

## 8. DOSE-RESPONSE ASSESSMENT: CARCINOGENIC EFFECTS

### 8.1. INTRODUCTION

Dose-response assessment defines the relationship between the exposure/dose of an agent and the degree of carcinogenic response, and evaluates potential cancer risks to humans at exposure/dose levels of interest. Most often, the exposure-dose-response of interest is well below the range of observation. As a result, dose-response assessment usually entails an extrapolation from the generally high exposures in studies in humans or laboratory animals to the exposure levels expected from human contact with the agent in the environment. It also includes considerations of the scientific validity of these extrapolations based on available knowledge about the underlying mechanisms or modes of carcinogenic action. The complete sequence of biological events that must occur to produce an adverse effect is defined as “mechanism of action.” In cases where only partial information is available, the term “mode of action” is used to refer to the mechanisms for key events that are judged to be sufficient to inform about the shape of the dose-response curve beyond the range of observation.

This chapter evaluates the available exposure-dose-response data, discusses extrapolation issues in estimating the cancer risk of environmental exposure to diesel exhaust (DE). It is concluded that available data are inadequate to confidently derive a cancer unit risk estimate for DE or its component, diesel particulate matter (DPM). Unit risk is one possible output from a dose-response assessment and is defined as the estimated upper-bound cancer risk at a specific exposure or dose from a continuous average lifetime exposure of 70 years (in this case, cancer risk per  $\mu\text{g}/\text{m}^3$  of DPM). In lieu of unit-risk-based quantitative risk estimates, this chapter provides some perspective about potential risk at environmental levels. Approaches to dose-response assessment for DE follow EPA’s guidelines for carcinogen risk assessment (U.S. EPA, 1986, 1996).

Subsequent sections of this chapter discuss issues related to dose-response evaluation of human cancer risk to DE, including the target tumor site and underlying mode of action, suitable measures of dose, approaches to low-dose extrapolation, and appropriate data to be used in the dose-response analysis. This is followed by a simple analysis of the possible degree and extent of risk from environmental exposure to DE. Appendix D provides a summary review of dose-response assessments conducted to date by other organizations and investigators.

### 8.2. MODE OF ACTION AND DOSE-RESPONSE APPROACH

According to EPA’s 1996 Proposed Guidelines for Carcinogen Risk Assessment, dose-response assessment is performed in two steps: assessment of observed data to derive a point of departure, followed by extrapolation to lower exposures to the extent necessary. Human data are

1 always preferred over animal data, if available, as their use obviates the need for extrapolation  
2 across species. Mode of action information is critical to dose-response evaluation, as it informs  
3 about the relevance of animal data to assessment of human hazard and risk, the shape of the dose-  
4 response curve at low doses, and the most appropriate measure(s) of dose and response.

5 If there are sufficient quantitative data (humans and/or animals) and adequate  
6 understanding of the carcinogenic process, the preferred approach is to use a biologically based  
7 model for both the range of observation and extrapolation below that range. Otherwise, as a  
8 default procedure, a standard mathematical model is used to curve-fit the observed dose-response  
9 data to obtain a point of departure, which is the lower 95% confidence limit of the lowest  
10 exposure/dose that is associated with a selected magnitude of excesses of cancer risk in human or  
11 animal studies. Default approaches for low-dose extrapolation should be consistent with current  
12 understanding of the mode(s) of action. These include approaches that assume linearity or  
13 nonlinearity, or both. Linear extrapolation is used when there is insufficient understanding of the  
14 modes of action, or the mode of action information indicates that the dose-response curve at low-  
15 dose is, or is expected to be, linear. Linear extrapolation involves the calculation of the slope of  
16 the line drawn from the point of departure to zero exposure or dose (i.e., above background).  
17 When there is sufficient evidence for a nonlinear mode of action but not enough data to construct  
18 a biologically based model for the relationship, a margin of exposure is used as a default  
19 approach. A margin-of-exposure analysis compares the point of departure (i.e., the lowest  
20 exposure associated with some cancer risk) with the dose associated with the environmental  
21 exposure(s) of interest and determines whether or not the exposure margins are adequate. Both  
22 default approaches may be used for a tumor response, if it is mediated by linear and nonlinear  
23 modes of action.

24 As reviewed in Chapter 7, there is substantial evidence from combined human and  
25 experimental evidence that DE likely poses a cancer hazard to humans at anticipated levels of  
26 environmental exposure. The critical target organ is the lung. Limited evidence exists for a  
27 casual relationship between risk for lung cancer and occupational exposure to DE in certain  
28 occupational workers such as railroad workers, truck drivers, heavy equipment operators, transit  
29 workers, etc. In addition, it has been shown unequivocally in several studies that DE can cause  
30 benign and malignant lung tumors in rats in a dose-related manner following chronic inhalation  
31 exposure to sufficiently high concentrations.

