6. QUANTITATIVE APPROACHES TO ESTIMATING HUMAN NONCANCER HEALTH RISKS OF DIESEL EXHAUST

1 6.1. INTRODUCTION

As discussed earlier in this document (Chapter 2, Section 2.2.2), diesel exhaust (DE) consists of a complex mixture of gaseous pollutants and particles. In attempting to estimate potential health risks associated with human exposure to DE, researchers have focused attention mostly on the particulate matter (PM) components, based, in part, on comparisons of relative toxicity of unfiltered versus filtered DE (with gaseous components removed), as discussed in Chapter 5.

8 Diesel particulate matter (DPM) consists mainly of: (a) elemental carbon (EC) particles; 9 (b) soluble organic carbon, including 5-ring or higher polycyclic aromatic hydrocarbons (PAHs) 10 such as benzo-a-pyrene (BaP), and other 3- or 4-ring compounds distributed between gas and 11 particle phases; and (c) metallic compounds. DPM also typically contains small amounts of 12 sulfate/sulfuric acid and nitrates, trace elements, and water, plus some unidentified components. 13 DPM is almost entirely fine particles $<1.0 \ \mu$ m, with many very small ultrafine particles (i.e., 14 $<0.10 \ \mu$ m).

15 Health concerns have long focused on diesel particles, which have very large surface areas that allow for adsorption of organics from the diesel combustion process and adsorb additional 16 17 compounds during transport in ambient air. The small particles and large surface area likely 18 provide an enhanced potential for subcellular interactions with important cellular components of 19 respiratory tissues once the particles are inhaled by humans or other species. Also of growing 20 health concern in recent years is the potential for enhanced toxic effects of ultrafine particles 21 (compared with particles of the same chemical composition but of larger size). Although many 22 questions remain regarding specific aspects of DPM "aging," these fine and ultrafine particles are 23 viewed as likely important toxic components of the overall mix of combustion-related fine 24 particles typically found in most urban airsheds.

25 One approach for deriving quantitative estimates of potential human health risks 26 associated with ambient (nonoccupational) DE exposures is to treat the DE constituent DPM as a 27 toxicologically important component of ambient fine particle mixes and to assume that 28 quantitative estimates of risk for ambient fine particle exposure effects in general also apply to 29 DPM specifically. Risk estimates or exposure guidance derived for ambient fine particles in 30 general would presumably then represent a plausible upper limit for levels of risk potentially 31 associated with DE measured as DPM (given that the latter is one of numerous constituents of 32 typical ambient fine particle mixes). The bases for deriving risk estimates for fine particles 33 recently used by EPA in setting new ambient air fine particle (PM_{2.5}) standards are concisely

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1 summarized and their relationships to ambient air DPM discussed in the next two sections

2 (Sections 6.2 and 6.3).

3 Another approach to evaluating noncancer risks of ambient DE exposures is to combine 4 key elements from evaluation of specific DPM noncancer effects in animals and humans 5 (described in Chapter 5) with use of quantitative dosimetry models (described in Chapter 3), for 6 estimating DPM concentrations to which humans may be exposed throughout their lives (i.e., 7 chronically) without experiencing any untoward or adverse noncancer effects. This can be accomplished via analysis of dose-response relationships where the adverse response is considered 8 as a function of a corresponding measure of dose. Chapter 5 is replete with dose-response 9 10 information on adverse (but nonlethal) noncancer health effects observed in long-term 11 (chronic/lifetime) exposure studies to DE in general and to DPM in particular, albeit in animals. 12 Chapter 3 presents methods that convert external exposure concentrations of DPM in animal 13 studies to estimates of a human equivalent concentration (HEC). Later sections (6.4 to 6.6) of 14 this chapter assess and integrate this information to derive a chronic reference concentration 15 (RfC), using a well-established Agency method for developing dose-response assessments of 16 noncancer effects for toxic air pollutants other than those identified below in Section 6.2 as being 17 regulated by National Ambient Air Quality Standards (NAAQS).

Estimates of DE levels associated with effects occurring under less than lifetime exposure scenarios (such as acute) are not addressed in this chapter. Acute studies of DE exposure, discussed in Chapter 5, are accompanied by scant dose-response information, with singleexposure studies for various specialized endpoints (e.g., allergenicity/adjuvancy) and other multiple-exposure-level studies reporting only data on mortality. Based on currently available methodologies, these studies do not yet appear to provide a sufficient basis from which to derive a dose-response assessment for an acute DE exposure scenario.

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6.2. DEVELOPMENT OF THE PM_{2.5} NAAQS

Historically, EPA has developed NAAQS to protect sensitive human population groups against adverse health effects associated with ambient exposures to certain widespread air pollutants, including PM, ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and lead (Pb). The U.S. Clean Air Act, as amended in 1977 and 1990, requires that EPA periodically review and revise as appropriate the criteria (scientific bases) and standards for a given pollutant or class of pollutants (e.g., PM) regulated by NAAQS.

