Section 7.2.4.5), application of the criteria for causality
2 provides evidence that the increased risks observed in available epidemiologic studies are
3 consistent with a causal association between exposure to DE and occurrence of lung cancer.
4 Overall, the human evidence for potential carcinogenicity for DE is judged to be strong, but less
5 than sufficient for DE to be considered as a human carcinogen, because of exposure uncertainties
6 (lack of historical exposure of workers to DE) and an inability to satisfactorily account for all
7 confounders.

8 9 **7.5.2. Animal Evidence**

10 DE and its organic constituents, both in the gaseous and particle phase, have been
11 extensively tested for carcinogenicity in many experimental studies using several animal species
12 and with different modes of administration. Several well-conducted studies have consistently
13 demonstrated that chronic inhalation exposure to sufficiently high concentrations of DE produced
14 dose-related increases in lung tumors (benign and malignant) in rats. In contrast, chronic
15 inhalation studies of DE in mice showed mixed results whereas negative findings were
16 consistently seen in hamsters. The gaseous phase of DE (filtered exhaust without particulate
17 fraction), however, was found not to be carcinogenic in rats, mice, or hamsters.

18 In several intratracheal instillation studies, diesel particulate matter (DPM), DPM extracts,
19 and carbon black, which was virtually devoid of PAHs, have been found to produce increased
20 lung tumors in rats. When directly implanted into the rat lung, DPM condensate containing
21 mainly four- to seven-ring PAHs induced increases in lung tumors. In several dermal studies in
22 mice, DPM extracts have also been shown to cause skin tumors and sarcomas in mice following
23 subcutaneous injection.

24 Overall, there is sufficient evidence for the potential carcinogenicity of whole DE in the rat
25 at high exposure concentration or administered dose, both by inhalation and intratracheal
26 instillation. Available data indicate that both the carbon core and the adsorbed organics have
27 potential roles in inducing lung tumors in the rat, although their relative contribution to the
28 carcinogenic response remains to be determined. The gaseous phase of DE, however, does not
29 appear to have any significant role in DE-induced lung cancer response in the rat.

30 Available data also indicate that among the traditional animal test species, the rat is the
31 most sensitive species to DE. As reviewed in Section 7.4, the lung cancer responses in rats from
32 high-concentration exposures to DE appear to be mediated by impairment of lung clearance
33 mechanisms through particle overload, resulting in persistent chronic inflammation and
34 subsequent pathologic and neoplastic changes in the lung. Overload conditions are not expected
35 to occur in humans as a result of environmental or most occupational exposures to DE. Thus, the
36 animal evidence (i.e., increased lung tumors in the rat) provides additional support for identifying

1 potential cancer hazard to humans, but is not considered suitable for dose-response analysis and
2 estimation of human risk to DE.

3 The consistent findings of carcinogenic activity by the organic extracts of DPM in
4 noninhalation studies (intratracheal instillation, lung implantation, skin painting) further contribute
5 to the overall animal evidence for a human hazard potential for DE.
6

7 **7.5.3. Other Key Data**

8 Other key data, although not as extensive as the human and animal carcinogenicity data,
9 are judged to be supportive of potential carcinogenicity of DE. As discussed in Chapter 2, DE is
10 a complex mixture of hundreds of constituents in either gaseous phase or particle phase.

11 Although present in small amounts, several organic compounds in the gaseous phase (e.g. PAHs,
12 formaldehyde, acetaldehyde, benzene, 1,3-butadiene) are known to exhibit mutagenic and/or
13 carcinogenic activities. PAHs and PAH derivatives, including nitro-PAHs, present on the diesel
14 particle are also known to be mutagenic and carcinogenic. As reviewed in Chapter 4, DPM and
15 DPM organic extracts have been shown to induce gene mutations in a variety of bacteria and
16 mammalian cell test systems. In addition, DE, DPM and DPM extracts have been found to cause
17 chromosomal aberrations, aneuploidy, and sister chromatid exchange in both in vivo and in vitro
18 tests.

19 There is also suggestive evidence for the bioavailability of the organics from DE (Chapter
20 3). Elevated levels of DNA adducts in lymphocytes have been reported in workers exposed to
21 DE. In addition, animal studies showed that some of the radiolabeled organic compounds are
22 eluted from DE particles following deposition in the lungs (Section 3.6).

23 **7.5.4. Mode of Action**

24 As discussed in Section 7.4, the modes of action of DE-induced carcinogenicity in humans
25 are not well understood. It is likely that multiple modes of action are involved. These may include:
26 (a) mutagenic and genotoxic events (e.g., direct and indirect effects on DNA and effects on
27 chromosomes) by organic compounds in the gaseous and particle phases; (b) indirect DNA
28 damage via the production of reactive oxygen species (ROS) induced by particle-associated
29 organics; and (c) particle-induced chronic inflammatory response leading to oxidative DNA
30 damage through the release of cytokines, ROS, etc., and an increase in cell proliferation.

31 The particulate phase appears to have the greatest contribution to the carcinogenic effects,
32 and both the particle core and the associated organic compounds have demonstrated carcinogenic
33 properties, although a role for the gas-phase components cannot be ruled out. The carcinogenic
34 activity of DE also appears to be related to the small size of the particles. Moreover, the relative
35 contribution of the various modes of action may be different at different exposure levels.
36 Available evidence from animal studies indicates the importance of the role of the DE particles in

1 mediating lung tumor response at high exposure levels. Thus, the role of the adsorbed organic
2 compounds may take on increasing importance at lower exposure levels.

3
4 **7.5.5. Characterization of Overall Weight of Evidence: EPA’s 1986 Carcinogen Risk**
5 **Assessment Guidelines**

6 The totality of evidence supports the conclusion that DE is a *probable human carcinogen*
7 (*Group B1*). This conclusion is based on:

- 8
9
- 10 • Limited human evidence (less than sufficient) for a causal association between DE
11 exposure and increased lung cancer risk among workers of different occupations;
 - 12 • Sufficient animal evidence for the induction of lung cancer in the rat from inhalation
13 exposure to high concentrations of DE, DPM, and the carbon core; and supporting
14 evidence of carcinogenicity of DPM and the associated organics in rats and mice by
15 noninhalation route of exposure; and
 - 16 • Extensive supporting data including the demonstrated mutagenic and/or chromosomal
17 effects of DE and its organic constituents, suggestive evidence for the bioavailability of
18 the organics from DE, and the known mutagenic and/or carcinogenic activity of a
19 number of individual organic compounds present on the particles and in the gaseous
20 phase.

21 **7.5.6. Weight-of-Evidence Hazard Narrative: EPA’s Proposed Revised Carcinogen Risk**
22 **Assessment Guidelines (1996b, 1999)**

23 The combined evidence supports the conclusion that DE is *likely to be carcinogenic to*
24 *humans* by inhalation exposure at any exposure condition. In comparison with other agents
25 designated as likely to be carcinogenic to humans, the weight of evidence for DE is at the upper
26 end of the spectrum. The weight of evidence of human carcinogenicity is based on:

- 27
- 28 • Strong but less than sufficient epidemiologic evidence for a causal association between
29 occupational exposure and elevated risk of lung cancer;
 - 30 • Consistent evidence of increases of lung tumors in rats from chronic inhalation
31 exposure to high concentration of whole DE, DPM, or the particle elemental carbon
32 core;
 - 33 • Supportive evidence of carcinogenicity in rats for the diesel particle (DPM) via
34 intratracheal instillation, and for DPM organic extracts in rats and mice in noninhalation
35 studies (intratracheal instillation, lung implantation, skin painting, subcutaneous
36 injection);

- 1 • Extensive evidence of mutagenic and chromosomal effects of DE and its organic
2 constituents;
- 3 • Suggestive evidence of the bioavailability of the DPM organics in studies of humans
4 and animals; and
- 5 • The presence of a number of individual organic compounds on the diesel particles (e.g.,
6 PAHs and derivatives) and in the gaseous phase (e.g., benzene, acetaldehydes) that are
7 known to exhibit mutagenic and/or carcinogenic properties.

8
9 A major uncertainty in characterizing the potential cancer hazard for DE at low levels of
10 environmental exposure is the incomplete understanding of its mode of action for the induction of
11 lung cancer in humans. Nonetheless, available data indicate that DE-induced lung carcinogenicity
12 seems to be mediated by mutagenic and nonmutagenic events by both the particles and the
13 associated organic compounds, although a role for the organics in the gaseous phase cannot be
14 ruled out. Given that there is some evidence for a mutagenic mode of action, a cancer hazard is
15 presumed at any exposure level. This is consistent with EPA's science policy position, which
16 assumes a nonthreshold effect for carcinogens in the absence of definitive data demonstrating a
17 nonlinear or threshold mechanism. Accordingly, linear low-dose extrapolation should be assumed
18 in dose-response assessment. Because of insufficient information, the human carcinogenic
19 potential of DE by oral and dermal exposures cannot be determined.

20 21 **7.6. EVALUATIONS BY OTHER ORGANIZATIONS**

22 Several organizations have reviewed the relevant data and evaluated the potential human
23 carcinogenicity of DE or its particulate component. The conclusions reached by these
24 organizations are generally comparable to the evaluation made in this assessment using EPA's
25 Carcinogen Risk Assessment Guidelines. A summary of available evaluations conducted by other
26 organizations is provided in Table 7-9.

27 28 **7.7. CONCLUSION**

29 It is concluded that environmental exposure to DE may present a cancer hazard to
30 humans. The particulate phase appears to have the greatest contribution to the carcinogenic
31 effects, and both the particle core and the associated organic compounds have demonstrated
32 carcinogenic properties, although a role for the gas-phase components cannot be ruled out.
33 Using either EPA's 1986 Carcinogen Risk Assessment Guidelines (U.S. EPA, 1986) or the
34 proposed revisions (U.S. EPA, 1996b, 1999), DE is judged to be a probable human carcinogen,
35 or likely to be carcinogenic to humans by inhalation, respectively. The weight of evidence for
36 potential human carcinogenicity for DE is considered strong, even though inferences are involved

1 in the overall assessment. Major uncertainties of the hazard assessment include the following
2 unresolved issues:

- 3 • There has been a considerable scientific debate about the significance of the available
4 human evidence for a causal association between occupational exposure and increased
5 lung cancer risk. Many experts view the evidence as weak while many others consider
6 the evidence as strong. This is due to a lack of consensus about whether the effects of
7 smoking have been adequately accounted for in key studies, and the lack of historical
8 DE exposure data for the available studies.
- 9 • Although the mode of action for DE-induced lung tumors in rats from high exposure is
10 sufficiently understood, the mode of action for lung cancer risk in humans is not fully
11 known. To date, available evidence for the role of both the adsorbed organics and the
12 carbon core particle has been shown to be associated with high exposure conditions.
13 There is virtually no information about the relative role of DE constituents in mediating
14 carcinogenic effects at the low exposure levels. Furthermore, there is only a limited
15 understanding regarding the relationship between particle size and carcinogenicity.
- 16 • DE is present in ambient PM (e.g., PM_{2.5} or PM₁₀); however, a cancer hazard for
17 ambient PM has not been clearly identified.

18 Additional research is needed to address these issues to reduce the uncertainty associated with
19 the potential cancer hazard of exposure to DE.

Table 7-1. Epidemiologic studies of the health effects of exposure to diesel exhaust: cohort mortality studies

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Waller (1981)	Approximately 20,000 male London transportation workers Aged 45 to 64 years 25 years follow-up (1950-1974)	Five job categories used to define exposure Environmental benzo[a]pyrene concentrations measured in 1957 and 1979	SMR = 79 for lung cancer for the total cohort SMRs for all five job categories were less than 100 for lung cancer	Exposure measurement of benzo[a]pyrene showed very little difference between inside and outside the garage Incomplete information on cohort members No adjustment for confounding such as other exposures, cigarette smoking, etc. No latency analysis
Howe et al. (1983)	43,826 male pensioners of the Canadian National Railway Company Mortality between 1965 and 1977 among these pensioners was compared with mortality of general Canadian population	Exposure groups classified by a group of experts based on occupation at the time of retirement Three exposure groups: Nonexposed Possibly exposed Probably exposed	RR = 1.2 ($p=0.013$) and RR = 1.3 ($p=0.001$) for lung cancer for possible and probable exposure, respectively A highly significant dose-response relationship demonstrated by trend test ($p<0.001$)	Incomplete exposure assessment due to lack of lifetime occupational history Mixed exposures to coal dust/combustion products and diesel exhaust No validation of method was used to categorize exposure Lack of data on smoking but use of internal comparison group to compute RRs minimizes the potential confounding by smoking No latency analysis

Table 7-1. Epidemiologic studies of the health effects of exposure to diesel exhaust: cohort mortality studies (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Rushton et al. (1983)	8,490 male London transport maintenance workers Mortality of workers employed for 1 continuous year between January 1, 1967, and December 31, 1975, was compared with mortality of general population of England and Wales	100 different job titles were grouped in 20 broad categories The categories were not ranked for diesel exhaust exposure	SMR = 133 ($p < 0.03$) for lung cancer in the general hand job group Several other job categories showed SS increased SMRs for several other sites based on fewer than five cases	Ill-defined diesel exhaust exposure without any ranking Average 6-year follow-up i.e., not enough time for lung cancer latency No adjustment for confounders
Wong et al. (1985)	34,156 male heavy construction equipment operators Members of the local union for at least 1 year between January 1, 1964, and December 1, 1978	20 functional job titles grouped into three job categories for potential exposure Exposure groups (high, low, and unknown) based on job description and proximity to source of diesel exhaust emissions	SMR = 166 ($p < 0.05$) for liver cancer for total cohort SMR = 343 (observed = 5, $p < 0.05$) for lung cancer for high-exposure bulldozer operators with 15-19 years of membership, 20+ years of follow-up SMR = 119 (observed = 141, $p < 0.01$) for workers with no work histories	No validation of exposure categories, which were based on surrogate information Incomplete employment records Employment history other than from the union not available 15 year follow-up may not provide sufficient time for lung cancer latency No data on confounders such as other exposures, alcohol, smoking, etc.
Edling et al. (1987)	694 male bus garage employees Follow-up from 1951 through 1983 Mortality of these men was compared with mortality of general population of Sweden	Three exposure groups based on job titles: High exposure, bus garage workers Intermediate exposure, bus drivers Low exposure, clerks	No SS differences were observed between observed and expected for any cancers by different exposure groups	Small sample size No validation of exposure No data on confounders such as other exposures, smoking, etc.