32 The mechanism(s) by which DE induces lung cancer in humans has not been established.  
33 As discussed in Section 7.4, several modes of action have been postulated based on available  
34 mechanistic studies, including direct DNA effects (gene mutations) by the adsorbed organic  
35 compounds and the gaseous fractions, indirect DNA effects (e.g., chromosomal aberrations, sister  
36 chromatid exchange [SCE], micronuclei) by DE and DPM, oxidative DNA damage by DPM via

1 release of reactive oxygen species (ROS), and particle-induced chronic inflammatory response  
2 leading to epithelial cell cytotoxicity and regenerative cell proliferation via release of cytokines,  
3 growth factors, and ROS. It is likely that a combination of modes of action contribute to the  
4 overall carcinogenic activity of DE, and that the relative contribution of the various modes of  
5 action may vary with different exposure levels.

6 In the absence of a full understanding of the relative roles of DE constituents in inducing  
7 lung cancer in humans, and because there is some evidence for a mutagenic mode of action, this  
8 assessment takes the position that linear low-dose extrapolation is most appropriate and prudent  
9 (U.S. EPA, 1986, 1996). It should be noted that other individuals and organizations have used  
10 either linear risk extrapolation models and or mechanistically based models to estimate cancer risk  
11 from environmental exposure to DE (e.g., IPCS, 1996; Cal EPA, 1998; also see Appendix D).

12 On the other hand, there is an adequate understanding of how DE causes lung tumors in  
13 the rat under experimental exposure conditions. Prolonged exposure to high concentrations of a  
14 variety of insoluble particles including DPM (and its carbon core, devoid of organics) causes lung  
15 tumors in rats through a mode of action that involves impairment of lung clearance mechanisms  
16 (referred to as “lung overload response”), leading to persistent chronic inflammation, cell  
17 proliferation, metaplasia, and ultimately the development of lung tumors (ILSI, 2000). Because  
18 this mode of action is not expected to be operative at environmental exposure conditions, the rat  
19 lung tumor dose-response data are not considered suitable for predicting human risk at low  
20 environmental exposure concentrations.

### 21 22 **8.3. USE OF EPIDEMIOLOGIC STUDIES FOR QUANTITATIVE RISK ASSESSMENT**

23 As discussed above, human data are considered more appropriate than animal data in  
24 estimating environmental cancer risk for DE. Still, there are many uncertainties in using the  
25 available epidemiologic studies that have quantitative exposure data to extrapolate the risk to the  
26 general population for ambient-level DE exposure.

#### 27 28 **8.3.1. Sources of Uncertainty**

29 The greatest uncertainty in estimating DE-induced cancer risk from epidemiologic studies  
30 is the lack of knowledge of actual historical exposures for individual workers, particularly for the  
31 early years. Reconstruction of historic exposures are based on job exposure categories, industrial  
32 hygiene measurements, and assumptions made about exposure patterns.

33 Another related uncertainty is the choice of markers of exposure to DE. As discussed  
34 above, the modes of action for DE-induced lung cancer in humans are not fully understood, and  
35 thus the best measure of DE exposure is unknown. Various markers of DPM (e.g., respirable-

1 sized particles, elemental carbon [EC]) have been used as dosimeters for DE. Though EC is more  
2 sensitive and more specific than respirable-sized particles, both are considered appropriate  
3 dosimeters. Related to the choice of dosimeter, having a relatively constant relationship between  
4 the organics (on the particle) and the particle mass would be consistent with a possible mode of  
5 action role for both the particle and organic components. However, evidence of such a constant  
6 historic relationship remains unclear. As discussed in Chapter 2 (Section 2.5.2), it appears that  
7 newer model on-road engine exhaust may have somewhat less organics adsorbed onto the particle  
8 compared with older model engines. On the other hand, with regard to DE in the ambient air,  
9 there is significant variation of the amounts of DPM organic emitted because of aged vehicles in  
10 the on-road fleet, driving patterns, and the additional presence of nonroad DE (e.g., marine  
11 vessels and locomotives, which generally use older technology than on-road engines).

12 Another major uncertainty associated with many of the DE epidemiologic studies was the  
13 inability to fully control for smoking effects, resulting in possible errors in estimating relative risk  
14 increases. Changes in adjustments for smoking could result in considerable changes in relative  
15 risk because smoking has a much larger effect on relative lung cancer risk than is likely for DE. It  
16 is difficult to effectively control for a smoking effect in a statistical analysis because cigarette  
17 smoke contains an array of biologically active compounds and affects multiple steps of  
18 carcinogenesis, thus probably making smokers more susceptible to DE-induced lung cancer than  
19 are nonsmokers. A traditional statistical analysis (e.g., logistic regression) would not be able to  
20 adjust for such an effect. Although both case-control and cohort studies are subjected to the same  
21 difficulty, controlling for smoking effects is more problematic in case-control studies than in  
22 cohort studies because a majority of the lung cancer cases (about 85%; U.S. Surgeon General,  
23 1982) are usually also smokers.

24 Another uncertainty is the use of occupational worker data to extrapolate cancer hazard  
25 risk to the general population and sensitive subgroups. By sex, age, and general health status,  
26 workers are not fully representative of the general population. There is virtually no information to  
27 determine whether infants and children or people in poor health respond differently to DE  
28 exposure than do workers. Finally, the use of linear low-dose extrapolation may contribute  
29 significantly to uncertainty in estimating environmental risks.