The original total suspended particulate (TSP) NAAQS set in 1971 included both inhalable and noninhalable particles, ranging in size up to 25-50 μ m. A later periodic review of the PM criteria and NAAQS led to the setting in 1987 of "PM₁₀" NAAQS (150 μ g/m³, 24-h;

36 50 μ g/m³, annual average) aimed at protecting against health effects of inhalable particles

- 1 $(\leq 10.0 \ \mu m)$ capable of penetrating to lower (thoracic) regions of the human respiratory tract and 2 depositing in tracheobronchial and alveolar tissue of the lung (Federal Register, 1987). As for the 3 most recently completed PM NAAQS review, assessment of the latest available scientific 4 information characterized in the EPA document Air Quality Criteria for Particulate Matter or "PM 5 CD" (U.S. EPA, 1996a) and additional exposure and risk analyses in an associated EPA PM Staff 6 Paper (U.S. EPA, 1996b) led EPA to promulgate decisions to retain, in modified form, the 1987 7 PM_{10} NAAQS and to add new PM_{25} NAAQS (65 μ g/m³, 24 h; 15 μ g/m³, annual average) to 8 protect against adverse health effects associated with exposures to fine particles (Federal Register,
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1997).

10 The 1997 PM NAAQS decisions were based, in part, on important distinctions highlighted in the PM CD between fine and coarse ambient air particles with regard to size, chemical 11 12 composition, sources, and transport. Also of key importance was the assessment and 13 interpretation of new epidemiologic findings on airborne particle health effects. The PM CD 14 (U.S. EPA, 1996a) and Staff Paper (U.S. EPA, 1996b) highlighted more than 80 newly published 15 community epidemiology studies, of which more than 60 found significant associations between 16 increased mortality and/or morbidity risks and various ambient PM indicators. The main findings of concern were community epidemiology results showing ambient PM exposures to be 17 18 statistically associated with increased mortality (especially among people over 65 years of age and 19 those with preexisting cardiopulmonary conditions) and morbidity (indexed by increased hospital 20 admissions, respiratory symptom rates, and decrements in lung function). As noted in the PM 21 CD, several viewpoints emerged on how best to interpret the epidemiology findings: (a) reported 22 PM-related effects are attributable to PM components (per se) of the air pollution mixture and 23 reflect independent PM effects; (b) PM exposure indicators serve as surrogate measures of 24 complex ambient air pollution mixtures, with reported PM-related effects representing those of 25 the overall mixture; or (c) PM can be viewed both as a surrogate indicator and as a specific cause 26 of the observed health effects. See Appendix C for a summary overview of key epidemiologic 27 findings supporting the 1997 NAAQS decisions.

28 As indicated in Appendix C, time-series mortality studies reviewed in the 1996 PM CD 29 (U.S. EPA, 1996a) provide strong evidence that ambient PM air pollution is associated with 30 increases in daily human mortality. These studies provided evidence that such effects occur at 31 routine ambient PM levels, extending to 24-h concentrations below the 150 μ g/m³ level of the 32 PM₁₀ NAAQS set in 1987. Overall, as noted in Table C-1 of Appendix C, the PM₁₀ relative risk 33 estimates derived from the recent PM₁₀ total mortality studies suggest that a 24-h average 50 μ g/m³ PM₁₀ increase in acute exposure has an effect on the order of RR = 1.025 to 1.05 in the 34 35 general population. Higher relative risks are indicated for the elderly and for those with 36 preexisting respiratory conditions, both of which represent subpopulations at special risk for

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mortality implications of acute exposures to air pollution, including PM. Results are very similar
 over a range of statistical models used in the analyses, and are not artifacts of the methods by
 which the data were analyzed. Figure C-1 in Appendix C illustrates the coherence and
 consistency of the PM₁₀ epidemiology findings.

5 The PM CD (U.S. EPA, 1996a) also highlighted that a growing body of evidence suggests 6 that fine particles are more strongly related than inhalable coarse particles to excess morality in 7 both acute and chronic exposure studies. Such evidence notably includes the results of analyses of 8 the type illustrated in Figure C-2 of Appendix C, where a stronger linear relationship is seen 9 between acute (24-h) exposure estimates for fine particles (<2.5 μ m) and increased mortality risks 10 than for acute exposure estimates for thoracic coarse particles (PM_{15-2.5}). Table C-2 of Appendix C summarized results from a wide array of U.S. and Canadian studies that showed 11 12 increased risks of mortality and morbidity to be related to short-term (24-h) ambient fine particle 13 exposures. On the basis of such studies, EPA proposed (Federal Register, 1996) and then later 14 promulgated (Federal Register, 1997) the new 24-h PM_{2.5} NAAQS of 65 μ g/m³.

15 More importantly for present purposes, EPA also promulgated a long-term PM_{2.5} NAAQS of 15 μ g/m³ (annual average) to protect against effects of chronic exposures to ambient fine 16 17 particles (which include DPM as a notable constituent for which extensive toxicologic evidence 18 highlights the importance of chronic exposure effects). Appendix C discusses two key 19 prospective studies of long-term PM exposure effects that were of particular importance: the 20 Harvard Six Cities Study (Dockery et al., 1993) and the American Cancer Society (ACS) Study 21 (Pope et al., 1995). These two studies agree in their findings of strong associations between fine 22 particles and excess mortality. The RR estimates for total mortality are large and highly 23 significant in the Six Cities study. With their 95% confidence intervals, the RR for 50 μ g/m³ PM₁₅ is 1.42 (1.16, 2.01), the RR for 25 μ g/m³ PM₂₅ is 1.31 (1.11, 1.68), and the RR for 15 μ g/m³ SO₄ 24 25 is 1.46 (1.16, 2.16). The ACS study estimates for total mortality are smaller, but also more precise: RR = 1.17 for 25 μ g/m³ PM_{2.5} (1.09, 1.26), and RR = 1.10 for 15 μ g/m³ SO₄ (1.06, 26 27 1.16). Both studies used Cox regression models and were adjusted for similar sets of individual 28 covariates. In each case, however, caution must be applied in use of the stated quantitative risk 29 estimates, given that the lifelong cumulative exposures of the study cohorts (especially in the 30 dirtiest cities) included distinctly higher past PM exposures than those indexed by the more 31 current PM measurements used to estimate chronic PM exposures in the study. Thus, somewhat 32 lower risk estimates than the published ones may well apply.