Table 7-1. Epidemiologic studies of the health effects of exposure to diesel exhaust: cohort mortality studies (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Boffetta and Stellman (1988)	46,981 male volunteers enrolled in the American Cancer Society's Prospective Mortality Study of Cancer in 1982 Aged 40 to 79 years at enrollment First 2-year follow-up	Self-reported occupations were coded into 70 job categories Employment in high diesel exhaust exposure jobs were compared with nonexposed jobs	Total mortality (SS) elevated for railroad workers (RR=1.43), heavy equipment operators (RR=1.7), miners (RR=1.34), and truck drivers (RR=1.19) Lung cancer mortality (SS) adjusted for age & smoking, elevated for total cohort (RR=1.31), miners (RR=2.67), and heavy equipment operators (RR=2.6) Lung cancer mortality (SNS) elevated among railroad workers and truck drivers Truck drivers also showed a dose-response	Exposure information based on self-reported occupation for which no validation was done Volunteer population, probably healthy population

Table 7-1. Epidemiologic studies of the health effects of exposure to diesel exhaust: cohort mortality studies (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Garshick et al. (1988)	55,407 white male railroad workers Aged 40 to 64 years in 1959 Started work 10-20 years earlier than 1959	Industrial hygiene data correlated with job titles to dichotomize the jobs as “exposed” or “not exposed”	RR = 1.45 (40-44 year age group) RR = 1.33 (45-49 year age group) Both SS After exclusion of workers exposed to asbestos RR = 1.57 (40-44 year age group) RR = 1.34 (45-49 year age group) Both SS	Years of exposure used as surrogate for dose Not possible to separate the effect of time since first exposure and duration of exposure Lack of smoking data but case-control study showed very little difference between those exposed to diesel exhaust versus those who were not
Garshick (1991)			Dose response indicated by increasing lung cancer risk with increasing cumulative exposure Further analysis using attained age, limited through 1976 showed youngest workers still had the highest risk	
Crump et al. (1991)	Reanalysis of Garshick et al., 1988 data		Dose response found to be positive or negative depending upon how the age was controlled in the model	
Crump et al. (1999)			Negative dose-response upheld in the latest analysis	
California EPA (1998)	Reanalysis of Garshick et al., 1988		Positive dose response using age at 1959 and interaction term of age & calendar year	

Table 7-1. Epidemiologic studies of the health effects of exposure to diesel exhaust: cohort mortality studies (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Gustavsson et al. (1990)	695 male workers from 5 bus garages in Stockholm, Sweden, who had worked for 6 months between 1945 and 1970 34 years follow-up (1952-1986) Nested case-control study 17 cases, six controls for each case matched on age \pm 2 years	Four diesel exhaust indices were created: 0 to 10, 10 to 20, 20-30, and >30 based on job tasks and duration of work	SNS SMRs of 122 and 115 (OA and GP), respectively Case-control study results showed dose response: RR = 1.34 (10 to 20) RR = 1.81 (20 to 30) RR = 2.43 (>30) All SS with 0-10 as comparison group	Exposure matrix based on job tasks (not on actual measurements) Small cohort, hence low power Lack of smoking data is unlikely to confound the results since it is a nested case-control study
Hansen (1993)	Cohort of 57,249 unskilled laborers, ages 15 to 74, in Denmark (nationwide census file) November 9, 1970 Follow-up through November 9, 1980	Diesel exhaust exposure assumed based on diesel-powered trucks	SS SMRs for lung cancer : SMR = 160 for total population SMR = 229 for age 55-59 years SMR = 227 for age 60-64 years	No actual exposure data available Lack of smoking data but population survey showed very little difference between rural and urban smoking habits Job changes may have occurred from laborer to driver Short follow-up period
Saverin et al. (1999)	Cohort of 5,536 potash miners who had worked underground for at least 1 year after 1969 Subcohort of 3,258 who had worked for at least 10 years underground Follow-up from 1970 to 1994	Diesel exhaust exposure categories defined as: production (high) maintenance (medium) workshop (low) 225 air samples obtained: for total carbon, organics, & fine dust in 1992	SNS increased RRs adjusted for smoking: 1.68 and 2.7 for total cohort & subcohort, respectively	Small, young cohort Few deaths No latency analysis

**Table 7-1. Epidemiologic studies of the health effects of exposure to diesel exhaust: cohort mortality studies
(continued)**

Abbreviations: RR = relative risk; SMR = standardized mortality ratio; SNS = statistically nonsignificant; SS = statistically significant;
O = occupationally active; GP = general population.

Table 7-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer

Authors	Population studied	Diesel exhaust exposure	Results	Limitations
Hall and Wynder (1984)	502 histologically confirmed lung cancers Cases diagnosed 12 mo prior to interviews 502 matched hospital controls without tobacco-related diseases, matched for age, sex, race, and geographical area Population from 18 hospitals in controls	Based on previous Industrial Hygiene Standards for a particular occupation, usual lifetime occupation coded as “probably high exposure” and “no exposure” NIOSH standards used to classify exposures: High Moderate Low	SNS excess risk after adjustment for smoking for lung cancer: RR = 1.4 (1st criteria) and RR = 1.7 (NIOSH criteria)	Complete lifetime employment history not available Self-reported occupation history not validated No analysis by dose, latency, or duration of exposure No information on nonoccupational diesel exposure
Damber and Larsson (1987)	589 lung cancer cases who had died prior to 1979 reported to Swedish registry between 1972 and 1977 582 matched dead controls (sex, age, year of death, municipality) drawn from National Registry of Cause of Death 453 matched living controls (sex, year of birth, municipality) drawn from National Population Registry	Occupations held for at least 1 year or more A 5-digit code was used to classify the occupations according to Nordic Classification of Occupations	For underground miners: SS OR = 2.7 (≥ 1 year of employment) SS OR = 9.8 (≥ 20 years of employment) For professional drivers: SNS OR = 1.2 (≥ 20 years of employment) with dead controls All ORs adjusted for smoking	Uncertain diesel exhaust exposure No validation of exposure done Underground miners data not adjusted for other confounders such as radon, etc.

7/25/00

7-118

DRAFT—DO NOT CITE OR QUOTE

Table 7-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer (continued)

Authors	Population studied	Diesel exhaust exposure	Results	Limitations
Lerchen et al. (1987)	506 lung cancer cases from New Mexico tumor registry (333 males and 173 females) Aged 25-84 years Diagnosed between January 1, 1980, and December 31, 1982 771 (499 males and 272 females) frequency matched with cases, selected from telephone directory	Lifetime occupational history and self-reported exposure history were obtained Coded according to Standard Industrial Classification Scheme	No excess of relative odds were observed for diesel exhaust exposure	Exposure based on occupational history and self-report, which was not validated 50% occupational history provided by next of kin Absence of lung cancer association with asbestos suggests misclassification of exposure
Garshick et al. (1987)	1,319 lung cancer cases who died between March 1, 1981, and February 28, 1982 2,385 matched controls (two each, age and date of death) Both cases and controls drawn from railroad worker cohort who had worked for 10 or more years	Personal exposure assessed for 39 job categories This was corrected with job titles to dichotomize the exposure into: Exposed Not exposed Industrial hygiene sampling done	SS OR = 1.41 (≤ 64 year age group) SS OR = 1.64 (≤ 64 year age group) for ≥ 20 years diesel exhaust exposure group when compared to 0- to 4-year exposure group All ORs adjusted for lifetime smoking and asbestos exposure	Probable misclassification of diesel exhaust exposure jobs Years of exposure used as surrogate for dose 13% of death certificates not ascertained Overestimation of smoking history
Benhamou et al. (1988)	1,260 histologically confirmed lung cancer cases 2,084 non-tobacco-related disease matched controls (sex, age at diagnosis, hospital admission, and interviewer) Occurring between 1976 and 1980 in France	Based on exposures determined by panel of experts The occupations were recorded blindly using International Standard Classification of Occupations as chemical or physical exposures	Significant excess risks were found in motor vehicle drivers (RR = 1.42) and transport equipment operators (RR = 1.35) (smoking adjusted)	Exposure based on occupational histories not validated Exposures classified as chemical and physical exposures, not specific to diesel exhaust

Table 7-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer (continued)

Authors	Population studied	Diesel exhaust exposure	Results	Limitations
Hayes et al. (1989)	Pooled data from three different studies consisting of 2,291 male lung cancer cases 2,570 controls	Occupational information from next of kin for all jobs held Jobs classified with respect to potential exposure to known and suspected pulmonary carcinogens	SS OR = 1.5 for truck drivers (>10 years of employment) SS positive trend with increasing employment as truck driver Adjusted for age, smoking, & study area	Exposure data based on job description given by next of kin, which was not validated Could have been mixed exposure to both diesel and gasoline exhausts Job description could have led to misclassification
Steenland et al. (1990)	1,058 male lung cancer deaths between 1982 and 1983 1,160, every sixth death from entire mortality file, sorted by Social Security number (excluding lung cancer, bladder cancer, and motor vehicle accidents) Cases and controls were from Central State Teamsters who had filed claims (requiring 20-year tenure)	Longest job held: diesel truck driver, gasoline truck driver, both types of trucks, truck mechanic, and dockworkers	As 1964 cut-off point: SS OR = 1.64 for long-haul drivers with 13+ years of employment Positive trend test for long-haul drivers ($p=0.04$) SS OR = 1.89 for diesel truck drivers of 35+ years of employment Adjusted for age, smoking, & asbestos	Exposure based on job titles not validated Possible misclassification of exposure and smoking, based on next-of-kin information Lack of sufficient latency
Steenland et al. (1998)	Exposure-response analyses of their 1990 case-control study	Industrial hygiene data of elemental carbon in trucking industry collected by Zaubst et al. (1991) used to estimate individual exposures Cumulative exposures calculated based on estimated lifetime exposures	For mechanics: OR = 1.69 (had the highest diesel exhaust exposure) Lowest diesel exhaust exposure and lowest OR = 0.93 observed for dockworkers Increasing risk of lung cancer with increasing exposure Adjusted for age & smoking	

Table 7-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer (continued)

Authors	Population studied	Diesel exhaust exposure	Results	Limitations
Boffetta et al. (1990)	From 18 hospitals (since 1969), 2,584 male lung cancer cases matched to either one control (69) or two controls (2,515) were drawn. Matched on age, hospital, and year of interview	A priori aggregation of occupations categorized into low probability, possible exposure (19 occupations), and probable exposure (13 occupations) to diesel exhaust	OR slightly below unity SNS Adjusted for smoking	No verification of exposure Duration of employment used as surrogate for dose Number of individuals exposed to diesel exhaust was small
Emmelin et al. (1993)	50 male lung cancer cases from 15 ports (worked for at least 6 months between 1950 and 1974), 154 controls matched on age and port	Indirect diesel exhaust exposure assessment done based on (1) exposure intensity, (2) characteristics of ventilation, (3) measure of proportion of time in higher exposure jobs	SS OR for high-exposure group = 6.8 Positive trend for diesel exhaust observed (trend much steeper for smokers than nonsmokers) Adjusted for smoking	Numbers of cases and controls are small Very few nonsmokers Lack of exposure information on asbestos No latency analysis
Swanson et al. (1993)	Population based case-control study in metropolitan Detroit 3,792 lung cancer cases and 1,966 colon cancer (cases) controls, diagnosed between 1984 and 1987 in white and black males (aged between 40-84)	Telephone interviews with the individual or surrogate about lifetime work history Occupation and industry data coded per 1980 U.S. Census Bureau classification codes Certain occupations and industries were selected as unexposed to carcinogens	SS excess ORs observed for - black farmers OR= 10.4 for 20+ years employment - white railroad industry workers OR= 2.4 for 10+ years employment Among white trend tests were SS for -drivers of heavy duty trucks - drivers of light duty trucks - farmers - railroad workers Among blacks trend test was SS for farmers only All the ORs were adjusted for age at diagnosis, pack-years of cigarette smoking and race	Lack of direct information on specific exposures No latency analysis

Table 7-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer (continued)

Authors	Population studied	Diesel exhaust exposure	Results	Limitations
Hansen et al. (1998)	Population-based case-control study of professional drivers in Denmark Male lung cancer cases diagnosed between 1970-1989, controls matched by year of birth and sex	Information about past employment obtained by linkage with nationwide pension fund Employment as lorry/bus drivers (n=1,640) and taxi drivers (n=426) was used as surrogate for exposure to diesel exhaust	For lorry/bus drivers: SS OR = 1.31 For taxi drivers: SS OR = 1.64, which increased to 2.2 in > 5-year employment with no lag time & 3.0 in > 5 year employment with 10-year lag time SS trend test for increasing risk with increasing employment for both lorry/bus drivers & taxi drivers (p<0.001) All ORs adjusted for socioeconomic status	Lack of information on the type of fuel (personal communication with the principal investigator confirmed that diesel fuel is used for the lorry/buses and taxis since early 1960s) Even though direct adjustment was not done for smoking/asbestos, indirect methods indicate that the results are not likely to be confounded by these factors

Table 7-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer (continued)

Authors	Population studied	Diesel exhaust exposure	Results	Limitations
Brüske-Hohlfeld et al. (1999)	<p>Pooled analysis of two case-control studies (3,498 cases & 3,541 controls)</p> <p>Controls frequency matched on sex, age, & region, randomly selected from the compulsory population registry</p> <p>Inclusion criteria: (1) born in or after 1913/less than 75 years old, (2) German nationality/resident of the region - lived in Germany for more than 25 years, & (3) lung cancer diagnosis should be 3 months prior to the study</p> <p>Information obtained by personal interview on:</p>	<p>Lifetime detailed occupational & smoking histories obtained from each individual in a personal interview</p> <p>Based on job codes (33 job titles & 21 industries) potential diesel exhaust exposure classified in 4 categories: A- professional drivers of trucks, buses, & taxis; B- other traffic related i.e., switchman, locomotive, & forklift drivers; C- bulldozer operators, graders, & excavators; D- farm tractor drivers</p> <p>Cumulative diesel exhaust exposures and pack-years (smoking) calculated for each individual</p>	<p>SS higher risk adjusted for smoking observed for all 4 categories:</p> <p>A- ORs ranged from 1.25 to 2.53 B- ORs ranged from 1.53 to 2.88 C- ORs ranged from 2.31 to 4.3 D- 6.81 (exposure < 30 years)</p> <p>Risk increased with increasing exposure</p>	Lack of data on actual exposure to diesel exhaust

Abbreviations: OR = odds ratio; RR = relative risk; SNS = statistically nonsignificant; SS = statistically significant.