### 30 **8.3.2. Evaluation of Key Epidemiologic Studies for Potential Use in Quantitative Risk** 31 **Estimates**

32 Among the available epidemiologic studies, only the railroad worker studies and the  
33 Teamster truck driver studies have quantitative exposure data for possible use in deriving a unit  
34

1 risk estimate for DE-induced lung cancer. This section evaluates the strengths and limitations of  
2 these data and their suitability for dose-response analysis.

### 3 4 **8.3.2.1. *Railroad Worker Studies***

5 Garshick and colleagues conducted both cohort and case-control studies of lung cancer  
6 mortalities among U.S. railroad workers registered with the U.S. Railroad Retirement Board  
7 (RRB).

8 In the cohort study (Garshick et al., 1988), lung cancer mortality was ascertained through  
9 1980 in 55,407 railroad workers, age 40 through 64 in 1959, with at least 10 years of work in  
10 selected railroad jobs (39 job titles). The cohort was selected on the basis of job titles in 1959.  
11 Industrial hygiene evaluations and descriptions of job activities were used to classify jobs as  
12 exposed or unexposed to diesel emissions. Workers with recognized asbestos exposure were  
13 excluded from the job categories selected for study. However, a few jobs with some potential for  
14 asbestos exposure were included in the cohort. Each subject's work history was determined from  
15 a yearly job report filed by his employer with the RRB from 1959 until death or retirement. The  
16 year 1959 was chosen as the effective start of DE exposure for this study because by this time  
17 95% of the locomotives in the United States were diesel powered. The author reported  
18 statistically significant relative risk increases of 1.57 for the 40-44 year age group and 1.34 for the  
19 45-49 year age group, after exclusion of workers exposed to asbestos and controls for smoking.  
20 Age groups were determined by their ages in 1959.

21 A main strength of the cohort study is the large sample size (55,407), which allowed  
22 sufficient power to detect small risks. This study also permitted the exclusion of workers with  
23 potential past exposure to asbestos. The stability of job career paths in the cohort ensured that of  
24 the workers 40 to 64 years of age in 1959 classified as DE-exposed, 94% of the cases were still in  
25 DE-exposed jobs 20 years later.

26 The main limitation of the cohort study is the lack of quantitative data on exposure to DE.  
27 The number of years exposed to DE was used as a surrogate for dose. The dose, based on  
28 duration of employment, has inaccuracies because individuals were working on both steam and  
29 diesel locomotives during the transition period. It should be noted that the investigators included  
30 only exposures after 1959; the duration of exposure prior to 1959 was not known. Other  
31 limitations of this study include its inability to examine the effect of years of exposure prior to  
32 1959 and the less-than-optimal latency period for lung cancer expression. No adjustment for  
33 smoking was made in this study. For a detailed description of this study please refer to Section  
34 7.2.1.7.

1 Garshick and colleagues also conducted a case-control study of railroad workers who  
2 died of lung cancer between 1981 and 1982 (Garshick et al., 1987). The author reported  
3 statistically significant increased odds ratios (with asbestos exposure accounted for) of 1.41 for  
4 the  $\leq 64$  year age group and 1.64 for the  $\leq 64$  year age group with  $\geq 20$  years of exposure when  
5 compared to the 0-4 year exposure group. The population base for this case-control study was  
6 approximately 650,000 active and retired male U.S. railroad workers with 10 years or more of  
7 railroad service who were born in 1900 or later. The cases were selected from deaths with  
8 primary lung cancer, which was the underlying cause of death in most cases. Each case was  
9 matched to two deceased controls whose dates of birth were within 2.5 years of the date of birth  
10 of the case and whose dates of death were within 31 days of the date of death noted in the case.  
11 Controls were selected randomly from workers who did not have cancer noted anywhere on their  
12 death certificates and who did not die of suicide or of accidental or unknown causes. A total of  
13 1,256 cases and 2,385 controls were selected for the study. Among younger workers,  
14 approximately 60% had exposure to DE, whereas among older workers, only 47% were exposed  
15 to DE. DE exposure surrogates for workers were similar to those in the cohort study. Asbestos  
16 exposure was categorized on the basis of jobs held in 1959, or on the last job held if the subject  
17 retired before 1959. Smoking history information was obtained from the next of kin.

18 The strengths of the case control study are consideration of confounding factors such as  
19 asbestos exposure and smoking; classification of DE exposures by job titles and industrial hygiene  
20 sampling; and exploration of interactions between smoking, asbestos exposure, and DE exposure.  
21 Major limitations of this study include: (a) possible overestimation of cigarette consumption by  
22 surrogate respondents; (b) use of the Interstate Commerce Commission (ICC) job classification as  
23 a surrogate for exposure, which may have led to misclassification of DE exposure jobs with low  
24 intensity and intermittent exposure, such as railroad police and bus drivers, as unexposed; (c) lack  
25 of data on the contribution of unknown occupational or environmental exposures and passive  
26 smoking; and (d) a suboptimal latency period of 22 years, which may not be long enough to  
27 observe a full expression of lung cancer. For a detailed description of this study, please see  
28 Section 7.2.2.4.