An additional line of evidence concerning long-term effects may be seen in comparing some specific causes of death in the prospective cohort studies. Appendix C tabulates relative risk estimates for total mortality, lung cancer deaths, cardiopulmonary deaths, and other deaths in the Six Cities study and the ACS study. The relative risks for the most versus least polluted cities in the two studies are very similar for total, cardiopulmonary, and other causes of mortality.
 However, for lung cancer, statistically significant increased relative risk was only found for
 sulfates in the ACS study, and not for PM_{2.5} in either study. The credibility of the air pollution related findings of the two studies is enhanced by both generating very similar elevated risk
 estimates for smokers versus nonsmokers for cardiopulmonary and cancer mortality.

6 The PM CD (U.S. EPA, 1996a) also discussed early results reported for another 7 prospective cohort study of long-term PM exposure effects, i.e., the Adventist Health Study of 8 Smog (AHSMOG). As noted in the PM CD, Abbey et al. (1991) reported no significant 9 associations between any mortality or morbidity endpoints and TSP levels, except for respiratory 10 cancers and female cancers (any site). Follow-up analyses reported by Abbey et al. (1995) considered exposures to PM₁₀ (estimated from site-specific regressions on TSP), PM_{2.5} (estimated 11 12 from visibility), sulfates (SO₄), and visibility per se (extinction coefficient). No significant 13 associations with nonexternal mortality were reported, and only high levels of TSP or PM₁₀ were 14 associated with airways obstructive disease or bronchitis symptoms. Further follow-up analyses 15 of the same California AHSMOG database have been reported recently by Abbey et al. (1999). These latter analyses (not considered in the 1996 PM CD or 1997 PM NAAQS decisions) do 16 17 provide evidence indicative of increased risk of mortality from contributing nonmalignant 18 respiratory causes being associated with long-term PM exposures. Other AHSMOG analyses 19 reported by Abbey et al. (1999) and Beeson et al. (1998) also provide suggestive indications of 20 increased risk of lung cancer mortality being associated with long-term PM₁₀ exposures.

21 The chronic exposure studies, taken together, suggest that there may be increases in 22 mortality in disease categories that are consistent with long-term exposure to airborne fine 23 particles. At least some fraction of these deaths are likely a consequence of cumulative long-term 24 exposure effects beyond the additive impacts of acute exposure episodes, in terms of immediate 25 harvesting of seriously health-compromised individuals in danger of near-future death. If this is correct, then at least some individuals may experience some reduction of life as a consequence of 26 27 PM exposure. This issue, of better quantifying the life-shortening consequences of ambient PM 28 exposure, is being addressed more explicitly by research studies underway since completion of the 29 1996 PM CD (U.S. EPA, 1996b).

The PM Staff Paper (U.S. EPA, 1996b) drew upon the quantitative epidemiology information concisely summarized above to derive a rationale for selection of an annual-average PM_{2.5} standard of 15 μ g/m³. First, major reliance was placed on several acute (24-h) exposure studies showing significantly increased risks of daily mortality (Schwartz et al., 1996) and morbidity indexed by hospital admissions (Thurston et al., 1994) and respiratory symptoms/lung function decrements in children (Neas et al., 1995) in relationship to fine particle indicators (PM_{2.5}, PM_{2.1}). It was judged that such effects of short-term exposures to fine PM were most

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1 strongly related to fine particle levels above the annual-average concentrations for the cities 2 evaluated in each of these studies. More specifically, statistically significant increases in relative 3 risks for daily mortality or morbidity were most clearly observed in these studies to be associated 4 with 24-h fine particle concentrations in cities with annual mean fine particle concentrations that 5 exceeded 15 μ g/m³, as described in Federal Register (1996).

Selection of 15 μ g/m³ as an acceptable level for an annual-average fine particle (PM_{2.5}) 6 7 NAAQS was further supported by the findings of the long-term fine PM exposure studies, e.g., 8 the Harvard Six Cities and ACS studies. The first noticeable increment in mortality risk 9 demonstrated by the Harvard Six Cities study occurred for Watertown (Boston), with mean annual-average PM_{2.5} around 15 μ g/m³, and more clearly increased risks were evident for the 10 other three cities, with $PM_{2.5}$ annual-average values around 20 μ g/m³ or higher. This comported 11 12 well with evidence of increased risks of mortality in the ACS study, which were also most clearly attributable to PM exposures in excess of $PM_{2.5}$ annual median values of 18 μ g/m³ or more, and 13 14 with the findings of fine particle-related respiratory symptom and lung function decrement risks 15 observed by Razienne et al. (1996).