Table 7-3. Summary of animal inhalation carcinogenicity studies

Study	Species/ strain	Sex/total number	Exposure atmosphere	Particle concentration (mg/m ³)	Other treatment	Exposure protocol	Post- exposure observation	Tumor type and incidence (%) ^a				Comments
								<u>Adenomas</u>				
Karagianes et al. (1981)	Rat/Wistar	M, 40	Clean air	8.3	None	6 hr/day,	NA	0/6 (0)				
		M, 40	Whole exhaust		None	5 days/week, for up to 20 mo		1/6 (16.6)				
								<u>Bronchoalveolar carcinoma</u>				
								0/30 (0)				
Kaplan et al. (1983)	Rat/F344	M, 30	Clean air	0	None	20 hr/day,	8 mo	1/30 (3.3)				
		M, 30	Whole exhaust	0.25	None	7 days/week,	8 mo	3/30 (10.0)				
White et al. (1983)		M, 30	Whole exhaust	0.75	None	for up to	8 mo	1/30 (3.3)				
		M, 30	Whole exhaust	1.5	None	15 mo	8 mo					
								<u>Adenomas</u>	<u>Carcinomas</u>	<u>Squamous cell tumors</u>	<u>All tumors</u>	
Heinrich et al. (1986a,b)	Rat/Wistar	F, 96	Clean air	4	None	19 hr/day,	NA	0/96 (0)	0/96 (0)	0/96 (0)	0/96 (0)	
		F, 92	Filtered exhaust		None	5 days/week for up to		0/92 (0)	0/92 (0)	0/92 (0)	0/92 (0)	
Mohr et al. (1986)		F, 95	Whole exhaust		None	35 mo		8/95 (8.4)	0/95 (0)	9/95 (9.4)	17/95 (17.8) ^f	
								<u>Adenomas</u>	<u>Adenocarcinoma and adenosquamous carcinoma</u>	<u>Large cell and squamous cell carcinomas</u>	<u>All tumors</u>	
Iwai et al. (1986)	Rat/F344	F, 24	Clean air	4.9	None	8 hr/day,	NA	1/22 (4.5)	0/22 (0)	0/22 (0)	1/22 (4.5) ^f	
		F, 24	Filtered exhaust		None	7 days/week, for 24 mo		0/16 (0)	0/16 (0)	0/16 (0)	0/16 (0)	
		F, 24	Whole exhaust		None			3/19 (0)	3/19 (15.8)	2/19 (10.5)	8/19 (42.1) ^{c,g}	
								<u>Adenomas</u>	<u>Adenoma</u>	<u>Carcinoma</u>		
Takemoto et al. (1986)	Rat/F344	F, 12	Clean air	0	None	4 hr/day,	NA	0/12 (0)		0/12 (0)		
		F, 21	Clean air	0	DIPN ^h	4 days/week,		10/21 (47.6)		4/21 (19)		
		F, 15	Whole exhaust	2-4	None	18-24 mo		0/15 (0)		0/15 (0)		
		F, 18	Whole exhaust	2-4	DIPN ^h			12/18 (66.7)		7/18 (38.9)		
								<u>Adenomas</u>	<u>Adenocarcinoma + squamous cell carcinoma</u>	<u>Squamous cysts</u>	<u>All tumors</u>	
Mauderly et al. (1987)	Rat/F344	M + F, 230 ^b	Clean air	0	None	7 hr/day,	NA	(0)	(0.9)	(0)	(0.9)	
		M + F, 223	Whole exhaust	0.35	None	5 days/week		(0)	(1.3)	(0)	(1.3)	
		M + F, 221	Whole exhaust	3.5	None	up to 30 mo		(2.3)	(0.5)	(0.9)	(3.6) ^c	
		M + F, 227	Whole exhaust	7.1	None			(0.4)	(7.5)	(4.9)	(12.8) ^c	

Study	Species/ number	Sex/total number	atmosphere	Particle concentration 3)	treatment	Exposure	Post- exposure	Tumor type and incidence (%) ^a			
								Adenomas	Squamous carcinomas	All tumors	
Ishinishi et al. (1988a)	Rat/F344	M + F, 123	Clean air	0	None	16 hr/day, for up to 30 mo	NA	0/123 (0)	0/123 (0)	1/123 (0.8)	
			Whole exhaust	0.5				0/123 (0)	0/123 (0)	0/123 (0)	
			Whole exhaust	1.8				0/123 (0)	0/123 (0)	4/123 (3.3) ^c	
engine		M + F, 124		3.7	None			6/124 (4.8)	0/123 (0)		
Ishinishi et al. Light duty	Rat/F344	NS, 8 NS, 11 NS, 9 NS, 11 NS, 5 NS, 9 NS, 5 NS, 6	Whole exhaust	0.1	None	6 days/week, for 12 mo	12 mo	0/8 (0)	0/8 (0)	0/8 (0)	
			Whole exhaust	0.1	None		18 mo	0/11 (0)	0/11 (0)	0/11 (0)	
			Whole exhaust	1.1	None		12 mo	0/9 (0)	0/9 (0)	0/9 (0)	
			Whole exhaust	1.1	None		18 mo	0/11 (0)	0/11 (0)	0/11 (0)	
			Whole exhaust	0.5	None	16 hr/day, 6 days/week,	6 mo	0/5 (0)	0/5 (0)	0/5 (0)	
			Whole exhaust	0.5	None		12 mo	0/9 (0)	0/9 (0)	0/9 (0)	
			Whole exhaust	1.8	None		6 mo	0/5 (0)	0/5 (0)	0/11 (0)	
			Whole exhaust	1.8	None		12 mo	0/6 (0)	0/6 (0)	0/6 (0)	
Brightwell et (1989a)	Rat/344	M + F, 260	Clean air	0	None	16 hr/day, 5 days/week,	NA		3/260 (1.2)	Tumor	
			exhaust (medium)	0	None					all rats dying or sacrificed	
			Filtered exhaust (high)						0/143 (0)		
			Whole exhaust	0.7	None				1/143 (0.7)		♀ 24/25 (96%) after 24 mo
			Whole exhaust	2.2	None						12/27 (44%) after 24 mo
										55/143 (38.5)	
Lewis et al.	Rat/Wistar	M + F, 288	Clean air	0	DPN	19 hr/day,		No tumors		0/192 (0)	
			Whole exhaust	0	DPN ^d	for 24 to 30 mo					
			Filtered	0	^d				(4.4)	(67.4)	
			Whole exhaust	0	DPN				(4.4)	(93.8)	
			Whole exhaust	0	DPN ^e					(16.7) ^c	(89.6)
			exhaust					(14.6)			

Table 7-3. Summary of animal inhalation carcinogenicity studies (continued)

Study	Species/ strain	Sex/total number	Exposure atmosphere	Particle concentration (mg/m ³)	Other treatment	Exposure protocol	Post- exposure observation	Tumor type and incidence (%) ^a				Comments
								Adenosquamous carcinomas	Squamous cell carcinomas	All tumors		
Takaki et al. (1989)	Rat/F344	M + F, 123	Clean air	0	None	16 hr/day,	NA	1/23 (0.8)	2/123 (1.6)	1/23 (0.8)	4/123 (3.3)	
		M + F, 123	Whole exhaust	0.1	None	6 days/week,		1/23 (0.8)	1/23 (0.8)	1/23 (0.8)	3/123 (2.4)	
		M + F, 125	Whole exhaust	0.4	None	for up to		1/25 (0.8)	0/125 (0)	0/125 (0)	1/125 (0.8)	
		M + F, 123	Whole exhaust	1.1	None	30 mo		0/23 (0)	5/123 (4.1)	0/123 (0)	5/123 (4.1)	
Light-duty engine		M + F, 124	Whole exhaust	2.3	None			1/24 (8.1)	2/124 (1.6)	0/124 (0)	3/124 (2.4)	
Heinrich et al. (1995)	Rat/Wistar	F, 220	Clean air	0	None	18 hr/day,	6 mo	0/217 (0)	1/217 (<1)	0/217 (0)	0/217 (0)	
		F, 200	Whole exhaust	0.8	None	5 days/week,		0/198 (0)	0/198 (0)	0/198 (0)	0/198 (0)	
		F, 200	Whole exhaust	2.5	None	for up to		2/200 (1)	1/200 (<1)	0/200 (0)	7/200 (3.5)	
		F, 100	Whole exhaust	7.0	None	24 mo		4/100 (4)	4/100 (4)	2/100 (2)	14/100 (14)	Tumor
		F, 100	Carbon black	11.6	None			13/100 (13)	13/100 (13)	4/100 (4)	20/100 (20)	incidences
	F, 100	TiO ₂	10.0	None		4/100 (4)	13/100 (13)	3/100 (3)	20/100 (20)	after 30 mo		
Nikula et al. (1995)	Rat/F344	M + F, 214 ^b	Clean air	0	None	16 hr/day,	6 weeks	1/214 (<1)	1/214 (<1)	1/214 (<1)	0/214 (0)	0/214 (0)
		M + F, 210	Whole exhaust	2.5	None	5 days/week		7/210 (3)	4/210 (2)	3/210 (1)	0/210 (0)	0/210 (0)
		M + F, 212	Whole exhaust	6.5	None	for up to		23/212 (11)	22/212 (10)	3/212 (1)	1/212 (<1)	0/212 (0)
		M + F, 213	Carbon black	2.5	None	24 mo		3/213 (1)	7/213 (3)	0/213 (0)	0/213 (0)	1/213 (<1)
		M + F, 211	Carbon black	6.5	None			13/211 (6)	21/211 (10)	3/211 (1)	2/211 (<1)	0/211 (0)
Iwai et al. (1997)	F/344	121, F	Clean air	0	None	NA	NA	5/121(4%) type not stated				
		108, F	Filtered air	0	None	48-56 hr/day		2/108(4%) type not stated				
		153, F	Whole exhaust	3.2-9.4	None	48-56 hr/day		53/153(35%) 61.3% adenoma, 25.8% adenocarcinoma, 2.2% benign squamous cell tumor, 7.5% squamous cell carcinoma, 3.2% adenosquamous carcinoma				Cumulative exposure dose ranged from 154-274 mg/m ³
Orthoefer et al. (1981) (Peipelko and Peirano, 1983)	Mouse/ Strong A	M, 25	Clean air	0	None	20 hr/day, 7 days/week, for 7 weeks	26 weeks	3/22 (13.6)				0.13 tumors/ mouse
			Whole exhaust	6.4	None			7/19 (36.8)				0.63 tumors/ mouse
			Whole exhaust	6.4	UV irradiated			6/22 (27.3)				0.27 tumors/ mouse
								<u>Lung tumors</u>				

Study	Species/ atmosphere	Sex/total number	Particle concentration 3)	treatment	Exposure	Post- exposure	Tumor type and incidence (%) ^a		
(1982)	Mouse/ Jackson A	M + F, 40	Clean air	None	7 days/week, for 8 weeks	8 weeks	0.5 tumors/		
			Whole exhaust	6.4		8 weeks	11/34 (32.3)	0.4 tumors/ mouse	
	Jackson A	F, 60		0	None	7 days/week, for approx.	4/58 (6.9)		
			Clean air	6.4	Urethan		0.25 tumors/		
		F, 60	Whole exhaust	6.4	None	14/56 (25.0)			
			Whole exhaust	6.4	Urethan	22/59 (37.3)			
		M, 429	Clean air		None	0.23 tumors/			
			Whole exhaust	6.4	None	66/368 (17.9)		0.20 tumors/ mouse	
	Mouse	M, 458 M, 18	Clean air	1.5	None	7 days/week, for 3 mo	<u>Pulmonary adenomas</u>		
			Clean air		None ^k		144/458 (31.4)		
(1983)	Mouse/ A/J	M, 388 M, 399	Clean air	0	20 hr/day,	NA			
			Whole exhaust	0.75	7 days/week,		131/388 (33.8)		
			Whole exhaust	1.5	8 mo		109/399 (27.3)		
Pepelko and Peirano (1983)	Sencar	M + F, 260	Clean air	None	Continuous	NA	<u>Adenomas</u>	<u>Carcinomas</u>	<u>All tumors</u>
			Clean air	Urethan ^t			(12.2)	(0.5)	(2.8)
			Whole exhaust	BHT ^l			(8.1) ^c	(0.9)	(9.0) ^c
			Whole exhaust				(5.4) ¹	(1.0)	(8.1)
							(2.6)		

Table 7-3. Summary of animal inhalation carcinogenicity studies (continued)

Study	Species/ strain	Sex/total number	Exposure atmosphere	Particle concentration (mg/m ³)	Other treatment	Exposure protocol	Post- exposure observation	Tumor type and incidence (%) ^a				Comments	
Pepelko and Peirano (1983)	Mouse/Strain A	M + F, 90	Clean air	1212012	None		NA	<u>All tumors</u>				0.29 tumors/ mouse	
									21/87 (24)				
			Clean air							59/237 (24.9)			0.27 tumors/ mouse
			Whole exhaust Whole exhaust						Exposure (darkness)		10/80 (12.5) 22/250 (0.10)		
			Clean air Whole exhaust		Urethan ^m Urethan ^m			66/75 (88) 42/75 (0.95)		2.80 0.95			
Heinrich et al. (1986a,b)	Mouse/ NMRI	M + F, 84	Clean air	4	None	19 hr/day, 5 days/week for up to 30 mo	NA	<u>Adenomas</u>	<u>Adenocarcinoma</u>	<u>Squamous cell tumors</u>	<u>All tumors</u>	11/84 (13) 29/93 (31) ^c	
		M + F, 93	Filtered exhaust						9/84 (11) 11/93 (12)	2/84 (2) 18/93 (19) ^c	—		—
		M + F, 76	Whole exhaust						11/76 (15)	13/76 (17) ^c	—		24/76 (32) ^c
Takemoto et al. (1986)	Mouse/IRC	M + F, 45	Clean air	0	None	4 hr/day, 4 days/week, for 19-28 mo	NA		<u>Adenoma</u>	<u>Adenocarcinoma</u>			
		M + F, 69	Whole exhaust					2-4	None		3/45 (6.7) 6/69 (8.7)	1/45 (2.2) 3/69 (4.3)	
Heinrich et al. (1995)	Mouse/ C57BL/6N	F, 120	Clean air	4.5	None	18 hr/day, 5 days/week, for up to 21 mo	6 mo		<u>Adenomas</u>	<u>Adenocarcinoma</u>		5.1% tumor rate	
		F, 120	Whole exhaust						8/38 (21.1)	0/12 (0) 3/38 (7.9)		8.5% tumor rate	
		F, 120	Particle-free exhaust							3/38 (7.9)		3.5% tumor rate	
	Mouse/ NMRI	F, 120	Clean air	0	None	18 hr/day, 5 days/week for up to 13.5 mo	9.5 mo		<u>Adenomas</u>	<u>Adenocarcinomas</u>			
		F, 120	Whole exhaust						(25)	(15.4)			
			Carbon black TiO ₂					11.6 10	None None		(21.8) (11.3) (11.3)	(15.4) (10) (2.5)	
	Mouse/ NMRI	F, 120	Clean air	4.5	None	18 hr/day, 5 days/week, 23 mo	None		<u>Adenomas</u>	<u>Adenocarcinomas</u>			
F, 120		Whole exhaust						(25)	(8.8)				
F, 120		Particle-free exhaust						(18.3)	(5.0)				
								(31.7)	(15)				

Table 7-3. Summary of animal inhalation carcinogenicity studies (continued)

Species/ strain	number	Exposure	Particle concentration (mg/m ³)	Other	Exposure protocol	exposure observation	^a			Comments
							Multiple	Adenomas/ carcinoma	bronchiolar adenoma	bronchiolar carcinoma
							<u>adenomas</u>			
(1996)	Mouse/CD-1 M + F, 171	Clean air	0.35	None	7 hr/day, 5	1/157 (0.6)	2/157 (1.3)		10/157 (6.4)	7/157 (4.5)
	M + F, 186	Whole exhaust	3.5	None	for up to 24	2/171 (1.2)		1/171 (0.6)	16/171 (9.4)	
		Whole exhaust		None	mo	0/186 (0)	0/186 (0)	0/155 (0)	10/186 (5.4)	6/155 (3.9) 4/186 (2.2)
								Squamous		
(1986a,b)	Hamster/ M + F, 96	Clean air		None	19 hr/day	0/96(0)	<u>Adenocarcinoma</u>	<u>tumors</u>	<u>All tumors</u>	
	M + F, 96	Filtered exhaust		None	for up to 30 mo	0/96(0)	0/96(0)	0/96	0/96(0)	
			4	None						
							<u>Primary lung tumors</u>			
al.	Syrian	M + F, 202	Clean air	None	16 hr/day,	NA				Respiratory tract tumors not
(1989)	Golden	M + F, 104	Filtered	DEN	5 days/week,			7/202 (3.5)		
			(medium dose)	DEN ^j				9/104 (8.7)		exhaust exposure for
			exhaust (high dose)					2/101 (2.0)		groups
		M + F, 101								
		M + F, 102	Whole exhaust	DEN				4/101 (3.9)		
		M + F, 204	Whole exhaust	DEN ^j				1/204 (0.5)		
			exhaust (high dose)	None						
		M + F, 203								

^aNumber of animals examined for tumors.