29 As a part of these epidemiologic studies Woskie et al. (1988a) conducted an industrial  
30 hygiene survey in the early 1990s for selected jobs in four small northern railroads. DE exposure  
31 was considered as a yes/no variable based on job in 1959 and estimated years of work in a diesel-  
32 exposed job as an index of exposure. Thirty-nine job titles were originally identified and were  
33 then collapsed into 13 job categories and, for some statistical analyses, into 5 categories (clerks,  
34 signal maintainers, engineers/firers, brakemen/conductors/hostlers, and shop workers) (Woskie et

1 al., 1988b; Hammond et al., 1988). As discussed below, these exposure estimations were used by  
2 Crump et al. (1991) and by Cal EPA (1998) for their dose-response analyses.

3  
4 **8.3.2.1.1. *Potential for the data to be used for dose-response modeling.*** Usually dose-response  
5 analyses are performed on data from cohort studies. Case-control studies can also be used for  
6 dose-response analysis if exposure for each case and control is available. Control of a smoking  
7 effect is important when lung cancer is the disease of interest. However, as discussed previously  
8 (see Section 8.3.1), one may not be able to control smoking completely in a dose-response  
9 analysis.

10 Garshick et al. (1988) reported a positive relationship of relative risk and duration of  
11 exposure by modeling age in 1959 as a covariate in an exposure-response model. The positive  
12 relationship disappeared when attained age was used instead of age in 1959 and a negative dose-  
13 response was observed (Crump et al., 1991). This negative dose-response continued to be upheld  
14 in a subsequent reanalysis (Crump, 1999). Garshick (letter to Chao Chen, U.S. EPA, dated  
15 August 15, 1991) performed further analysis and reported that the relationship between years of  
16 exposure, when adjusted for attained age and calendar year, was flat to negative depending upon  
17 which model was used. In contrast, California EPA (Cal EPA, 1998) found a positive dose-  
18 response by using age in 1959 but allowing for an interaction term of age and calendar year in the  
19 model.

20 Crump et al. (1991) also found, and Garshick (letter to Chao Chen, U.S. EPA, dated  
21 August 15, 1991) confirmed, that in the years 1977-1980 the death ascertainment was not  
22 complete. About 20% to 70% of deaths were missing, depending upon the calendar year.  
23 Further analysis, based on job titles in 1959 and limited to deaths occurring through 1976, showed  
24 that the youngest workers still had the highest risk of dying of lung cancer.

25 Extensive statistical analyses were conducted by a panel convened by HEI (1999) to  
26 investigate the utility of the railroad worker cohort for use in dose-response based quantitative  
27 risk assessment. Seven models were used to test the data, and the models were formed by varying  
28 a number of covariates in different combinations. The covariates included employment duration,  
29 cumulative exposure with and without correction for background exposure, and three job  
30 categories: clerks and signalmen, train workers (which include engineers/firers/brakers/  
31 conductors), and shop workers. The coefficient for each covariate in a model is used to calculate  
32 relative risk for the associated covariate. In summary, the panel found that effects of exposure as  
33 defined by an exposure-response curve were either flat or negative in all of the models. In these  
34 analyses, relative risk for each job category was assumed to be constant with respect to age.  
35 Further exploration of the data showed that the relative risk for train workers was not constant.

1 The panel's statistical analyses also revealed the complexity of the data and difficulties of  
2 providing an adequate summary measure of effect, probably because calendar year and cumulative  
3 exposure are highly correlated, which makes it especially difficult to sort out their separate  
4 effects. The difficulty of providing an adequate measure of DE effect was further demonstrated in  
5 Table C.3 of the HEI report, in which negative or positive effects for cumulative exposure (with  
6 background exposure adjustment) were obtained depending on whether or not job category was  
7 included in the model.

8 The diverging results about the presence or absence of exposure-response for the railroad  
9 worker data have become a source of continuing debate about the suitability of these data for  
10 estimating DE risk. Although it is difficult to identify the exact reason for the diverging findings,  
11 the "age effect" appears to be a main source of uncertainty because age, calendar year, and  
12 cumulative exposure are not mutually independent. An ideal dose-response analysis would  
13 account for the ages when exposure to DE began and terminated, along with the attained age and  
14 other covariates for each person, using exposure intensity over age rather than cumulative  
15 exposure as a dosimeter. This analysis would be possible for the railroad workers if information  
16 were available on the ages when exposure began and terminated.

17 Given the equivocal evidence for positive exposure-response, EPA has not derived a unit  
18 risk on the basis of the available railroad worker data. This determination should not be  
19 construed, however, to imply that the railroad worker studies contain no useful information on  
20 lung cancer risk from exposure to DE.

### 21 22 **8.3.2.2. *Teamsters Union Trucking Industry Studies***

23 Steenland et al. (1990) conducted a case-control study of lung cancer deaths in the Central  
24 States Teamsters Union to determine the risk of lung cancer among different trucking industry  
25 occupations. The study found statistically significant increased odds ratios for lung cancer of 1.89  
26 and 1.64, depending on years of employment. Cases comprised all deaths from lung cancer  
27 (1,288). The 1,452 controls comprised every sixth death from the entire file, excluding deaths  
28 from lung cancer, bladder cancer, and motor vehicle accidents. Individuals were required to have  
29 20 years tenure in the union to be eligible to claim benefits.