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6.3. DPM AND THE PM_{2.5} NAAQS

18 Chapter 2 of this document, as well as the PM CD (U.S. EPA, 1996a), documents the 19 extent to which DPM may be contributory to ambient PM_{2.5} concentrations. In some urban situations, the annual average fraction of PM2.5 attributable to DPM (according to mass 20 21 concentrations) is about 35% on the high end, although the proportion appears to be more 22 typically in the range of about 10% (see Table 2-23 and Section 2.4.2.1). The actual contribution of DPM to toxicologic effects of ambient PM2.5, however, may be disproportionately large 23 24 (compared with DPM's mass contribution), because of the large numbers of ultrafine particles in 25 DPM emissions and consequent increased surface area for possible interactions with other ambient air toxicants and pathophysiological impacts on subcellular components of lung tissues. 26

27 One approach to dealing with DPM would be (a) to view DPM as an exceptionally toxic 28 component of ambient fine particle mixes in general; (b) to treat any increased mortality and/or 29 morbidity risks attributable to ambient fine particle exposures (as assessed above) as if they were 30 wholly due to DPM; and (c) to assume, therefore, that any characterization of health risk 31 attributable to ambient fine particles would represent an upper-limit estimate of risk possibly 32 assignable to DPM. The findings of high particle counts for ultrafine particles in DPM and 33 possible consequent disproportionally enhanced impacts on ambient PM_{2.5} particle numbers (and any associated enhanced toxicity due to this) may support taking such an approach. 34

Another alternative would be to assume that DPM's potency is essentially equal to other
 fine particle constituents typically comprising ambient PM_{2.5}. Only very limited specific

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- 1 information can be cited as empirically supporting such an assertion. Some laboratory animal 2 studies indicate, for example, that DPM is no more potent at eliciting pulmonary pathology than 3 are other poorly soluble particles such as talc, titanium dioxide, or carbon black in rats or talc or 4 titanium dioxide in mice. This information provides some, but by no means definitive, support for 5 the notion that there is no clear basis to substantiate that DPM is more potent in eliciting 6 pulmonary pathology than any other poorly soluble particle that may be present in ambient PM_{2.5}. 7 In that case, a reasonably logical approach would be to attribute risks associated with ambient fine 8 particles in a roughly proportional way to constituent particles of different chemical composition 9 that typically make up ambient fine particle mixes. Then, one could estimate that keeping ambient DPM exposures below an approximate range of 1.5 μ g/m³ (10% × 15 μ g/m³) to 5 μ g/m³ 10 $(35\% \times 15 \ \mu g/m^3)$ would provide roughly equivalent protection against DE effects as does the 15 11
- 12 $\mu g/m^3 PM_{2.5}$ annual average NAAQS for fine particle effects in general.
- 13 Deriving a guidance value for DPM by apportioning the PM_{2.5} standard as above 14 represents a very generalized, nonspecific approach to estimating a safe air level for DE as 15 indexed by DPM. That approach relies principally on the accuracy of the apportionment of DPM from PM_{2.5}, is limited by assumptions such as that of equal particle potency, and is not based on 16 more detailed consideration of specific aspects of the DPM toxicity data. Given the uncertainties 17 18 inherent in most dose-response assessment processes, it may be informative to evaluate yet 19 another approach to quantifying potential risk associated with ambient DPM exposure on the 20 basis of the robust and specific database documented and evaluated in Chapter 5. A data-specific 21 approach for DPM could then complement the above apportionment estimates derived from more 22 general, ambient fine particle data; apportionment-derived values from PM_{2.5} (as noted above) 23 could serve as a rough benchmark by which to judge the credibility of estimates derived from the 24 DPM data-specific approach. That is, other procedures performed independently of the PM_{25} 25 database should yield values in the range of general, nonspecific estimates derived from evaluation of PM_{2.5} risks. This would presumably be the case for RfC values derived in Section 6.5 below, 26 27 based on application of the RfC methodology summarized in the next section.
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6.4. THE INHALATION REFERENCE CONCENTRATION APPROACH

Historically, approaches such as the Acceptable Daily Intake (ADI) were developed
whereby effect levels, such as no-observed-adverse-effect-levels (NOAELs) or lowest-observedadverse-effect-levels (LOAELs) from human or animal data, were combined with certain "safety
factors" to accommodate areas of uncertainty in order to make quantitative estimates of a safedose, i.e., that at which no adverse effect would likely occur. In response to the National
Academy of Sciences (NAS) report entitled "Risk Assessment in the Federal Government:
Managing the Process" (National Research Council, 1983), EPA developed two approaches

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1	similar to the ADI, i.e., the oral reference dose (RfD) (Barnes and Dourson, 1988) and the parallel					
2	inhalation reference concentration (RfC) with its formal methodology (U.S. EPA, 1994). Similar					
3	to ADIs in intent, the RfD/C approach is used for dose-response assessment for noncancer effects					
4	based upon explicitly delineated rigorous methodology adhering to the principles set forth in the					
5	1983 NRC report. The RfC methodology includes comprehensive guidance on a number of					
6	complex issues, including consistent application to effect levels of "uncertainty factors" (UFs)					
7	rather than the ADI "safety factors" for consideration of uncertainty. Basically, these approaches					
8	attempt to estimate a likely subthreshold concentration in the human population. Use of the					
9	RfD/C approach is one of the principal current agency methods for deriving dose-response					
10	assessments.					
11	A chronic RfC is defined as:					
12	An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous					
13	inhalation exposure to the human population (including sensitive subgroups) that is likely					
14	to be without an appreciable risk of deleterious noncancer effects during a lifetime.					
15	The RfC approach involves the following general steps:					
16						
17	• identification of a critical effect relevant to humans, i.e., the effect that occurs at the					
18	lowest exposure/dose in human or animal studies;					
19	• selection of appropriate dose-response data to derive a point of departure for					
20	extrapolation of a key study (or studies) that provides a NOAEL, LOAEL, or					
21	benchmark concentration $(BMCL_x)^1$;					
22	• Obtain HECs when animal exposure-response data are used (via use of					
23	PBPK/dosimetry models);					
24	• application of UFs to the point of departure (e.g., NOAEL, LOAEL, $BMCL_x$) to					
25	address extrapolation uncertainties (e.g., interindividual variation, interspecies					
26	differences, adequacy of database); and					
27	• characterization of the confidence of the dose-response assessment and resultant RfC.					
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29	The basic quantitative formula for derivation of an RfC, given in Equation 6-1, has as its					
30	basic components an effect level, here a NOAEL, expressed in an HEC and UFs. The units of an					
31	RfC are mg/m^3 .					
	NOAEL					
32	$RfC = \frac{1100}{UF} $ (6-1)					