^bSignificantly different from clean air controls.

^cDipentyl nitrosamine; 12.5 mg/kg/week s.c. during first 25 weeks of exposure.

^dSplenic lymphomas also detected in controls (8.3%), filtered exhaust group (37.5%) and whole exhaust group (25%).

^e5.3% incidence of large cell carcinomas.

^fIncludes adenomas, squamous cell carcinomas, adenocarcinomas, adenosquamous cell carcinoma, and

^g4.5 mg/diethylnitrosamine (DEN)/kg, s.c., 3 days prior to start of inhalation exposure.

^hSingle i.p. dose 1 mg/kg at start of exposure.

ⁱto 52.

^mfrom 12 weeks of age to termination of exposure. Prior exposure (in utero) and of parents

ⁿ120-121 males and 71-72 females examined histologically.

^oexposure.

NS = Not specified.

7-129

DRAFT—DO NOT CITE OR QUOTE

Table 7-4. Tumor incidences in rats following intratracheal instillation of diesel exhaust particles (DPM), extracted DPM, carbon black (CB), benzo[*a*]pyrene (BaP), or particles plus BaP

Experimental group	Number of animals	Total dose	Animals with tumors (percent)	Statistical significance^a
Control	47	4.5 mL	0 (0)	-
DPM (original)	48	15 mg	8 (17)	< 0.01
DPM (extracted)	48	30 mg	10 (21)	< 0.001
DPM (extracted)	48	15 mg	2 (4)	NS
CB (printex)	48	15 mg	10 (21)	< 0.001
CB (lampblack)	48	14 mg	4 (8)	NS
BaP	47	30 mg	43 (90)	< 0.001
BaP	48	15 mg	12 (25)	< 0.001
DEP + BaP	48	15 mg + 170 µg BaP	4 (8)	NS
CB (printex) + BaP	48	15 mg + 443 µg BaP	13 (27)	< 0.001

Table 7-5. Tumorigenic effects of dermal application of acetone extracts of DPM

Number of animals	Strain/sex	Sample material	Time to first tumor (mo)	Survivors at time of first tumor	Total tumors	Duration of experiment (mo)
52	C57BL/40 F C57BL/12 M	Extract of DPM obtained during warmup	13	33	2	22
50	Strain A/M	Extract of DPM obtained during full load	15	8	4	23
25	Strain A/F	Extract of DPM obtained during full load	13	20	17	17

Source: Kotin et al., 1955.

Table 7-6. Tumor incidence and survival time of rats treated by surgical lung implantation with fractions from diesel exhaust condensate (35 rats/group)

Material portion by weight (%)	Dose (mg)	Median survival time in weeks (range)	Number of carcinomas^a	Number of adenomas^b	Carcinoma incidence (%)
Hydrophilic fraction (I) (25)	6.7	97 (24-139)	0	1	0
Hydrophobic fraction (II) (75)	20.00	99 (50-139)	50601	1000	14.2
Nonaromatics +					
PAC ^c 2 + 3 rings (IIa) (72)	19.22	103 (25-140)			0
PAH ^d 4 to 7 rings (IIb) (0.8)	0.21	102 (50-140)			17.1
Polar PAC (IIc) (1.1)	0.29	97 (44-138)			0
Nitro-PAH (IId) (0.7)	0.19	106 (32-135)			2.8
Reconstituted hydrophobics (Ia, b, c, d) (74.5)	19.91	93 (46-136)	70027113	101000	20.0
Control, unrelated		110 (23-138)			0
Control (beeswax/trioctanoin)		103 (51-136)			0
Benzo[<i>a</i>]pyrene	0.3	69 (41-135)			77.1
	0.1	98 (22-134)			31.4
	0.03	97 (32-135)			8.6

^aSquamous cell carcinoma.

^bBronchiolar/alveolar adenoma.

^cPAC = polycyclic aromatic compounds.

^dPAH = polycyclic aromatic hydrocarbons.

Source: Adapted from Grimmer et al., 1987.

Table 7-7. Dermal tumorigenic and carcinogenic effects of various emission extracts

Sample	Tumor initiation		Complete carcinogenesis	Tumor promotion
	Papillomas ^a	Carcinomas ^b	Carcinomas ^b	Papillomas ^a
Benzo[a]pyrene	+/ ^c	+/+	+/+	+/+
Topside coke oven	+/+	-/+	ND ^d	ND
Coke oven main	+/+	+/+	+/+	+/+
Roofing tar	+/+	+/+	+/+	+/+
Nissan	+/+	+/+	-/-	ND
Oldsmobile	+/+	-/-	-/-	ND
VW Rabbit	+/+	-/-	I ^e	ND
Mercedes	+/-	-/-	ND	ND
Caterpillar	-/-	-/-	-/-	ND
Residential furnace	-/-	-/-	ND	ND
Mustang	+/+	-/+	ND	ND

^aScored at 6 mo.

^bCumulative score at 1 year.

^cMale/female.

^dND = Not determined.

^eI = Incomplete.

Source: Nesnow et al., 1982.

Table 7-8. Cumulative (concentration × time) exposure data for rats exposed to whole diesel exhaust

Study	Exposure rate/duration (hr/week, mo)	Total exposure time (hr)	Particle concentration (mg/m ³)	Cumulative exposure (mg-hr/m ³)		Tumor incidence (%) ^a
				Per week	Total	
Mauderly et al. (1987)	35, 30	4.20042004e+	0	0	147014700298	0.9
	35, 30	15	0.35	12.25	20	1.3
	35, 30		3.5	122.5		3.6
	35, 30		7.1	248.5		12.8
Nikula et al. (1995)	80, 23	73607360736	0	0	1840047840	1.0
	80, 23	0	2.5	200.0		7.0
	80, 23		6.5	520.0		18.0
Heinrich et al. (1986a)	95, 35	1330013300	4.24	402.8	56392	17.8
	95, 35					
Heinrich et al. (1995)	90, 24	8.64086409e+	0	0	740021800617	0
	90, 24	15	0.8	72.0	00	0
	90, 24		2.5	225.0		5.5
	90, 24		7.0	630.0		22.0
Ishinishi et al. (1988a) (Light-duty engine) (Heavy-duty engine)	96, 30	1.15201152e+	0	0	1.1524	3.3
	96, 30	49	0.1	9.6	60813e+37	2.4
	96, 30		0.4	38.4		0.8
	96, 30		1.1	105.6		4.1
	96, 30		2.3	220.8		2.4
	96, 30		0	0		0.8
	96, 30		0.5	48.0		0.8
	96, 30		1.0	96.0		0
	96, 30		1.8	172.8		3.3
96, 30		3.7	355.2		6.5	

Table 7-8. Cumulative (concentration × time) exposure data for rats exposed to whole diesel exhaust (continued)

Study	Exposure rate/duration (hr/week, mo)	Total exposure time (hr)	Particle concentration (mg/m ³)	Cumulative exposure (mg-hr/m ³)		Tumor incidence (%) ^a
				Per week	Total	
Brightwell et al. (1989)	80, 24	7.6807681e+1	0	0	537616896506	1.2
	80, 24	5	0.7	56.0	88	0.7
	80, 24		2.2	176.0		9.7
	80, 24		6.6	528.0		38.5
Kaplan et al. (1983)	140, 15	8.4008401e+1	0	0	210063001260	0
	140, 15	5	0.25	35.0	0	3.3
	140, 15		0.75	105.0		10.0
	140, 15		1.5	210.0		3.3
Iwai et al. (1986)	56, 24	53765376	4.9	274.4	26342	36.8
	56, 24					
Takemoto et al. (1986)	16, 18-24	1,152-1,536	0	0	0	0
	16, 18-24	1,152-1,536	2-4	32-64	3,456-4,608	
Karagianes et al. (1981)	30, 20	24002400	8.3	249	19920	16.6
	30, 20					
Iwai et al. (1997)	56, 24	53764992561	9.4	526154275	5.47041597e+1	421242
	48, 24	6	3.2		4	
	54, 24		5.1			

Table 7-9. Evaluations of diesel exhaust as to human carcinogenic potential

Organization	Human data	Animal data	Overall evaluation
NIOSH (1988)	Limited	Confirmatory	Potential occupational carcinogen
IARC (1989)	Limited	Sufficient	Probably carcinogenic to humans
IPCS (1996)	N/A ^a	N/A	Probably carcinogenic to humans
California EPA (1998)	“Consistent evidence for a causal association”	“Demonstrated carcinogenicity”	DPM as a “toxic air contaminant” (California Air Resources Board)
U.S. DHHS (2000)	“Elevated lung cancer in occupationally exposed groups”	“Supporting animal and mechanistic data”	Reasonably anticipated to be a carcinogen

^a Not applicable.

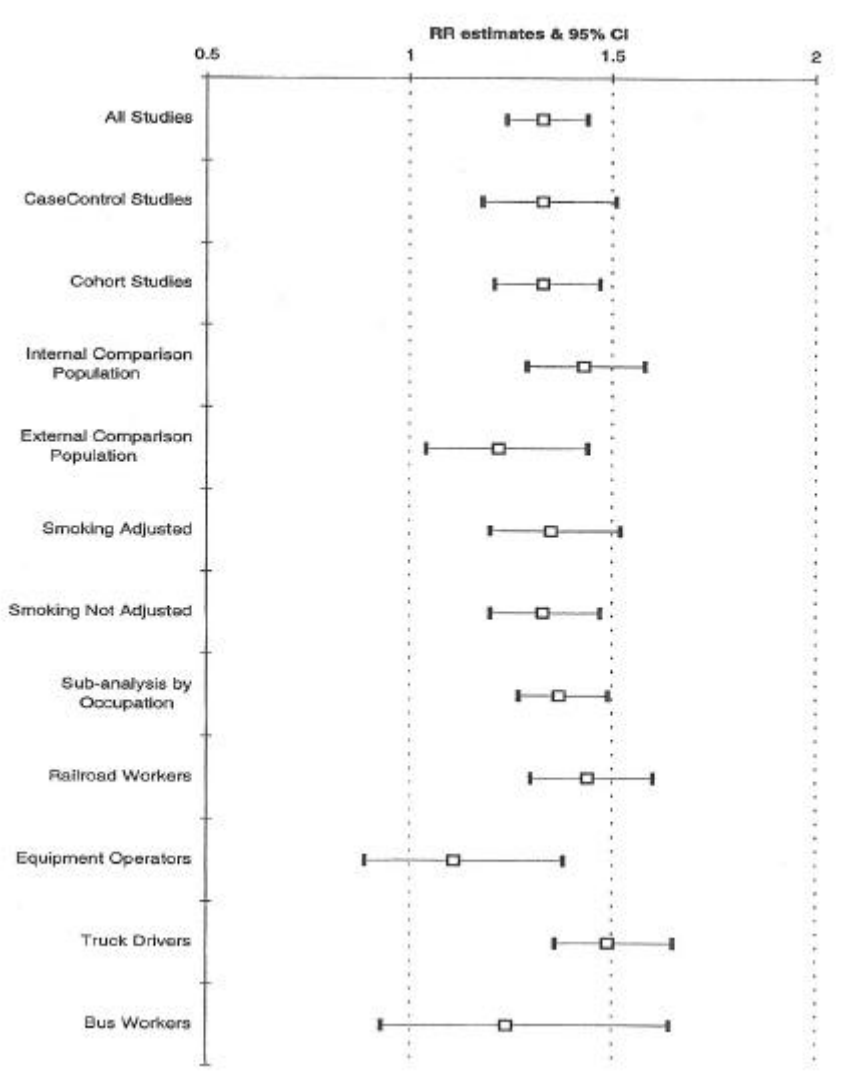
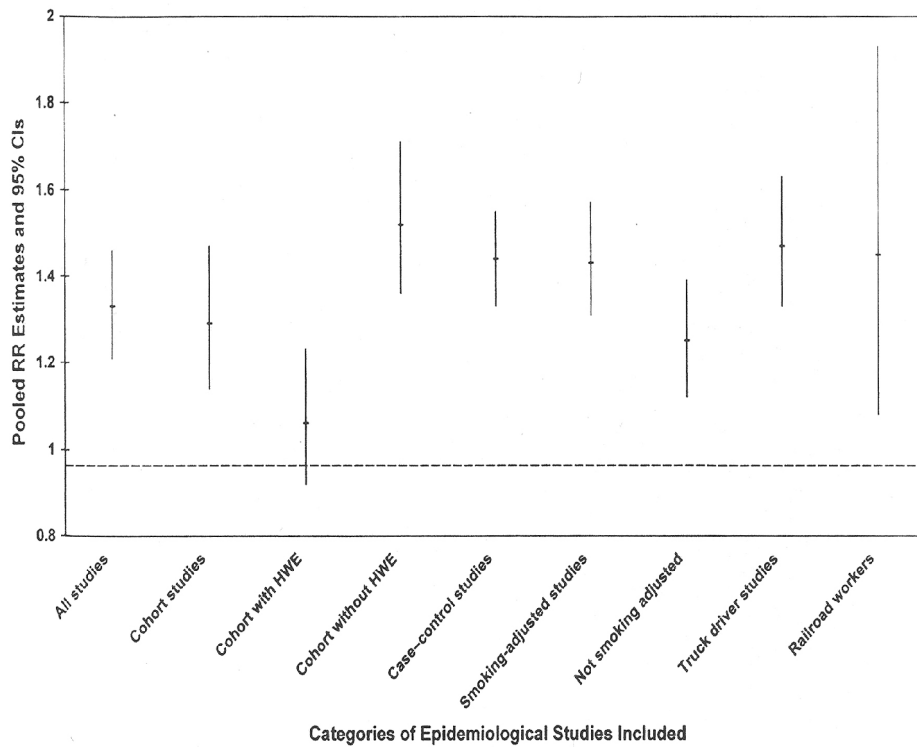


Figure 7-1. Pooled relative risk estimates and heterogeneity-adjusted 95% confidence intervals for all studies and subgroups of studies included in the meta-analysis.