30 Detailed information on work history and potential confounders such as smoking, diet,  
31 and asbestos exposure was obtained by questionnaire. On the basis of interview data and the  
32 1980 census occupation and industry codes, subjects were classified either as nonexposed or as  
33 having held other jobs with potential DE exposure. The Teamsters Union work history file did  
34 not have information on whether men drove diesel or gasoline trucks, and the four principal

1 occupations were long-haul drivers, short-haul or city drivers, truck mechanics, and dockworkers.  
2 Subjects were assigned the job category in which they had worked the longest.

3 The main strengths of the study are the availability of detailed records from the Teamsters  
4 Union, a relatively large sample size, availability of smoking data, and measurement of possible  
5 asbestos exposures. Some limitations of this study include possible misclassifications of exposure  
6 and smoking habits, as information was provided by next of kin; lack of sufficient latency to  
7 observe lung cancer excess; and a small nonexposed group (n = 120).

8 Steenland et al. (1998) conducted an exposure-response analysis by supplementing the  
9 data from their earlier case-control study of lung cancer and truck drivers in the Teamsters Union  
10 with exposure estimates based on a 1990 industrial hygiene survey of elemental carbon (EC)  
11 exposure (Zaebst, 1991), a surrogate for DE in the trucking industry. Available data indicate that  
12 exposure to workers in the trucking industry in 1990 averaged 2-27  $\mu\text{g}/\text{m}^3$  of EC. The 1990  
13 exposure information was used by Steenland as a baseline exposure measurement to reconstruct  
14 past exposure (in the period of 1949 to 1983) by assuming that the exposure for workers in  
15 different job categories is a function of highway mileages traveled by heavy-duty vehicles, and  
16 efficiency of the engine over the years.

17 The industrial hygiene survey by Zaebst et al. (1991) of EC exposures in the trucking  
18 industry provided exposure estimates for each job category in 1990. The EC measurements were  
19 generally consistent with the epidemiologic results, in that mechanics were found to have the  
20 highest exposures and relative risk, followed by long-haul and short-haul drivers. Dockworkers  
21 who had the lowest exposures also had the lowest relative risks.

22 Past exposures were estimated assuming that they were a function of (1) the number of  
23 heavy-duty trucks on the road, (2) the particulate emissions (grams/mile) of diesel engines over  
24 time, and (3) leaks from truck exhaust systems for long-haul drivers. Estimates of past exposure  
25 to EC (as a marker for DE exposure) were made based on the assumption that average 1990  
26 levels for a particular job category could be assigned to all subjects in that category, and that  
27 levels prior to 1990 were directly proportional to vehicle miles traveled by heavy-duty trucks and  
28 the estimated emission levels of diesel engines. For example, a 1975 exposure level was estimated  
29 by the following equation:  $1975 \text{ level} = 1990 \text{ level} \times (\text{vehicle miles } 1975 / \text{vehicle miles } 1990) \times$   
30  $(\text{emissions } 1975 / \text{emissions } 1990)$ . Once estimates of exposure for each year of work history were  
31 derived for each subject, analyses were conducted by cumulative level of estimated carbon  
32 exposure.

1 **8.3.2.2.1. Potential for the data to be used for dose-response modeling.** Steenland et al. (1998)  
2 analyzed their case-control data and showed a significant positive trend in lung cancer risk with  
3 increasing cumulative exposure to DE. The study by Steenland et al. (1998) provides a  
4 potentially valuable database for calculating unit risk for DE emissions. The strength of this data  
5 set is that the smoking histories of workers were obtained to the extent possible. Smoking is  
6 especially important in assessing the lung cancer risk due to DE exposure because smoking has  
7 much higher relative risk (or odds ratio) of lung cancer than does DE. In the Steenland et al.  
8 (1998) study, the overall (ever-smokers vs. nonsmokers) odds ratio for smoking is about 7.2,  
9 which is about five-fold larger than the 1.4 relative risk increase from a large synthesis of many  
10 DE epidemiologic studies. It is possible that a modest change of information on smoking and  
11 diesel exposure might alter the conclusion and risk estimate.

12 Another strength of the Teamster data for use in environmental risk assessment for the  
13 general population is that exposures of Teamsters are closer to ambient exposures than are those  
14 of railroad workers. The Teamsters Union truck driver case control workers had cumulative  
15 exposure ranging from 19 to 2,440  $\mu\text{g}/\text{m}^3$ -years of EC, with the median and 95<sup>th</sup> percentile,  
16 respectively, of 358 and 754  $\mu\text{g}/\text{m}^3$ -years of EC. The median and 95<sup>th</sup> percentile of an  
17 environmentally equivalent exposure would be 3 and 6  $\mu\text{g}/\text{m}^3$ , respectively.<sup>1</sup> These environmental  
18 equivalent exposures for the Teamsters Union truck drivers are close to the estimated ambient  
19 exposures of <1.0  $\mu\text{g}/\text{m}^3$  to 4.0  $\mu\text{g}/\text{m}^3$  (see Table 2-30). It should be noted that Steenland's study  
20 is a case-control study in which both case and control could be exposed to DE. Therefore, it is  
21 not informative to merely observe that environmental and occupational exposures overlap, thus  
22 the 95<sup>th</sup> percentile exposure of 6  $\mu\text{g}/\text{m}^3$  for the truck drivers should be used for comparison to  
23 ensure that the exposure is likely to be associated with the observed increment of cancer  
24 mortality.