 $^{^{1}}BMCL_{x}$ is defined as the lower 95% confidence limit of the dose that will result in a level of "x" response (e.g., BMCL₁₀ is the lower 95% confidence limit of a dose for a 10% increase in a particular response).

1 Alternatively, the numerator in Equation 6-1 may be a LOAEL or BMCL. The 2 benchmark concentration (BMC) approach and its application in this assessment are documented 3 in Appendix B. Also, a modifying factor (MF) may be used in the denominator of this equation to account for scientific uncertainties in the study chosen as the basis for the RfC. Further specifics 4 5 of RfC derivation procedures are discussed as they are used in the following sections. All such 6 procedures are described in detail in the RfC Methodology (U.S. EPA, 1994).

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6.5. CHRONIC REFERENCE CONCENTRATION FOR DIESEL EXHAUST

9 As concluded in Chapter 5, chronic respiratory effects are the principal noncancer human 10 hazard from long-term environmental exposure to DE. Other effects (e.g., neurological, liver) are 11 observed in animal studies at higher exposures than the respiratory effects. Thus, the respiratory effects are considered the "critical effect" for the derivation of a chronic RfC for DE. The human 12 13 and animal data for the immunological effects of DE are considered inadequate for dose-response 14 evaluation.

The evidence for chronic respiratory effects is based mainly on animal studies showing 15 consistent findings of inflammatory, histopathological (including fibrosis), and functional changes 16 17 in the pulmonary and tracheobronchial regions of laboratory animals, including the rat, mouse, 18 hamster, guinea pig, and monkey. Occupational studies of DE provide some corroborative 19 evidence of possible respiratory effects (e.g., respiratory symptoms and possible lung function 20 changes), although those studies are generally deficient in exposure-response information.

21 Mode-of-action information about respiratory effects from DE exposure indicates that, at 22 least in rats, the pathogenic sequence following the inhalation of DPM begins with the 23 phagocytosis of diesel particles by alveolar macrophages (AMs). These activated AMs release 24 chemotactic factors that attract neutrophils and additional AMs. As the lung burden of DPM 25 increases, there are aggregations of particle-laden AMs in alveoli adjacent to terminal bronchioles, 26 increases in the number of Type II cells lining particle-laden alveoli, and the presence of particles 27 within alveolar and peribronchial interstitial tissues and associated lymph nodes. The neutrophils 28 and AMs release mediators of inflammation and oxygen radicals, and particle-laden macrophages 29 are functionally altered, resulting in decreased viability and impaired phagocytosis and clearance 30 of particles. The latter series of events may result in pulmonary inflammation, fibrosis, and 31 eventually lesions like those described in the studies reviewed in Chapter 5. Although 32 information describing the possible pathogenesis of respiratory effects in humans is not available, 33 the effects reported in studies of humans exposed to DE are not inconsistent with the findings in 34 controlled animal studies.

1 There are several reasons the dose-response data in rats are considered appropriate for use 2 in characterizing noncancer health effects in humans and deriving a chronic RfC for DE. First, 3 similar noncancer respiratory effects are seen in other species (mouse, hamster, guinea pig, and 4 monkey). Second, rats and humans exhibit similar noncancer responses (macrophage response 5 and interstitial fibrosis) to other particles such as coal mine dust, silica, and beryllium (Haschek 6 and Witschi, 1991; Oberdörster, 1994). Third, an expert panel convened by ILSI recommends 7 that response data on persistent inflammatory processes may be used to assess non-neoplastic responses of poorly soluble particles such as DPM (ILSI, 2000). 8

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6.5.1. Principal Studies for Dose-Response Analysis: Chronic, Multiple-Dose Level Rat Studies

12 The experimental protocols and results from the long-term repeated-exposure chronic 13 studies demonstrating and characterizing the critical effect of pulmonary fibrotic changes and 14 inflammation are discussed in Chapter 5. Salient points of these studies, including species/sex 15 of the test species, the exposure regime and concentrations reported in mg DPM/m³, and effect 16 levels, are abstracted in Table 6-1 for further consideration. The effect levels are designated as 17 N for no-observed-adverse-effect-level, A for adverse-effect-level, and BMCL₁₀ for the 18 benchmark concentration at 10% incidence (see Appendix B).

19 The purpose of many of the chronic studies listed in this table was not the elucidation of 20 the concentration-response character of DPM. The studies of Heinrich et al. (1982, 1986) in 21 hamsters, mice, and rats; of Iwai et al. (1986) in rats; of Heinrich et al. (1995) in mice; of Lewis 22 et al. (1989) in monkeys; and of Pepelko (1982a) in rats are all single dose-level studies that have 23 as their genesis mechanistic or species-comparative purposes. As discussed in Chapter 5, many of 24 these studies provide valuable supporting information for designation of the critical effect of 25 pulmonary histopathology. The lack of any clear dose-response information, however, precludes 26 consideration of these studies as the basis for RfC derivation.