Source: Bhatia et al., 1998.



Note. CI = confidence interval; HWE = healthy worker effect.

Figure 7-2. Pooled estimates of relative risk of lung cancer in epidemiological studies involving occupational exposure to diesel exhaust (random-effects models).

Source: Lipsett and Campleman, 1999.

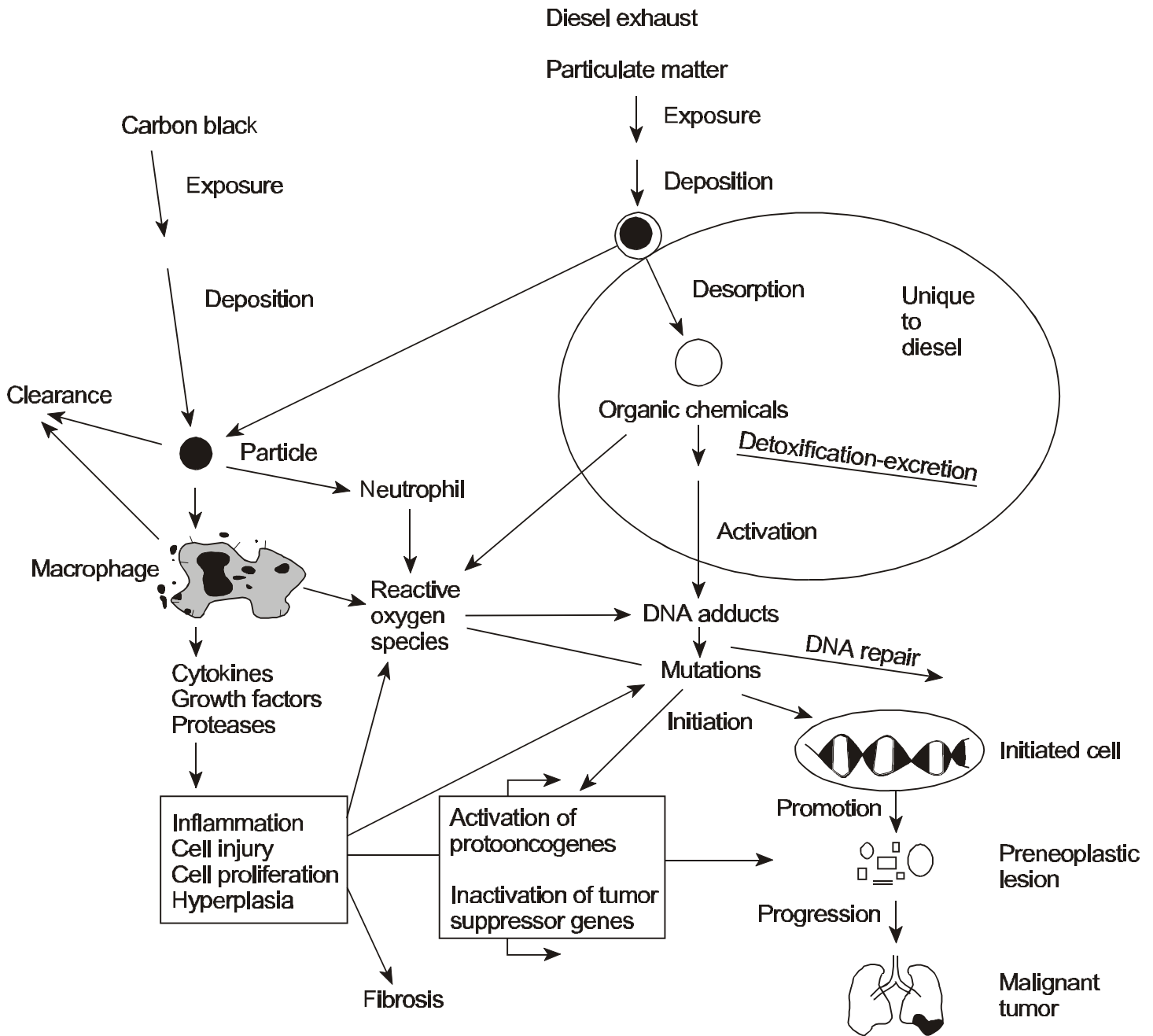


Figure 7-3. Pathogenesis of lung disease in rats with chronic, high-level exposures to particles.

Source: Modified from McClellan, 1997.

1 **7.8. REFERENCES**

2
3 **Adamson, IYR; Bowden, DH. (1978) Adaptive response of the pulmonary macrophagic system to carbon. II. Morphologic studies. Lab Invest 38:430-438.**

4
5
6 **Ahlberg, J; Ahlbom, A; Lipping, H; et al. (1981) [Cancer among professional drivers—a problem-oriented register-based study]. Läkartidningen 78:1545-1546.**

7
8
9 **Allen, RC; Loose, LD. (1976) Phagocytic activation of a luminol-dependent chemiluminescence in rabbit alveolar and peritoneal macrophages. Biochem Biophys Commun 69:245-252.**

10
11
12 **Ames, BN. (1983) Dietary carcinogens and anticarcinogens. Science 221:1256-1264.**

13
14 **Aronsen, KJ; Siemiatycki, J; Dewar, R; et al. (1996) Occupational risk factors for prostate cancer: results from a case-control study in Montreal, Quebec, Canada. Am J Epidemiol 143(4):363-373.**

15
16
17 **Balarajan, R; McDowell, ME. (1983) Malignant lymphomas and road transport workers. J Epidemiol Community Health 37:316-317.**

18
19
20 **Balarajan, R; McDowall, ME. (1988) Professional drivers in London: a mortality study. Br J Ind Med 45:483-486.**

21
22
23 **Ball, JC; Green, B; Young, WC; et al., (1990) S9-activated Ames assays of diesel particle extracts: detecting indirect-acting mutagens in samples that are direct-acting. Environ Sci Technol 24:890-894.**

24
25
26 **Beall, GD; Repine, JE; Hoidal, JR; et al. (1977) Chemiluminescence by human alveolar macrophages: stimulation with heat killed bacteria or phorbol myristate acetate. Infect Immunol 17:117-120.**

27
28
29 **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.**

30
31
32 **Bender, AP; Parker, DL; Johnson, RA; et al. (1989) Minnesota Highway Maintenance Workers Study: cancer mortality. Am J Ind Med 15:545-556.**

33
34
35 **Bhatia, R; Lopipero, P; Smith, A. (1998) Diesel exhaust exposure and lung cancer. Epidemiology 9(1):84-91.**

36
37 **Bitterman, PB; Aselberg, S; Crystal, RG. (1983) Mechanism of pulmonary fibrosis: spontaneous release of the alveolar macrophage-derived growth factor in interstitial lung disorders. J Clin Invest 72:1801-1813.**

38
39
40 **Boffetta, P; Stellman, SD. (1988) Association between diesel exhaust exposure and multiple myeloma: an example of confounding. Prev Med 17:236-237.**

1 **Boffetta, P; Harris, RE; Wynder, EL. (1990) Case-control study on occupational exposure to diesel exhaust**
2 **and lung cancer risk. Am J Ind Med 17:577-591.**
3
4 **Bohning, DE; Atkins, HL; Cohn, SH. (1982) Long-term particle clearance in man: normal and impaired.**
5 **Ann Occup Hyg 26:259-271.**
6
7 **Bond, JA; Mitchell, CE; Li, AP. (1983) Metabolism and macromolecular covalent binding of benzo[a]pyrene**
8 **in cultured Fischer-344 rat lung type II epithelial cells. Biochem Pharmacol 32:3771-3776.**
9
10 **Bond, JA; Butler, MM; Medinsky, MA; et al. (1984) Dog pulmonary macrophage metabolism of free and**
11 **particle-associated [¹⁴C]benzo[a]pyrene. J Toxicol Environ Health 14:181-189.**
12
13 **Bond, JA; Johnson, NF; Snipes, MB; et al. (1990) DNA adduct formation in rat alveolar type II cells: cells**
14 **potentially at risk for inhaled diesel exhaust. Environ Mol Mutagen 16:64-69.**
15
16 **Boorman, GA; Brockman, M; Carlton, WW; et al. (1996) Classification of cystic keratinizing squamous**
17 **lesions of the rat lung:report of a workshop. Toxicol Pathol 24:564-572.**
18
19 **Borm, PJA; Knaapen, AM; Schins, RFP; et al. (1997) Neutrophils amplify the formation of DNA adducts by**
20 **benzo[a]pyrene in lung target cells. Environ Health Perspect 105 (Suppl 5):1089-1093.**
21
22 **Bowden, DH; Adamson, IYR. (1978) Adaptive responses of the pulmonary macrophagic system to carbon. I.**
23 **Kinetic studies. Lab Invest 38:422-438.**
24
25 **Boyd, MR. (1984) Metabolic activation and lung toxicity: a basis for cell-selective pulmonary damage by**
26 **foreign chemicals. Environ Health Perspect 55:47-51.**
27
28 **Brightwell, J; Fouillet, X; Cassano-Zoppi, AL; et al. (1986) Neoplastic and functional changes in rodents**
29 **after chronic inhalation of engine exhaust emissions. In: Carcinogenic and mutagenic effects of diesel engine**
30 **exhaust. Ishinishi, N; Koizumi, A; McClellan, R; et al., eds. Amsterdam: Elsevier; pp. 471-485.**
31
32 **Brightwell, J; Fouillet, X; Cassano-Zoppi, AL; et al. (1989) Tumors of the respiratory tract in rats and**
33 **hamsters following chronic inhalation of engine exhaust emissions. J Appl Toxicol 9:23-31.**
34
35 **Brüske-Hohlfeld, I; Mohner, M; Ahrens, W; et al. (1999) Lung cancer risk in male workers occupationally**
36 **exposed to diesel motor emissions in Germany. Am J Ind Med 36:405-414.**
37
38 **Buiatti, E; Kriebel, D; Geddes, M; et al. (1985) A case control study of lung cancer in Florence, Italy. I.**
39 **Occupational risk factors. J Epidemiol Commun Health 39:244-250.**
40
41 **California Environmental Protection Agency. (Cal-EPA, OEHHA) (April, 1998) Health risk assessment for**
42 **diesel exhaust. Public and Scientific Review Draft.**

1 Claxton, LD. (1983) Characterization of automotive emissions by bacterial mutagenesis bioassay: a review.
2 Environ Mutagen 5:609-631.
3
4 Coggon, D; Pannett, B; Acheson, ED. (1984) Use of job-exposure matrix in an occupational analysis of lung
5 and bladder cancers on the basis of death certificates. J Natl Cancer Inst 72:61-65.
6
7 Cohen, AJ; Higgins, MWP. (1995) Health effects of diesel exhaust: epidemiology. In: Diesel exhaust: a
8 critical analysis of emissions, exposure, and health effects. Cambridge, MA: Related HEI Publications; pp.
9 251-292.
10
11 Cohen, SM; Ellwein, LB. (1991) Genetic error, cell proliferation and carcinogenesis. Cancer Res 51:6493-
12 6505.
13
14 Commins, BT; Waller, RE; Lawther, PJ. (1957) Air pollution in diesel bus garages. Br J Ind Med 14:232-
15 239.
16
17 Cordier, S; Clavel, J; Limasset, JC; et al. (1993) Occupational risks of bladder cancer in France: a
18 multicenter case-control study. Int J Epidemiol 22:403-411.
19
20 Cox, LA. (1997) Does diesel exhaust cause human lung cancer? J Risk Anal 17(6):807-829.
21
22 Crump, KS. (1999) Lung cancer mortality and diesel exhaust: reanalysis of a retrospective cohort study of
23 U.S. railroad workers. Inhal Toxicol 11:1-17.
24
25 Crump, KS; Lambert, T; Chen, C; et al. (1991) Assessment of risk from exposure to diesel engine emissions.
26 Clement International Corporation. Prepared for U.S. EPA under contract no. 68-02-4601; 56.
27
28 Damber, LA; Larsson, LG. (1987) Occupation and male lung cancer: a case-control study in northern
29 Sweden. Br J Ind Med 44:446-453.
30
31 Daniel, JH. (1984) The use of diesel-powered equipment in U.S. underground coal operations. Presented at:
32 American Mining Congress International Coal Show; May, 1984; Chicago, IL. Washington, DC:
33 Department of the Interior, Bureau of Mines.
34
35 Dasenbrock, C; Peters, L; Creutzenberg, O; et al. (1996) The carcinogenic potency of carbon particles with
36 and without PAH after repeated intratracheal administration in the rat. Toxicol Lett 88:15-21.
37
38 Depass, LR; Chen, KC; Peterson, LG. (1982) Dermal carcinogenesis bioassays of diesel particulates and
39 dichloromethane extract of diesel particulates in C3H mice. In: Toxicological effects of emissions from diesel
40 engines. Lewtas, J, ed. Amsterdam: Elsevier; pp. 321-326.
41