25 Steenland et al. (1998) stated that their risk assessment is exploratory because it depends  
26 on estimates about unknown past exposures. Reanalysis of DE exposure for this study is  
27 underway. In a recent review, HEI (1999) concluded that the Teamsters studies may be useful for  
28 quantitative risk assessment, but significant further evaluation and development are needed. Given  
29 the ongoing reanalysis of exposure, EPA will not, at this time, use the Steenland (1998)  
30 occupational risk assessment findings to derive equivalent environmental parameters and cancer  
31 unit risk estimates.

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<sup>1</sup>The conversion assumes (1) DPM = 40% EC as reported by Steenland et al. (1998), (2) environmental equivalent exposure is approximately = 0.21 x occupational exposure, and (3) 70  $\mu\text{g}/\text{m}^3$ -years is equivalent to a lifetime of exposure at 1  $\mu\text{g}/\text{m}^3$ .

1 **8.3.3. Conclusion**

2 Because of uncertainties associated with the key epidemiologic data and related exposure  
3 information, this health assessment is not deriving a cancer unit risk or cancer unit risk range that  
4 can be confidently used to estimate population risk. Two significant activities are underway to  
5 improve the epidemiologic database for dose-response assessment: (1) to correct the  
6 undercounting of mortality in the Garshick et al. (1988) railroad worker study, and (2) to improve  
7 exposure estimates for Teamsters Union truck drivers (Steenland et al., 1998). These activities  
8 are being pursued by EPA, NIOSH, and the investigators of these studies. EPA will monitor  
9 ongoing research, including the longer term work by NCI-NIOSH regarding a new study of  
10 miners and the shorter term work reanalysis of epidemiology-exposure studies, and at a later date  
11 determine the merit of conducting additional dose-response analysis and unit risk derivation.  
12

13 **8.4. PERSPECTIVES ON CANCER RISK**

14 Although the available data are considered inadequate to confidently establish a cancer  
15 unit risk, this does not mean there is no information about the possible cancer risk of DE. To  
16 examine the significance of the potential cancer hazard from environmental exposure to DE, all  
17 relevant epidemiologic and exposure data as well as simple risk assessment tools can be used.  
18 Such an approach does not produce confident estimates of cancer unit risk. Rather, these  
19 approaches provide a perspective on the possible magnitude of cancer risk and thus insight about  
20 the significance of the hazard. This section describes approaches and methods that are used to  
21 gauge the magnitude of potential cancer risk from ambient exposure to DE.

22 The first approach involves examining the differences between the levels of occupational  
23 and ambient environmental exposures, and assuming that cancer risk to DE is proportional  
24 linearly with cumulative lifetime exposure. Risks to the general public would be low in  
25 comparison with occupational risk, if the differences in exposure are large (i.e., about three orders  
26 of magnitude or more). On the other hand, if the differences are smaller (i.e., within one to two  
27 orders of magnitude), the environmental risks are of concern, as they would approach workers'  
28 risk as observed in epidemiologic studies of past occupational exposures.

29 Table 8-1 shows occupational exposure estimates representative of some of the  
30 occupational groups where increased relative risks of lung cancer have been observed. Given the  
31 limited availability of exposure data, a broad estimate of DPM concentrations in the workplace is  
32 also included as a surrogate for high and low bounding of the exposures, recognizing that actual  
33 exposures from such concentration ranges would probably be less. These exposure or

1 concentration estimates<sup>2</sup> are not intended to be precise, or to match with specific epidemiologic  
2 data, but rather to provide a broad range of probable exposures. Environmental exposure data  
3 from on-road vehicle emissions are based on the 1990 nationwide exposure estimates from the  
4 HAPEM model (see Section 2.4.3.3.1). Both average (0.8 µg/m<sup>3</sup>) and high-end exposure (4  
5 µg/m<sup>3</sup>) are used.

6 In order to compare differences between occupational and environmental exposures, it is  
7 necessary to convert occupational exposure to continuous exposure (i.e., environmental  
8 equivalent exposure = 0.21 × occupational exposure, see Section 2.4.3.1). Accordingly, Table 8-  
9 1 shows equivalent environmental levels and the ratios of occupational to environmental  
10 exposures, referred to as exposure margins (EMs). An EM of 1 or less indicates that  
11 environmental exposure is comparable to occupational exposure. An EM >1 means that the  
12 occupational equivalent exposure is greater than the environmental exposure.

13 Table 8-1 shows that the EMs based on the average nationwide environmental exposure  
14 (0.8 µg/m<sup>3</sup>) approach three orders of magnitude. However, the EMs based on a high-end  
15 environmental exposure (i.e., 4 µg/m<sup>3</sup>) range from within an order of magnitude to less than two  
16 orders of magnitude. This analysis, therefore, indicates that cancer risks from environmental  
17 exposure to DE are of potential public health concern. This exposure analysis, however, only  
18 addresses on-road sources for DE exposure. With additional DE exposures from non-road  
19 sources, which cannot be quantified at this time, there is a potential for greater concern for DE-  
20 induced cancer risk.