Likewise, multiple-level exposure chronic studies involving species other than rats, i.e.,
hamsters (Pepelko, 1982b), cats (Plopper et al., 1983), and guinea pigs (Barnhart et al., 1981,
1982), provide cross-species corroboration of the critical effects of pulmonary histopathology and
inflammatory alteration.

The remaining studies showing exposure-response relationships in rats for the critical effects include those of Ishinishi et al. (1986, 1988), Mauderly et al. (1987a), Heinrich et al. (1995), and Nikula et al. (1995). As described in Chapter 5, all of these studies were conducted and reported in a thorough, exhaustive manner on the critical effects and little, if any, basis exists for choosing one over another for purposes of RfC derivation. One way of taking advantage of this high degree of methodological and scientific merit would be to array data from all these

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studies and their effect levels (NOAEL, LOAEL, $BMCL_x$) subsequent to normalization of the exposure conditions, i.e., conversion of the exposure regimes via the model of Yu et al. (1991) to yield an HEC. This exercise would result in an interstudy concentration-response continuum that would further facilitate the choice of a concentration to fulfill the purposes of an RfC.

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6.5.2. HEC Derivation

7 Pharmacokinetic, or PK, models can be used to project across species the concentrations 8 of a toxicant that would result in equivalent internal doses. When used for these purposes, PK 9 models may be termed dosimetric models. Chapter 3 reviewed and evaluated a number of 10 dosimetric models applicable to DPM. The model developed by Yu et al. (1991) accounts for species differences in deposition efficiency, normal and particle overload lung clearance rates, 11 12 respiratory exchange rates, and particle transport to lung-associated lymph nodes. Of the models 13 considered in Chapter 3 and currently available, that of Yu et al. (1991) is the only recent model 14 parameterized for both animals and humans that is capable of performing animal-to-human 15 extrapolation; a major assumption of this model is that the phenomenon of particle overload 16 would occur in humans at the same lung burdens (expressed as mass per unit surface area) as in 17 rats. This assumption allows for the development of a diesel-particle-specific human retention 18 model, thereby allowing for extrapolation from exposures in rat studies to exposures in humans. 19 Chapter 3 and Appendix A further discuss the model and its limitations, and document its use in 20 this assessment. Note that this procedure would address species differences in dose (i.e., 21 toxicokinetics), although not necessarily comparative response, or toxicodynamics, the second 22 aspect of uncertainty in interspecies extrapolation.

23 A principal and critical decision in utilizing any dosimetric model is the measure of dose. 24 DPM is composed of an insoluble carbonaceous core with a surface coating of relatively soluble 25 organic constituents. Because macrophage accumulation, pulmonary histopathology, and reduced clearance have been observed in rodents exposed to high concentrations of chemically inert 26 27 particles (Morrow, 1992), the toxicity of DPM may be considered to result from the 28 carbonaceous core rather than the associated organics. However, the organic component of 29 diesel particles, consisting of a large number of PAHs and heterocyclic compounds and their 30 derivatives (Chapter 2), has been implicated in toxicity. The model of Yu et al. (1991) considers 31 the interspecies kinetics of organics (as slowly and fast-cleared) desorbed from the carbonaceous 32 core. Other guidance on choice of dosimetrics for poorly soluble particles such as DPM states 33 that some estimate of lung burden is necessary, that the aerosol exposure parameters such as 34 MMAD, σ_{s} , particle surface area, and density are characterized such that different dose metrics 35 may be considered as new mechanistic insights are developed (ILSI, 2000). The whole particle,

1 as characterized in this assessment and utilized in the model of Yu et al. (1991), meets this 2 recommended guidance, and therefore $\mu g/m^3$ of DPM is used as the measure of dose.

3 The input data required to run the dosimetric model of Yu et al. (1991) include the 4 particle size characterization, expressed as mass median aerodynamic diameter (MMAD), and the 5 geometric standard deviation (σ g). Simulation data presented by Yu and Xu (1986) show that 6 across a range of MMAD and σg inclusive of the values reported in these studies, the pulmonary 7 deposition fraction differs by no more than 20%. The minimal effect of even a large distribution 8 of particle size on deposition probably results because the particles are still mostly in the 9 submicron range, where deposition is influenced primarily by diffusion. It has also been shown, 10 however, that the particle characteristics in a DE exposure study depend very much on the procedures used to generate the chamber atmosphere. Because of the rapid coagulation of 11 12 particles, the volume and temperature of the dilution gas are especially important. The differences 13 reported in particle sizes and distributions in various studies are relatively small and likely reflect 14 different analytical methods as well as real differences in the exposure chambers. Because the 15 particle diameter and size distribution were not reported in the two lowest exposure 16 concentrations in the Ishinishi studies, it was decided to use a representative DPM particle size of 17 MMAD = 0.2 μ m and σ g = 2.3 (values typically reported for DPM) for modeling of lung burden. 18 For consistency, the lung burdens for the other studies were also calculated using this assumption. 19 The difference in the HEC using the default particle size compared with the actual reported 20 particle size is no more than 4% in the Ishinishi studies (Ishinishi et al., 1986, 1988) and 19% in 21 the Mauderly et al. (1987b) study.