1 **Dontenwill, W; Chevalier, H-J; Harke, H-P; et al. (1973) Investigations on the effects of chronic cigarette**
2 **smoke inhalation in Syrian golden hamsters. J Natl Cancer Inst 51:1681-1832.**
3
4 **Drath, DB; Karnovsky, ML. (1975) Superoxide production by phagocytic leukocytes. J Exp Med**
5 **141:257-262.**
6
7 **Driscoll, K. (1995) Role of inflammation in the development of rat lung tumors in response to chronic**
8 **particle exposure. In: Proceedings of the MIT toxicology symposium: particle overload in the rat lung and**
9 **lung cancer: relevance for human risk assessment. Cambridge, MA: Massachusetts Institute of Technology;**
10 **29 pp.**
11
12 **Driscoll, KE. (1996) Mechanisms of rat lung tumors: Role of persistent inflammation. Inhal Toxicol 8:139-**
13 **153.**
14
15 **Driscoll, KE; Carter, JM; Howard, BW; et al. (1996) Pulmonary inflammatory, chemokine, and mutagenic**
16 **responses in rats after subchronic inhalation of carbon black. Toxicol Appl Pharmacol 136:372-380.**
17
18 **Driscoll, KE; Carter, JM; Hassenbein, DG; et al. (1997a) Cytokines and particle-induced inflammatory cell**
19 **recruitment. Environ Health Perspect 105 (Suppl 5):1159-1164.**
20
21 **Driscoll, KE; Deyo, LC; Carter, JM; et al. (1997b) Effects of particle exposure and particle-elicited**
22 **inflammatory cells on mutation in rat alveolar epithelial cells. Carcinogenesis 18:423-430.**
23
24 **Edling, C; Anjou, C-G; Axelson, O; et al. (1987) Mortality among personnel exposed to diesel exhaust. Int**
25 **Arch Occup Environ Health 59:559-565.**
26
27 **El-Bayoumy, K; Rivenson, A; Johnson, B; et al. (1988) Comparative tumorigenicity of 1-nitropyrene, 1-**
28 **nitrosopyrene, and 1-aminopyrene administered by gavage to Sprague-Dawley rats. Cancer Res 48:4256-**
29 **4260.**
30
31 **Emmelin, A; Nyström, L; Wall, S. (1993) Diesel exhaust exposure and smoking: a case-referent study of lung**
32 **cancer among Swedish dock workers. Epidemiology 4:237-244.**
33
34 **Enya, T; Suzuki, H; Watanabe, T; et al. (1997) 3-Nitrobenzanthrone, a powerful bacterial mutagen and**
35 **suspected human carcinogen found in diesel exhaust and airborne particulates. Environ Sci Technol 31:2772-**
36 **2776.**
37
38 **Evans, M; Shami, SG; Martinez, LA. (1986) Enhanced proliferation of pulmonary alveolar macrophages**
39 **after carbon instillation in mice depleted of blood monocytes by strontium-89. Lab Invest 54:154-159.**
40

1 Farrell, RL; Davis, GW. (1974) Effect of particulate benzo(a)pyrene carrier on carcinogenesis in the
2 respiratory tract of hamsters. In: Experimental lung cancer. Karbe, E; Davis, GW, eds. Berlin: Springer;
3 pp. 186-198.
4

5 Flodin, U; Fredriksson, M; Persson, B. (1987) Multiple myeloma and engine exhausts, fresh wood, and
6 creosote: a case-referent study. *Am J Ind Med* 12:519-529.
7

8 Gallagher, J; George, M; Kohan, M; et al. (1993) Detection and comparison of DNA adducts after in vitro
9 and in vivo diesel emission exposures. *Environ Health Perspect* 99:225-228.
10

11 Gallagher, J; Heinrich, U; George, M; et al. (1994) Formation of DNA adducts in rat lung following chronic
12 inhalation of diesel emissions, carbon black, and titanium dioxide particles. *Carcinogenesis* 15:1291-1299.
13

14 Garland, FC; Gorham, ED; Garland, CF; et al. (1988) Testicular cancer in US Navy personnel. *Am J*
15 *Epidemiol* 127:411-414.
16

17 Garshick, E; Schenker, MB; Munoz, A; et al. (1987) A case-control study of lung cancer and diesel exhaust
18 exposure in railroad workers. *Am Rev Respir Dis* 135:1242-1248.
19

20 Garshick, E; Schenker, MB; Munoz, A; et al. (1988) A retrospective cohort study of lung cancer and diesel
21 exhaust exposure in railroad workers. *Am Rev Respir Dis* 137:820-825.
22

23 Gerde, P; Medinsky, MA; Bond, JA. (1991a) Particle-associated polycyclic aromatic hydrocarbons--a
24 reappraisal of their possible role in pulmonary carcinogenesis. *Toxicol Appl Pharmacol* 188:1-13.
25

26 Gerde, P; Medinsky, MA; Bond, JA. (1991b) The retention of polycyclic aromatic hydrocarbons in the
27 bronchial airways—a theoretical comparison. *Toxicol Appl Pharmacol* 108:1-13.
28

29 Goldstein, IM; Roos, D; Kaplan, HB; et al. (1975) Complement and immunoglobulins stimulate superoxide
30 production by human leukocytes independently of phagocytosis. *J Clin Invest* 56:1155-1163.
31

32 Grimmer, G; Brune, H; Deutsch-Wenzel, R; et al. (1987) Contribution of polycyclic aromatic hydrocarbons
33 and nitro-derivatives to the carcinogenic impact of diesel engine exhaust condensate evaluated by
34 implantation into the lungs of rats. *Cancer Lett* 37:173-180.
35

36 Guberan, E; Usel, M; Raymond, L; et al. (1992) Increased risk for lung cancer and for cancer of the
37 gastrointestinal tract among Geneva professional drivers. *Br J Ind Med* 49:337-344.
38

39 Gustafsson, L; Wall, S; Larsson, LG; et al. (1986) Mortality and cancer incidence among Swedish dock
40 workers—a retrospective cohort study. *Scand J Work Environ Health* 12:22-26.
41

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

3
4 Hall, NEL; Wynder, EL. (1984) Diesel exhaust exposure and lung cancer: a case-control study. *Environ Res*
5 34:77-86.

6
7 Hansen, J; Raaschou-Nielsen, O; Olsen, JH; et al. (1998) Increased risk of lung cancer among different types
8 of professional drivers in Denmark. *Occup Environ Med* 55:115-118.

9
10 Hansen, ES. (1993) A follow-up study on the mortality of truck drivers. *Am J Ind Med* 23:811-821.

11
12 Hatch, GE; Gardner, DE; Menzel, DB. (1980) Stimulation of oxidant production in alveolar macrophages by
13 pollutant and latex particles. *Environ Res* 32:121-136.

14
15 Hayes, RB; Thomas, T; Silverman, DT; et al. (1989) Lung cancer in motor exhaust-related occupations. *Am*
16 *J Ind Med* 16:685-695.

17
18 Health Effects Institute. (HEI) (1995) Diesel exhaust: a critical analysis of emissions, exposure, and health
19 effects. Cambridge, MA: Related HEI Publications; p. 27.

20
21 Heinrich, U. (1990) Carcinogenicity of carbon black "Printex 90" in female Wistar rats. Presented at: U.S.
22 Environmental Protection Agency Diesel Emissions Peer Review Workshop; July 18-19; Chapel Hill, NC.

23
24 Heinrich, U. (1990) Presentation at workshop on health effects of diesel emissions. U.S. EPA, Research
25 Triangle Park, July 1990.

26
27 Heinrich, U; Peters, L; Funcke, W; et al. (1982) Investigation of toxic and carcinogenic effects of diesel
28 exhaust in long-term inhalation exposure of rodents. In: Lewtas, J, ed. *Toxicological effects of emissions from*
29 *diesel emissions*. Amsterdam: Elsevier; pp. 225-242.

30
31 Heinrich, U; Pott, F; Rittinghausen, S. (1986a) Comparison of chronic inhalation effects in rodents after
32 long-term exposure to either coal oven flue gas mixed with pyrolyzed pitch or diesel engine exhaust. In:
33 *Carcinogenic and mutagenic effects of diesel engine exhaust*. Ishinishi, N; Koizumi, A; McClellan, R; Stöber,
34 W, eds. Amsterdam: Elsevier; pp. 441-457.

35
36 Heinrich, U; Muhle, H; Takenaka, S; et al. (1986b) Chronic effects on the respiratory tract of hamsters,
37 mice and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine
38 emissions. *J Appl Toxicol* 6:383-395.

39
40 Heinrich, U; Peters, L; Fuhst, R; et al. (1989a) The effect of automotive exhaust exposure on the
41 carcinogenicity of diphenylnitrosamine (DPN) in the respiratory tract of rats. *Exp Pathol* 37:51-55.

1 Heinrich, U; Mohr, U; Fuhst, R; et al. (1989b) Investigation of a potential cotumorogenic effect of the
2 dioxides of nitrogen and sulfur, and of diesel-engine exhaust, on the respiratory tract of Syrian golden
3 hamsters. Research Report No. 26. Cambridge, MA: Health Effects Institute; pp. 27.

4
5 Heinrich, U; Dungworth, DL; Pott, F; et al. (1994) The carcinogenic effects of carbon black particles and
6 tar-pitch condensation aerosol after inhalation exposure of rats. *Ann Occup Hyg* 48 (suppl. 4):351-356.

7
8 Heinrich, U; Fuhst, R; Rittinghausen, S; et al. (1995) Chronic inhalation exposure of Wistar rats and two
9 different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. *Inhal Toxicol* 7:533-
10 556.

11
12 Hemminki, K; Pershagen, G. (1994) Cancer risk of air pollution: epidemiological evidence. *Environ Health*
13 *Perspect* 102(Suppl 4):187-192.

14
15 Hemminki, K; Söderling, J; Ericson, P; et al. (1994) DNA adducts among personnel servicing and loading
16 diesel vehicles. *Carcinogenesis* 15:767-769.

17
18 Hill, AG. (1965) The environment and disease: association or causation? *Proc R Soc Med* 58:295-300.

19
20 Hirafuji, M; Sakakibara, M; Endo, T; et al. (1995) Biological effects of diesel exhaust particles (DEP) on
21 tissues and cells isolated from respiratory tracts of guinea pigs. *Res Commun Mol Pathol Pharmacol* 90:221-
22 233.

23
24 Hirose, M; Lee, M-S; Wang, CY; et al. (1984) Induction of rat mammary gland tumors by 1-nitropyrene, a
25 recently recognized environmental mutagen. *Cancer Res* 44:1158-1162.

26
27 Hoar, SK; Hoover, R. (1985) Truck driving and bladder cancer mortality in rural New England. *J Natl*
28 *Cancer Inst* 74:771-774.

29
30 Hoidal, JR; Repine, JE; Beall, GD; et al. (1978) The effect of phorbol myristate acetate on metabolism and
31 ultrastructure of human alveolar macrophages. *Am J Pathol* 91:469-482.

32
33 Hou, S-M; Lambert, B; Hemminki, K. (1995) Relationship between hprt mutant frequency, aromatic DNA
34 adducts and genotypes for GSTM1 and NAT2 in bus maintenance workers. *Carcinogenesis* 16:1913-1917.

35
36 Howard, PC; Gerrard, JA; Milo, GE; et al. (1983) Transformation of normal human skin fibroblasts by 1-
37 nitropyrene and 6-nitrobenzo[a]pyrene. *Carcinogenesis* 4:353-355.

38
39 Howe, GR; Lindsay, JP. (1983) A follow-up study of a ten percent sample of the Canadian labour force: I.
40 Cancer mortality in males 1965-1973.

1 **Howe, GR; Burch, JD; Miller, AB; et al. (1980) Tobacco use, occupation, coffee, various nutrients, and**
2 **bladder cancer. J Natl Cancer Inst 64:701-713.**
3
4 **Howe, GR; Fraser, D; Lindsay, J; et al. (1983) Cancer mortality (1965-77) in relation to diesel fume and coal**
5 **exposure in a cohort of retired railway workers. J Natl Cancer Inst 70:1015-1019.**
6
7 **Huisingh, J; Bradow, R; Jungers, R; et al. (1978) Application of bioassay to the characterization of diesel**
8 **particle emissions. In: Application of short-term bioassay in the fractionation and analysis of complex**
9 **mixtures. Waters, MD; Nesnow, S; Huisingh, JL; et al., eds. New York: Plenum; pp. 381-418.**
10
11 **Humble, CG; Samet, JM; Skipper, BE. (1984) Comparison of self- and surrogate-reported dietary**
12 **information. Am J Epidemiol 119:86-98.**
13
14 **IARC. (International Agency for Research on Cancer) (1989) Monographs on the evaluation of carcinogenic**
15 **risks to humans. Vol. 46. Diesel and gasoline engine exhaust and some nitroarenes. Lyon, France: IARC.**
16
17 **Ichinose, T; Yajima, Y; Nagashima, M; et al. (1997a) Lung carcinogenesis and formation of 8-hydroxy-**
18 **deoxyguanosine in mice by diesel exhaust particles. Carcinogenesis 18:185-192.**
19
20 **Ichinose, T; Yamanushi, T; Seto, H; et al. (1997b) Oxygen radicals in lung carcinogenesis accompanying**
21 **phagocytosis of diesel exhaust particles. Int J Oncol 11:571-575.**
22
23 **International Life Sciences Institute (ILSI). (2000) ILSI Risk Science Institute workshop: the relevance of**
24 **the rat lung response to particle overload for human risk assessment. Gardner, DE, ed. Inhal Toxicol 12(1-**
25 **2).**
26
27 **IPCS. (1996) International Program on Chemical Safety Environmental Health Criteria 171. Diesel fuel and**
28 **exhaust emissions. Geneva: World Health Organization, pp.172-176.**
29
30 **Iscovich, J; Castelleto, R; Estevè, J; et al. (1987) Tobacco smoking, occupational exposure and bladder**
31 **cancer in Argentina. Int J Cancer 40:734-740.**
32
33 **Ishinishi, N; Kuwabara, N; Takaki, Y; et al. (1988a) Long-term inhalation experiments on diesel exhaust. In:**
34 **Diesel exhaust and health risks. Results of the HERP studies. Ibaraki, Japan: Research Committee for**
35 **HERP Studies; pp. 11-84.**
36
37 **Ishinishi, N; Inamasu, T; Hisanaga, A; et al. (1988b) Intratracheal instillation study of diesel particulate**
38 **extracts in hamsters. In: Diesel exhaust and health risk. Ibaraki, Japan: Research Committee for HERP**
39 **Studies; pp. 209-216.**
40

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

4
5 Iwai, K; Udwaga, T; Yamagishi, M; et al. (1986) Long-term inhalation studies of diesel exhaust on F344 SPF
6 rats. Dev Toxicol Environ Sci 13:349-360.

7
8 Iwai, K; Higuchi, K; Udagawa, T; et al. (1997) Lung tumor induced by long-term inhalation or intratracheal
9 instillation of diesel exhaust particles. Exp Pathol Toxicol 49:393-401.

10
11 Iyer, V; Harris, RE; Wynder, EL. (1990) Diesel exhaust exposure and bladder cancer risk. Eur J Epidemiol
12 6:49-54.

13
14 Jensen, OM; Wahrendorf, J; Knudsen, JB; et al. (1987) The Copenhagen case-referent study on bladder
15 cancer: risks among drivers, painters, and certain other occupations. Scand J Work Environ Health 13:129-
16 134.