21 To further characterize possible cancer risk to the general population from environmental  
22 exposure to DE, one can begin by examining the risk observed in DE exposed workers. As  
23 reviewed in Section 7.2, numerous epidemiologic studies have shown increased lung cancer risks  
24 (i.e., some are deaths, some are cases) among workers in certain occupations. The relative risks  
25 or odds ratios range from 1.2 to 2.6. Two independent meta-analyses show smoking adjusted  
26 relative risk increase of 1.35 (Bhatia et al., 1997) and 1.47 (Lipsett and Campleman, 1999). For  
27 the purpose of this analysis, a relative risk of 1.4 is selected as a reasonable estimate. The relative  
28 risk of 1.4 means that the workers faced an extra risk that is 40 % higher than the 5% background  
29 lifetime lung cancer risk in the U.S. population.<sup>3</sup> Thus, using the relationship [*excess risk* =

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<sup>2</sup> Concentration is defined as the amount of DPM in the air; exposure takes into account human exposure patterns

<sup>3</sup>The background rate of 0.05 is an approximated lifetime risk calculated by the method of lifetable analysis using age-specific lung cancer mortality data and probability of death in the age group taken from the National Health Statistics (HRS) monographs of Vital Statistics of the U.S. (Vol. 2, Part A, 1992). Similar values based on two rather crude approaches can also be obtained: (1)  $59.8 \times 10E-5 / 8.8 \times 10E-3 = 6.8 \times 10E-2$  where  $59.8 \times 10E-5$  and  $8.8 \times 10E-3$  are respectively the crude estimates of lung cancer deaths (including intrathoracic organs,

1 (*relative risk-1*) × *background risk*], these DE-exposed workers would have an excess risk of 2%  
2 ( $10^{-2}$ ) (i.e., to develop lung cancer) due to occupational exposure to DE [(1.4 -1) × 0.05]= 0.02].  
3

4 Next, one would consider the exposure margin (i.e., the EM ratio) between the  
5 occupational exposures and general-population environmental exposures. The DPM  
6 concentrations in the workplace, used as a surrogate for worker exposure, have been reported to  
7 range from 4 to 1,740  $\mu\text{g}/\text{m}^3$  (or an equivalent continuous exposure of 1-365  $\mu\text{g}/\text{m}^3$ ). Table 8-1  
8 shows that the DPM exposure margin ratio between occupational and environmental exposure,  
9 using the nationwide average exposure value of 0.8  $\mu\text{g}/\text{m}^3$ , may range from 1 to 457. Risks from  
10 environmental exposure depend on the shape of the dose-response curve in the range between  
11 occupational and environmental exposures. If lifetime risks in this range were to fall  
12 proportionately with reduced exposure, and if one assumes that past occupational exposures were  
13 at the high end, then the risk from average environmental exposure could be between  $10^{-5}$  and  $10^{-4}$   
14 ( $0.02 \div 450 = 4 \times 10^{-5}$ ). On the other hand, if occupational exposures for different groups were  
15 lower, risks from environmental exposure would be higher than  $10^{-4}$  -  $10^{-5}$ . For example, if  
16 occupational concentrations or exposures were closer to 100  $\mu\text{g}/\text{m}^3$ , a value that is represented in  
17 several data sets shown in Table 8-1 (with an equivalent environmental exposure of 20  $\mu\text{g}/\text{m}^3$  and  
18 a corresponding EM of 25), then risks from environmental exposure would approach  $10^{-3}$  ( $0.02 \div$   
19  $25 = 8 \times 10^{-4}$ ). If lifetime risks were to fall more than proportionately, then risks from  
20 environmental exposure would be lower. The latter two sources of dose-response uncertainty  
21 (i.e., the actual occupational exposures and the shape of the dose-response curve at low  
22 exposures) cannot be defined with currently available information, but they affect the  
23 environmental risk estimates in opposite directions.

24 The magnitude of the estimated lifetime cancer risk (between  $10^{-5}$  and  $10^{-4}$ ), derived from  
25 using a high-end occupational to environmental exposure difference, establishes a reasonable basis  
26 for concern that the general population faces possible risks higher than  $10^{-6}$ . Adding to this  
27 concern are two other areas where this analysis does not directly address the segments of the  
28 population that may be at highest risk: those who are additionally exposed to nonroad sources of  
29 DE, and children who may be more sensitive to early life DE exposure.

30 The analyses presented above are not intended to be precise but are useful in gauging the  
31 possible range of risk based on applying scientific judgment and simple risk exploration methods

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estimated to be less than 105 of the total cases) and total deaths for 1996 reported in Statistical Abstract of the U.S. (Bureau of the Census, 1998, 118<sup>th</sup> Edition), and (2)  $156,900/270,000,000 \times 76 = 0.045$ , where 156,900 is the projected lung cancer deaths for the year 2000 as reported in Cancer Statistics 9J of American Cancer Society, Jan/Feb 2000), 270,000,000 is the current U.S. population, and 76 is the expected lifespan.