22 The foregoing discussion addresses, in part, the variability in outcomes that may be 23 predicted from the Yu et al. (1991) model from deposition of DPM. Variability in output of the 24 model (lung soot burden) was also examined by Yu and Yoon (1990), who studied dependency 25 on tidal volume, respiration rate and clearance (in terms of the overall particle transport rate, $\lambda_{A}^{(1)}$). Analysis of the output dependency indicated that the model output is sensitive but not 26 overly so for these determinative parameters. A \pm 20% change in values for $\lambda_{A}^{(1)}$, for example, 27 28 were estimated to result in a 16%-26% change in soot burden at a 0.1 mg/m³ continuous diesel 29 exposure for 10 years. For a \pm 10% change in tidal volume, the model projected changes in soot 30 burden ranging from 14% to 22% for this same exposure scenario. That the changes in the model 31 outcome were comparable to changes in the input parameters such as tidal volume is an indication 32 that the variability of the model applied to the human population would be the variability of these 33 physiologic parameters in the human population. Variability within the human population is often 34 addressed by applying safety or uncertainty factors, usually in the range of 10 (Renwick and 35 Lazarus, 1998; U.S. EPA, 1994). This matter will be discussed further below.

As discussed in Chapter 3, evidence from Kuempel et al. (2000) suggests that the Yu model may underpredict the lung dust burdens in humans, as judged from occupational data obtained from coal miners (Freedman and Robinson 1988), ostensibly because of the lack of an interstitial compartment in the Yu model. However, further investigation is needed to ascertain whether transfer of particles to the interstitium would also describe the clearance and retention processes in the lungs of humans with exposures to particles at lower environmental concentrations, or to submicron particles such as DPM.

8 HECs were obtained for the dose levels and exposure scenarios presented in the studies of
9 Mauderly et al. (1987b), of Ishinishi et al. (1986, 1988), of Nikula et al. (1995), and of Heinrich
10 et al. (1995), the specifics of which are shown in Appendix A. The HECs are arrayed ordinally
11 according to their effect level (NOAEL, LOAEL, BMCL₁₀) in Table 6-2.

Further inspection of Table 6-2 shows that calculating and ordering the HECs created a concentration-response continuum based on an internal dose that blends from HECs with no observed adverse effects at concentrations as low as 0.032 mg/m³ to HECs that are associated with an adverse effect level that first appears definitively in the continuum probably at 0.33 mg/m³.

Inspection of the interstudy dose-response continuum in Table 6-2 to elucidate a point of 17 18 departure for an RfC entails some interpretation. Exposures at the lower end of this table show 19 that elevated chronic exposures to DPM consistently result in AELs. Conversely, entries in the 20 upper portion of this table show that low-level chronic exposures to DPM have minimal, if any, 21 effects within the capability of these studies to detect them. Intermediate chronic exposures from 22 0.128 mg/m^3 to 0.9 mg/m^3 , however, are less clear, and effect levels and exposures either have no 23 or few observable effects, or effects that are minimally adverse. In choosing from among levels 24 (e.g., NOAELs, LOAELs, BMCL_xs) as a point of departure for derivation of an RfC, the 25 methodology (U.S. EPA, 1994) provides guidance for choice of a highest no-effect level below an effect level; the interim guidance for the BMC suggests that for use as a point of departure, a 26 27 benchmark (e.g., BMCL₁₀) should be within the range of the observable response data so as to avoid excessive extrapolation, and take the shape of the dose-response curve into consideration 28 (Barnes et al., 1995; U.S. EPA, 1995b). The highest no-effect HECs (NOAEL_{HEC}) in this table 29 are 0.128 mg/m³ and 0.144 mg/m³ from the Ishinishi et al. (1988) study, nearly fivefold above 30 other no-effect levels of 0.032 and 0.038 mg/m³. The lower BMCL₁₀ (0.37 mg/m³) is at nearly 31 32 the same concentration as the lowest LOAEL of 0.33 mg/m³ and thus may be too high an estimate 33 for use as a point of departure, possibly because of excessive extrapolation (Appendix B). This 34 BMCL₁₀, generated directly from a modeled dose-response curve for chronic inflammation, lends 35 credence to these NOAELs as being associated with the dose-response curve at incidences of

considerably less than 10%. The value of 0.144 mg/m^3 is chosen as the point of departure for development of the RfC because it is the highest NOAEL_{HEC} among the available NOAELs.

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6.5.3. Consideration of Uncertainty Factors for the RfC

2 Uncertainty for the DE assessment exists in the following areas: inter-individual variability
3 and animal-to-human extrapolation. Each shall be addressed in this section.

Considerable qualitative but little, if any, quantitative information exists regarding 4 5 subgroups that could be sensitive to any respiratory tract effects of DPM. The population assumed in this assessment consists of individuals of average health in their adult years. It is 6 7 acknowledged that exposure to DPM could be additive to many other daily or lifetime exposures 8 to airborne organic compounds and nondiesel ambient PM. It is also likely that individuals who 9 predispose their lungs to increased particle retention through smoking or other high particulate 10 burdens, who have existing respiratory tract inflammation or infections, or who have chronic 11 bronchitis, asthma, or fibrosis could be more susceptible to adverse impacts from DPM exposure 12 (Chapter 5). Also, infants and children could have a greater susceptibility to the acute/chronic toxicity of DPM because of their greater breathing frequency and consequent potential for greater 13 14 particle deposition in the respiratory tract. Increased respiratory symptoms and decreased lung 15 function in children versus ambient PM levels, of which DPM is a part, have been observed (U.S. 16 EPA, 1996a). Likewise, a number of factors may modify normal lung clearance, including, aging, 17 gender, and disease. Although the exact role of these factors is not resolved, all would influence 18 the particle dose to the lung tissue from inhalation exposure. Activity patterns related to 19 occupation and habitation in the proximity of major roadways are certain to be contributory for 20 some subgroups in receiving higher DPM exposures (Chapter 2). In the absence of DE-specific 21 data, this assessment utilizes a default UF value of 10 to account for possible inter-individual 22 human variability (U.S. EPA, 1994; Renwick and Lazarus, 1998).