17
18 Jöckel, KH; Ahrens, W; Jahn, I; et al. (1995) Untersuchungen zu Lungenkrebs und Risiken am Arbeitsplatz
19 (Schlussbericht). Berlin: Wirtschaftsverlag NW. Fb 01 HK 546.

20
21 Jöckel, KH; Ahrens, W; Jahn, I; et al. (1998) Occupational risk factors for lung cancer—a case-control
22 study in West Germany. Int J Epidemiol 27:549-560.

23
24 Johnson, C; Finkelstein, J; Gelein, R; et al. (1993) Early alterations in the mRNA abundance of IL-1 α , IL-
25 1 β , iNOS, MIP-2, TGF β , and VEGF associated with ultrafine particle exposure. Fundam Appl Toxicol
26 50:138 (abstr).

27
28 Jordana, M; Richards, C; Irving, LB; et al. (1988) Spontaneous *in vitro* release of alveolar macrophage
29 cytokines after the intratracheal instillation of bleomycin in rats: characterization and kinetic studies. Am
30 Rev Respir Dis 137:1135-1140.

31
32 Kaplan, HL; Mackenzie, WF; Springer, KJ; et al. (1982) A subchronic study of the effects of exposure of
33 three species of rodents to diesel exhaust. In: Toxicological effects of emissions from diesel engines. Lewtas,
34 J, ed. New York: Elsevier Biomedical; pp. 161-220.

35
36 Kaplan, HL; Springer, KJ; MacKenzie, WF. (1983) Studies of potential health effects of long-term exposure
37 to diesel exhaust emissions. Final Report No. 01-0750-103 (SWRI) and No. 1239 (SFRE). San Antonio, TX:
38 Southwest Research Institute.

39
40 Kaplan, I. (1959) Relationship of noxious gases to carcinoma of the lung in railroad workers. J Am Med
41 Assoc 171:2039-2043.

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

3
4 Kawabata, Y; Iwai, K; Udagawa, T; et al. (1986) Effects of diesel soot on unscheduled DNA synthesis of
5 tracheal epithelium and lung tumor formation. In: *Carcinogenic and mutagenic effects of diesel engine*
6 *exhaust.* Ishinishi, N; Koizumi, A; McClellan, R; et al., eds. Amsterdam: Elsevier; pp. 213-232.

7
8 Kawabata, Y; Udagawa, T; Higuchi, K; et al. (1994) Early one year exposure to diesel engine exhaust causes
9 lung tumors. *Toxic and carcinogenic effects of solid particles on the respiratory tract.* In: *Toxic and*
10 *carcinogenic effects of solid particles in the respiratory tract.* Mohr, U; Dungworth, DL; Mauderly, JL; et
11 al., eds. Washington, DC: International Life Sciences Institute Press, pp. 429-431.

12
13 Kensler, TW; Egner, PA; Moore, KG; et al. (1987) Role of inflammatory cells in the metabolic activity of
14 polycyclic aromatic hydrocarbons in mouse skin. *Toxicol Appl Pharmacol* 90:337-346.

15
16 Klebanoff, SJ; Clark, RA. (1978) The metabolic burst. In: *The neutrophil: function and clinical disorders.*
17 Amsterdam: North-Holland; pp. 283-368.

18
19 Kolonel, LN; Hirohata, T; Nomura, AMY. (1977) Adequacy of survey data collected from substitute
20 respondents. *Am J Epidemiol* 106:476-484.

21
22 Kotin, P; Falk, H; Thomas, M. (1955) Aromatic hydrocarbons. III. Presence in the particulate phase of
23 diesel engine exhausts and the carcinogenicity of exhaust extracts. *Arch Ind Health* 11:113-120.

24
25 Kumagai, Y; Arimoto, T; Shinyashiki, M; et al. (1997) Generation of reactive oxygen species during
26 interaction of diesel exhaust particle components with NADPH cytochrome P450 reductase and involvement
27 of the bioactivation in the DNA damage. *Free Radical Biol Med* 22:479-487.

28
29 Kunitake, E; Shimamura, K; Katayama, H; et al. (1986) Studies concerning carcinogenesis of diesel
30 particulate extracts following intratracheal instillation, subcutaneous injection, or skin application. In:
31 *Carcinogenic and mutagenic effects of diesel engine exhaust.* Ishinishi, N; Koizumi, A; McClellan, R; et al.,
32 eds. Amsterdam: Elsevier; pp. 235-252.

33
34 Kunitake, E; Imase, A; Shimamura, K; et al. (1988) Skin application and subcutaneous injection
35 experiments of diesel particulate extracts using ICR mice and nude mice. In: *Diesel exhaust and health risks.*
36 *Results of the HERP studies.* Ibaraki, Japan: Research Committee for HERP Studies; pp. 217-225.

37
38 Langer, AM; Nolan, RP. (1994) Factors controlling the biological potential of inorganic dusts: surface area,
39 chemistry and character. In: *Toxic and carcinogenic effects of solid particles in the respiratory tract.*
40 Mohr, U; Dungworth, DL; Mauderly, JL; et al., eds. Washington, DC: International Life Sciences Institute
41 Press, pp. 147-156.

1 Lechner, JF; Mauderly, JL. (1994) Sequence of events in lung carcinogenesis: initiation and promotion,
2 protooncogenes and tumor suppressor genes and particulates. In: Toxic and carcinogenic effects of solid
3 particles in the respiratory tract. Mohr, U; Dungworth, DL; Mauderly, JL; et al., eds. Washington, DC:
4 International Life Sciences Institute Press, pp. 235-251.

5

6 Lee, KP; Henry, NW, III; Trochimowicz, HJ; et al. (1986) Pulmonary response to impaired lung clearance
7 in rats following excessive TiO₂ dust deposition. *Environ Res* 41:144-167.

8

9 Lehnert, BE; Valdez, YE; Bomalaski, SH. (1988) Analyses of particles in the lung free cell, tracheobronchial
10 lymph nodal, and pleural space compartments following their deposition in the lung as related to lung
11 clearance mechanisms. *Ann Occup Hyg* 32:125-140.

12

13 Lehnert, BE; Ortiz, JB; London, JE; et al. (1989) Migratory behavior of alveolar macrophages during
14 clearance of light to heavy lung burdens of particles. 1989 Annual Meeting of the American Thoracic
15 Society, Cincinnati, OH, May 14-17.

16

17 Lerchen, ML; Samet, JM. (1986) An assessment of the validity of questionnaire responses provided by a
18 surviving spouse. *Am J Epidemiol* 123:481-489.

19

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

22

23 Lewis, TR; Green, FHY; Moorman, WJ; et al. (1989) A chronic inhalation toxicity study of diesel engine
24 emissions and coal dust, alone and combined. *J Am Coll Toxicol* 8:345-375.

25

26 Lipsett, M; Campleman, S. (1999) Occupational exposure to diesel exhaust and lung cancer: a meta-
27 analysis. *Am J Public Health* 80(7):1009-1017.

28

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

31

32 Lowrie, DB; Aber, VR. (1977) Superoxide production by rabbit alveolar macrophages. *Life Sci* 21:1575-
33 1584.

34

35 Mauderly, JL. (1994) Toxicological and epidemiological evidence for health risks from inhaled engine
36 emissions. *Environ Health Perspect* 102(suppl 4):165-171.

37

38 Mauderly, JL; Jones, RK; Griffith, WC; et al. (1987) Diesel exhaust is a pulmonary carcinogen in rats
39 exposed chronically by inhalation. *Fundam Appl Toxicol* 9:208-221.

40

1 Mauderly, JL; Snipes, MB; Barr, EB; et al. (1991) Influence of particle-associated organic compounds on
2 carcinogenicity of diesel exhaust. Eighth Health Effects Institute Annual Conference, April 21-24, Colorado
3 Springs, CO.
4
5 Mauderly, JL. (1994) Toxicological and epidemiological evidence for health risks from inhaled engine
6 emissions. *Environ Health Perspec* 102(suppl 4):165-171.
7
8 Mauderly, JL; Banas, DA; Griffith, WC; et al. (1996) Diesel exhaust is not a pulmonary carcinogen in CD-1
9 mice exposed under conditions carcinogenic to F344 rats. *Fundam Appl Toxicol* 30:233-242.
10
11 McClellan, R. (1997) Use of mechanistic data in assessing human risks from exposure to particles. *Environ*
12 *Health Perspect* 105(Suppl 5):1-17.
13
14 McLaughlin, JK; Dietz, MS; Mehl, ES; et al. (1987) Reliability of surrogate information on cigarette
15 smoking by type of informant. *Am J Epidemiol* 126:144-146.
16
17 Miles, PR; Lee, P; Thrush, MA; et al. (1977) Chemiluminescence associated with phagocytosis of foreign
18 particles in rabbit alveolar macrophages. *Life Sci* 20:165-170.
19
20 Mohr, U; Takenaka, S; Dungworth, DL. (1986) Morphologic effects of inhaled diesel engine exhaust on lungs
21 of rats: comparison with effects of coal oven flue gas mixed with pyrolyzed pitch. In: *Carcinogenic and*
22 *mutagenic effects of diesel engine exhaust*. Ishinishi, N; Koizumi, A; McClellan, R; et al., eds. Amsterdam:
23 Elsevier; pp. 459-470.
24
25 Mokler, BV; Archibeque, FA; Beethe, RL; et al. (1984) Diesel exhaust exposure system for animal studies.
26 *Fundam Appl Toxicol* 4:270-277.
27
28 Mumford, JL; Chapman, RS; Harris, DB. (1989) Indoor air exposure to coal and wood combustion emissions
29 associated with a high lung cancer rate in Xuan Wei, China. *Environ Int* 15:315-320.
30
31 Murphy, SAM; Berube, KA; Richards, RJ. (1999) Bioreactivity of carbon black and diesel-exhaust particles
32 to primary Clara and type II epithelial cell cultures. *Occup Environ Med* 56:813-819.
33
34 Muscat, JE. (1996) Carcinogenic effects of diesel emissions and lung cancer: the epidemiologic evidence is
35 not causal. *J Clin Epidemiol* 49(8):891-892.
36
37 Muscat, JE; Wynder, EL. (1995) Diesel engine exhaust and lung cancer: an unproven association. *Environ*
38 *Health Perspect* 103:812-818.
39
40 Nagashima, M; Kasai, H; Yokota, J; et al. (1995) Formation of an oxidative DNA damage, 8-
41 hydroxydeoxyguanosine, in mouse lung DNA after intratracheal instillation of diesel exhaust particles and
42 effects of high-dietary fat and beta-carotene on this process. *Carcinogenesis* 16:1441-1445.

1 National Institute for Occupational Safety and Health. (1988) Carcinogenic effects of exposure to diesel
2 exhaust. NIOSH Current Intelligence Bulletin 50. DHHS (NIOSH) Publication No. 88-116. Atlanta, GA:
3 Centers for Disease Control.

4
5 National Toxicology Program. (2000) National Institute for Environmental Health Science- National
6 Institutes of Health. Report on Carcinogens, 9th Edition. Research Triangle Park, NC.

7
8 Nesnow, S; Evans, C; Stead, A; et al. (1982) Skin carcinogenesis studies of emission extracts. In:
9 Toxicological effects of emissions from diesel engines. Lewtas, J, ed. Amsterdam: Elsevier; pp. 295-320.

10
11 Nesnow, S; Triplett, LL; Slaga, TJ. (1984) Tumor initiating activities of 1-nitropyrene and its nitrated
12 products in Sencar mice. *Cancer Lett* 23:1-8.

13
14 Nielsen, PS; Autrup, H. (1994) Diesel exhaust-related DNA adducts in garage workers. *Clin Chem* 40:1456-
15 1458.

16
17 Nielsen, PS; Andreassen, A; Farmer, PB; et al. (1996a) Biomonitoring of diesel exhaust-exposed workers.
18 DNA and hemoglobin adducts and urinary 1-hydroxypyrene as markers of exposure. *Toxicol Lett* 86:27-37.

19
20 Nielsen, PS; de Pater, N; Okkels, H; et al. (1996b) Environmental air pollution and DNA adducts in
21 Copenhagen bus drivers—effect of (incomplete entry)

22
23 Nikula, KJ; Snipes, MB; Barr, EB; et al. (1995) Comparative pulmonary toxicities and carcinogenicities of
24 chronically inhaled diesel exhaust and carbon black in F344 rats. *Fundam Appl Toxicol* 25:80-94.

25
26 Nikula, KJ; Avila, KJ; Griffith, WC. (1997) Sites of particle retention and lung tissue responses to
27 chronically inhaled diesel exhaust and coal dust in rats and *Cynomolgus* monkeys. *Environ Health Perspect*
28 105(5):1231-1234.

29
30 Notani, PN; Shah, P; Jayant, K; et al. (1993) Occupation and cancers of the lung and bladder: a case-control
31 study in Bombay. *Int J Epidemiol* 22:185-191.

32
33 Oberdörster, G; Yu, CP. (1990) The carcinogenic potential of inhaled diesel exhaust: a particle effect? *J*
34 *Aerosol Sci* 21 (suppl. 1):S397-S401.

35
36 Oberdörster, G; Baggs, R; Gelein, R; et al. (1995) Pulmonary effects of inhaled carbon black in rats.
37 *Toxicologist* 15:46.

38
39 Orthofer, JG; Moore, W; Kraemer, D. (1981) Carcinogenicity of diesel exhaust as tested in strain A mice.
40 *Environ Int* 5:461-471.