1 to the relative risk findings from available epidemiologic studies. These analyses provide a sense  
2 of where an upper limit (or “upper bound”) of the cancer risk may be. The simple methodologies  
3 used are generic in that they are valid for any increased relative risk data and thus are not unique  
4 to the DE data. These analyses are subject to considerable uncertainties, particularly the lack of  
5 actual exposure information and the underlying assumption that cancer risk is linearly proportional  
6 to cumulative exposure. Nevertheless, these analyses indicate that environmental exposure to DE  
7 may pose a lifetime cancer risk ranging from  $10^{-5}$  to  $10^{-3}$ . These findings are general indicators of  
8 the potential significance of the lung cancer hazard, and should not be viewed as a definitive  
9 quantitative characterization of risk. Further research is needed to more accurately assess and  
10 characterize environmental cancer risks to DE.

## 11 12 **8.5. SUMMARY**

13 As concluded in Section 7.5, DE is considered likely to be a carcinogen to humans at  
14 environmental levels of exposure. There have been many quantitative dose-response assessments  
15 in the peer-reviewed literature using epidemiologic and or experimental data to estimate human  
16 cancer risk from environmental exposure to DE (see Appendix D). In light of increased  
17 mechanistic understanding in recent years about how DE causes lung tumors in the rat, the  
18 present scientific consensus is that the rat lung tumor dose-response data are not suitable for  
19 predicting human risk at low exposure concentrations. Therefore, EPA has focused on the use of  
20 epidemiological data in characterizing the exposure-response relationship in the observed range of  
21 occupational exposure and extrapolating to the presumably lower levels of environmental  
22 exposure to derive a dose/exposure-specific unit risk. As discussed in the section, in the absence  
23 of a complete understanding of the modes of action for DE-induced lung cancer in humans  
24 coupled with the consideration that DE contains many mutagenic and carcinogenic constituents,  
25 this assessment takes the position that linear low-dose extrapolation is appropriate (i.e., risk is  
26 proportional to total lifetime exposure).

27 This chapter evaluates the railroad worker studies (Garshick et al., 1987, 1988) and the  
28 Teamster Union truck driver studies (Steenland et al., 1990, 1998), which have the best available  
29 exposure data for possible use in establishing an exposure-response relationship and deriving a  
30 cancer unit risk. Because of the uncertainties about the exposure-response for the railroad  
31 workers and exposure uncertainties for the truck drivers, EPA is not developing a cancer unit risk  
32 estimate for DE from these data sets at this time.

33 In the absence of a cancer unit risk to assess environmental cancer risk, this assessment  
34 provides perspectives about the possible magnitude of risk from environmental exposure to DE.

1 The small exposure margins between some occupational and environmental levels indicates a  
2 likelihood of cancer risk from environmental exposure to DE. Furthermore, based on the  
3 observed lung cancer from occupational exposures, and conservative assumptions discussed  
4 previously, the environmental cancer risks from DE may range from  $10^{-5}$  to  $10^{-3}$ . These findings  
5 are general indicators of the potential significance of the lung cancer hazard and should not be  
6 viewed as a definitive quantitative characterization of risk. A major assumption used in these  
7 analyses is that cancer risk is linearly proportional to total lifetime exposure. Further research is  
8 needed to more accurately assess and characterize environmental cancer risks to DE.

**Table 8-1. DPM exposure margins for occupational vs. environmental exposures**

Occupational group	Estimated occupational exposure/concentration ( $\mu\text{g}/\text{m}^3$ )  <i>Environmental equivalent<sup>a</sup></i>	<u>Exposure margin ratio</u> for 0.8 $\mu\text{g}/\text{m}^3$ of environmental exposure <sup>b</sup>	<u>Exposure margin ratio</u> for 4.0 $\mu\text{g}/\text{m}^3$ of environmental exposure <sup>b</sup>	Reference <sup>c</sup>
Non-coal miners	10-1,280 <b>2-269</b>	3-336	0.5-67	Säverin et al., 1999
Public transit workers	15-98 <b>3-21</b>	4-26	0.8-5	Birch and Cary, 1996
U.S. railroad workers	39-191 <b>8-40</b>	10-50	2-10	Woskie et al., 1988b
Broad concentration range	4-1,740 <sup>d</sup> <b>1-365</b>	1-457	0.21-91	HEI, 1995

<sup>a</sup> Occupational exposure  $\times$  0.21 = equivalent environmental exposure, see Chapter 2, Section 2.4.3.1.

<sup>b</sup> 0.8  $\mu\text{g}/\text{m}^3$  = average 1990 nationwide exposure estimate from HAPEM model; the companion rural estimate is 0.5  $\mu\text{g}/\text{m}^3$ , and 4  $\mu\text{g}/\text{m}^3$  is a high-end estimate. The 1996 nationwide average is 0.7  $\mu\text{g}/\text{m}^3$ . The companion rural estimate is 0.2  $\mu\text{g}/\text{m}^3$ ; however, a high-end estimate is not available for 1996. See Chapter 2, Sections 2.4.3.2.1 and 2.4.3.2.2.

<sup>c</sup> See Table 2-27 for more details about Säverin, Birch and Clay, and Woskie.

<sup>d</sup> Broadest range of average concentrations across many occupational groups. Use of concentration as a surrogate for high and low boundary for exposure, may overstate exposure.

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