1 **Pepelko, WE; Peirano, WB. (1983) Health effects of exposure to diesel engine emissions. J Am Coll Toxicol**
2 **2:253-306.**
3
4 **Percy, C; Stanek, E, III; Gloeckler, L. (1981) Accuracy of cancer death certificates and its effect on cancer**
5 **mortality statistics. Am J Public Health 71:242-250.**
6
7 **Phillips, BJ; James, TEB; Anderson, D. (1984) Genetic damage in CHO cells exposed to enzymatically**
8 **generated active oxygen species. Mutat Res 126:265-271.**
9
10 **Pott, F; Stöber, W. (1983) Carcinogenicity of airborne combustion products observed in subcutaneous tissue**
11 **and lungs of laboratory rodents. Environ Health Perspect 47:293-303.**
12
13 **Pott, F; Heinrich, U. (1990) Relative significance of different hydrocarbons for the carcinogenic potency of**
14 **emissions from various incomplete combustion processes. In: complex mixtures and scientific risk. Scientific**
15 **publication 104. Vaino, A; Sorsa, M; McMichael, AJ; eds. Lyon, France: IARC; pp. 288-297.**
16
17 **Pott, F; Heinrich, U; Vainio, H; et al. (1990) Complex mixtures and cancer risk. In: Relative significance of**
18 **hydrocarbons for the carcinogenic potency of emissions from various incomplete combustion processes.**
19 **IARC, 288-297.**
20
21 **Pott, F; Dungworth, DL; Heinrich, U; et al. (1994) Lung tumours in rats after intratracheal instillation of**
22 **dusts. Ann Occup Hyg 38:357-363, Suppl. 1.**
23
24 **Qu, SX; Leigh, J; Koelmeyer, H; et al. (1996) Detection of DNA adducts in coal miners exposed to diesel**
25 **emissions in Australia. Fundam Appl Toxicol 50:237 (abstr).**
26
27 **Raffle, PAB. (1957) The health of the worker. Br J Ind Med 14:73-80.**
28
29 **Riebe-Imre, M; Aufderheide, M; Gärtner-Hübsch, S; et al. (1994) Cytotoxic and genotoxic effects of**
30 **insoluble poarticles in vitro. In: Toxic and carcinogenic effects of solid particles in the respiratory tract.**
31 **Mohr, U; Dungworth, DL; Mauderly, DL; et al., eds. Washington, DC: International Life Sciences Institute**
32 **Press, pp. 519-523.**
33
34 **Risch, HA; Burch, JD; Miller, AB; et al. (1988) Occupational factors and the incidence of cancer of the**
35 **bladder in Canada. Br J Ind Med 45:361-367.**
36
37 **Rister, M; Baehner, RL. (1977) Effect of hyperoxia on superoxide anion and hydrogen peroxide production**
38 **of polymorphonuclear leukocytes and alveolar macrophages. Br J Haematol 36:241-248.**
39
40 **Rittinghausen, S; Mohr, U; Dungworth, DL. (1997) Pulmonary cystic keratinizing squamous cell lesions after**
41 **inhalation/instillation of different particles. Exper Toxicol Pathol 49:433-446.**
42

1 Rogot, E; Reid, DD. (1975) The validity of data from next-of-kin in studies of mortality among migrants. *Int*
2 *J Epidemiol* 4:51-54.
3
4 Root, RK; Metcalf, JA. (1977) H₂O₂ release from human granulocytes during phagocytosis. *J Clin Invest*
5 60:1266-1279.
6
7 Rosenblatt, MB; Teng, PK; Kerpe, S; et al. (1971) Causes of death in 1,000 consecutive autopsies. *NY State J*
8 *Med* 71:2189-2193.
9
10 Rosenkranz, HS. (1996) Mutagenic nitroarenes, diesel emissions, particle-induced mutations and cancer: an
11 essay on cancer causation by a moving target. *Mutat Res* 367:65-72.
12
13 Rosenkranz, HS; Mermelstein, R. (1983) Mutagenicity and genotoxicity of nitroarenes: all nitro-containing
14 chemicals were not created equal. *Mutat Res* 114:217-267.
15
16 Rothman, KJ. (1986) *Modern epidemiology*. Boston/Toronto: Little, Brown and Co.; pp. 16-21.
17
18 Rushton, L; Alderson, MR. (1983) Epidemiological survey of oil distribution centres in Britain. *Br J Ind*
19 *Med* 40:330-339.
20
21 Rushton, L; Alderson, MR; Nagarajah, CR. (1983) Epidemiological survey of maintenance workers in
22 London Transport Executive bus garages at Chiswick Works. *Br J Ind Med* 40:340-345.
23
24 Sagai, M; Saito, H; Ichinose, T; et al. (1993) Biological effects of diesel exhaust particles. I. In vitro
25 production of superoxide and in vivo toxicity in mouse. *Free Radical Biol Med* 14:37-47.
26
27 Salmeen, IT; Pero, AM; Zator, R; et al. (1984) Ames assay chromatograms and the identification of
28 mutagens in diesel exhaust particle extracts. *Environ Sci Technol* 18:375-382.
29
30 Sandusky, CB; Cowden, MW; Schwartz, SL. (1977) Effect of particle size on regurgitive exocytosis by rabbit
31 alveolar macrophages. In: *Pulmonary macrophages and epithelial cells*. CONF-760927, National Technical
32 Information Service, U.S. Dept. of Commerce, pp. 85-105.
33
34 Saverin. R; Bräunlich, A; Dahman, D; et al. (1999) Diesel exhaust and lung cancer mortality in potash
35 mining. *Am J Ind Med* 36:415-422.
36
37 Scheepers, PJT; Bos, RP. (1992) Combustion of diesel fuel from a toxicological perspective. II. Toxicity. *Int*
38 *Arch Occup Environ Health* 64:163-177.
39
40 Schenker, MB; Smith, T; Munoz, A; et al. (1984) Diesel exposure and mortality among railway workers:
41 results of a pilot study. *Br J Ind Med* 41:320-327.
42

1 Schottenfeld, D; Eaton, M; Sommers, SC; et al. (1982) The autopsy as a measure of accuracy of the death
2 certificate. *Bull NY Acad Med* 58:778-794.

3
4 Sera, N; Fukuhara, K; Miyata, N; et al. (1994) Detection of nitro-azabenzol[a]pyrene derivatives in the
5 semivolatile phase originating from airborne particulate matter, diesel and gasoline vehicles. *Mutagenesis*
6 9:47-52.

7
8 Shefner, AM; Collins, SC; Dooley, L; et al. (1982) Respiratory carcinogenicity of diesel fuel emissions
9 interim results. In: *Toxicological effects of emissions from diesel engines*. Lewtas, J, ed. Amsterdam:
10 Elsevier; pp. 329-350.

11
12 Siemiatycki, J; Gérin, M; Stewart, P; et al. (1988) Associations between several sites of cancer and ten types
13 of exhaust and combustion products: results from a case-referent study in Montreal. *Scand J Work Environ*
14 *Health* 14:79-90.

15
16 Silverman, DT; Hoover, RN; Albert, S; et al. (1983) Occupation and cancer of the lower urinary tract in
17 Detroit. *J Natl Cancer Inst* 70:237-245.

18
19 Silverman, DT; Hoover, RN; Mason, TJ; et al. (1986) Motor exhaust-related occupations and bladder
20 cancer. *Cancer Res* 46:2113-2116.

21
22 Steenland, K. (1986) Lung cancer and diesel exhaust: a review. *Am J Ind Med* 10:177-189.

23
24 Steenland, K; Burnett, C; Osoria, AM. (1987) A case-control study of bladder cancer using city directories
25 as a source of occupational data. *Am J Epidemiol* 126:247-257.

26
27 Steenland, NK; Silverman, DT; Hornung, RW. (1990) Case-control study of lung cancer and truck driving in
28 the Teamsters Union. *Am J Public Health* 80:670-674.

29
30 Steenland, K; Deddens, J; Stayner, L. (1998) Diesel exhaust and lung cancer in the trucking industry:
31 exposure-response analyses and risk assessment. *Am J Ind Med* 34:220-228.

32
33 Steineck, G; Plato, N; Gerhardsson, M; et al. (1990) Increased risk of urothelial cancer in Stockholm during
34 1985-87 after exposure to benzene and exhausts. *Int J Cancer* 45:1012-1017.

35
36 Stenback, F; Rowland, J; Sellakumar, A. (1976) Carcinogenicity of benzo[a]pyrene and dusts in the hamster
37 lung (instilled intratracheally with titanium oxide, aluminum oxide, carbon and ferric oxide). *Oncology*
38 33:29-34.

39
40 Stenberg, U; Alsberg, T; Westerholm, R. (1983) Emission of carcinogenic components with automobile
41 exhausts. *Environ Health Perspect* 47:53-63.

1 Stern, FB; Lemen, RA; Curtis, RA. (1981) Exposure of motor vehicle examiners to carbon monoxide: a
2 historical prospective mortality study. *Arch Environ Health* 36:59-66.

3
4 Stöber, W. (1986) Experimental induction of tumors in hamsters, mice and rats after long-term inhalation of
5 filtered and unfiltered diesel engine exhaust. In: *Carcinogenic and mutagenic effects of diesel engine exhaust*.
6 Ishinishi, N; Koizumi, A; McClellan, R; et al., eds. Amsterdam: Elsevier; pp. 421-429.

7
8 Stöber, W; Abel, UR. (1996) Lung cancer due to diesel soot particles in ambient air? A critical appraisal of
9 epidemiological studies addressing this question. *Int Arch Occup Environ Health* 68(Suppl):S3-S61.

10
11 Strom, KA. (1984) Response of pulmonary cellular defenses to the inhalation of high concentrations of diesel
12 exhaust. *J Toxicol Environ Health* 13:919-944.

13
14 Swanson, GM; Lin, CS; Burns, PB. (1993) Diversity in the association between occupation and lung cancer
15 among black and white men. *Cancer Epidemiol Biomarkers Prev* 2:313-320.

16
17 Takaki, Y; Kitamura, S; Kuwabara, N; et al. (1989) Long-term inhalation studies of exhaust from diesel
18 engine in F-344 rats: the quantitative relationship between pulmonary hyperplasia and anthracosis. *Exp*
19 *Pathol* 37:56-61.

20
21 Takemoto, K; Yoshimura, H; Katayama, H. (1986) Effects of chronic inhalation exposure to diesel exhaust
22 on the development of lung tumors in di-isopropanol-nitrosamine-treated F344 rats and newborn C57BL and
23 ICR mice. In: *Carcinogenic and mutagenic effects of diesel engine exhaust*. Ishinishi, N; Koizumi, A;
24 McClellan, R; et al., eds. Amsterdam: Elsevier; pp. 311-327.

25
26 Takemoto, K; Katayama, H; Kuwabara, T; et al. (1988) Carcinogenicity by subcutaneous administration of
27 diesel particulate extracts in mice. In: *Diesel exhaust and health risks*. Ibaraki, Japan: Research Committee
28 for HERP Studies; pp. 227-234.

29
30 Thyssen, J; Althoff, J; Kimmerle, G; et al. (1981) Inhalation studies with benzo[a]pyrene in Syrian golden
31 hamsters. *J Natl Cancer Inst* 66:575-577.

32
33 Trotter, JR. (1980) Spontaneous cancer and its possible relationship to oxygen metabolism. *Proc Natl Acad*
34 *Sci* 77:1763-1767.

35
36 U.S. Environmental Protection Agency (U.S. EPA). (1993) Motor vehicle-related air toxics study. *Ann*
37 *Arbor, MI: Office of Mobile Sources. EPA/420/R-93/005*. Available from National Technical Information
38 Service, Springfield, VA, PB93-182590/XAB.

39
40 U.S. EPA. (1996a) Air quality criteria for particulate matter. Prepared by the National Center for
41 Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, NC.
42 EPA/600/P-95/001bF.

1 U.S. EPA. (1996b) Proposed guidelines for carcinogen risk assessment. Office of Research and Development.
2 Federal Register 61(79):17960-18011. EPA/600/P-92/003C.

3
4 U.S. EPA. (1999) Guidelines for carcinogen risk assessment-review draft. NCEA-F-0644 (July 1999).

5
6 Vineis, P; Magnani, C. (1985) Occupation and bladder cancer in males: a case-control study. *Int J Cancer*
7 35:599-606.

8
9 Vostal, JJ. (1986) Factors limiting the evidence for chemical carcinogenicity of diesel emissions in long-term
10 inhalation experiments. In: *Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the*
11 *international satellite symposium on toxicological effects of emissions from diesel engines; July 1986;*
12 *Tsukuba Science City, Japan. Ishinishi, N; Koizumi, A; McClellan, RO; et al., eds. (Developments in*
13 *toxicology and environmental science: v. 13.) Amsterdam: Elsevier Science Publishers BV; pp. 381-396.*

14
15 Waller, RE. (1981) Trends in lung cancer in London in relation to exposure to diesel fumes. *Environ Int*
16 5:479-483.

17
18 Ward, JM. (1983) Background data and variations in tumor rates of control rats and mice. *Prog Exper*
19 *Tumor Res* 26:241-258.

20
21 Waxweiler, RJ; Wagoner, JK; Archer, VE. (1973) Mortality of potash workers. *J Occup Med* 15:486-489.

22
23 Weinstein, IB; Troll, W. (1977) National Cancer Institute workshop on tumor promotion and cofactors in
24 carcinogenesis. *Cancer Res* 37:3461-3463.

25
26 Weiss, SJ; Rustagei, PK; LoBuglio, AF. (1978) Human granulocyte generation of hydroxyl radical. *J Exp*
27 *Med* 147:316-323.

28
29 Weitzman, SA; Stossel, TP. (1981) Mutation caused by human phagocytosis. *Science* 212:546-547.

30
31 White, HJ; Vostal, JJ; Kaplan, HL; et al. (1983) A long-term inhalation study evaluates the pulmonary
32 effects of diesel emissions. *J Appl Toxicol* 1:332.

33
34 Wichmann, HE; Kreienbrock, L; Kreuzer, M; et al. (1998) Lungenkrebrisiko durch Radon in der
35 Bundesrepublik Deutschland (West). In: *Fortschritte in der Umwelmedizin, ecomed Verlagsgesellschaft*
36 *Landsberg/Lech. Wichmann, HE; Schliepköter, HW; Fulgraff, G; et al., eds.*

37
38 Williams, RR; Stegens, NL; Goldsmith, JR. (1977) Associations of cancer site and type with occupation and
39 industry from the Third National Cancer Survey interview. *J Natl Cancer Inst* 59:1147-1185.

40
41 Wong, D; Mitchell, CE; Wolff, RK; et al. (1986) Identification of DNA damage as a result of exposure of rats
42 to diesel engine exhaust. *Carcinogenesis* 7:1595-1597.

1 **Wong, O; Morgan, RW; Kheifets, L; et al. (1985) Mortality among members of a heavy construction**
2 **equipment operators union with potential exposure to diesel exhaust emissions. Br J Ind Med 42:435-448.**
3
4 **Woskie, SR; Smith, TJ; Hammond, SK; et al. (1988a) Estimation of the diesel exhaust exposures of railroad**
5 **workers: I. Current exposures. Am J Ind Med 13:381-394.**
6
7 **Woskie, SR; Smith, TJ; Hammond, SK; et al. (1988b) Estimation of the diesel exhaust exposures of railroad**
8 **workers: II. National and historical exposures. Am J Ind Med 13:395-404.**
9
10 **Wynder, LE; Dieck, G; Hall, NE. (1985) A case control study of diesel exhaust exposure and bladder cancer.**
11 **Environ Res 34:475-489.**
12
13 **Zaebst, DD; Clapp, DE; Blade, LM; et al. (1991) Quantitative determination of trucking industry workers'**
14 **exposures to diesel exhaust particles. Am Ind Hyg Assoc J 52:529-541.**
15
16 **Zamora, PO; Gregory, RE; Brooks, AL. (1983) In vitro evaluation of the tumor-promoting potential of**
17 **diesel-exhaust-particle extracts. J Toxicol Environ Health 11:188-197.**