In terms of animal-to-human extrapolation, this dose-response assessment utilizes data from the rat to predict human response. To account for interspecies differences in toxicodynamics and kinetics, a default UF of 10 is typically used when there is no information about which test animal species best represents humans. For DE, available data indicate that the rat appears more sensitive to the inflammatory effects than humans. Furthermore, the toxicokinetic differences were accounted for by the use of a dosimetry model (Yu et al., 1991), hence, a UF is not needed.

In summary, the application of a factor of 10 to the HEC of 0.144 mg/m³ would be
 prudent to address the issue of human variability in response to effects from exposure to DPM.
 Use of other UFs is not considered necessary. It should be noted that, given the emerging

research on DE-induced immunological effects, it may be necessary at a later date to reconsider the basis for selection of the critical effect and UFs for derivation of the DE RfC.

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6.5.4. Derivation of the RfC for DE

On the basis of the above analysis, the value of 0.144 mg/m^3 DPM was selected as the 5 6 basis of the RfC evaluation. This value was derived from concentrations in rat chronic studies 7 that were modeled to obtain HECs. The pulmonary effects, histopathology and inflammation, 8 were determined to be the critical noncancer effects. Response data on inflammation was also 9 suggested by a specific scientific working group as a satisfactory surrogate for fibrogenic 10 responses in assessing the pulmonary responses of poorly soluble particles such as DPM (ILSI, 2000). Sufficient documentation from other studies showed that there is no effect in the 11 12 extrathoracic (nasopharyngeal) region of the respiratory system or in other organs at the lowest 13 levels that produce pulmonary effects in chronic exposures. Application of the dosimetric model 14 of Yu et al. (1991) to the exposure value from Ishinishi et al. (1988) of 0.46 mg/m³ yielded an 15 HEC of 0.144 mg/m³. Application of the UF for intraspecies variability would yield the following RfC: 16 ~ ¬

NOAEL_{HEC} ÷ UF = RfC $0.144 \text{ mg/m}^3 \div 10 = 0.0144 \text{ mg/m}^3 = 14 \text{ mg/m}^3.$

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6.6. CHARACTERIZATION OF THE NONCANCER ASSESSMENT FOR DE

Adverse health effects from short-term acute (high-level) exposures to DE such as occupational reports of decreases in lung function, wheezing, chest tightness, increases in airway resistance, and reports in laboratory animals of inflammatory airway changes and lung function changes are acknowledged but are not quantitatively assessed. Thus, the focus of this doseresponse assessment of is on the adverse noncancer health consequences of a lifetime low-level continuous air exposure of humans to DE.

This assessment uses the whole particle, termed DPM, as the key index or measure of DE dose. DPM includes any and all adsorbed organics, among which are a large number of PAHs, heterocyclic compounds, and their derivatives (Chapter 2), as well as the carbon core. It is not possible to separate the carbon core from the adsorbed organics to compare the toxicity. The dosimetric model used in the derivation of the RFC (Yu et al., 1991) is consistent with this designation as it considers DPM as well as the adsorbed organics as two types, slowly cleared and fast-cleared. Some studies with diesel do occasionally report levels of accompanying gaseous components of DE (NO_x, CO, etc.), but nearly all report particle concentration and
 characteristics.

Adverse responses occurring in the rat lung have been used in this assessment as the basis for characterizing non-neoplastic human lung responses. The basis for this presumption includes the fact that humans and rats exhibit similar responses to poorly soluble particles such as DPM (ILSI, 2000). Also, similar noncancer effects are seen in other species. Thus, when viewed across species (including humans), the non-neoplastic pulmonary effects of inflammation and fibrosis used in this assessment are dissociable from the cancer response and are of likely relevance to humans.

10 As a part of the RfC methodology (U.S. EPA, 1994), dose-response assessments are assigned levels of confidence that are intended to reflect the strengths and limitations of the 11 12 assessment as well as to indicate the likelihood of the assessment changing with any additional 13 information. Confidence levels of either low, medium, or high are assigned both to the study (or 14 studies) used in the assessment to characterize the critical effects and to the overall toxicological 15 database of the substance. An overall confidence level is also assigned to the entire assessment 16 and is usually limited to and the same as the confidence in the database. An assessment with a 17 substance having a database as extensive as DE would normally be characterized as having high 18 confidence. The critical effects are characterized using not one but multiple long-term chronic 19 studies conducted independently of one another (Table 6-2). The exhaustive manner in which 20 these studies were conducted and reported imparts a high degree of confidence.

21 The toxicological database for DE is relatively complete. Both developmental and 22 reproductive areas are addressed. Ancillary studies that address mechanistic aspects of DE 23 toxicity, either as the whole particle with adsorbed organics, or segregated as a poorly soluble 24 particle and extracted organics, are available and used in this assessment. Although only limited 25 human data are available, extensive consideration has been given to the relevancy of the animal studies to the human condition. A major point to consider in assigning confidence in this 26 27 assessment, and a reason that it may change in the future, is the emerging issue of allergenicity 28 caused or exacerbated by DE. Although information to evaluate allergenicity in parallel to the 29 present effects (pulmonary inflammation and histopathology) is currently lacking, future efforts to 30 elucidate and characterize this effect may well be a driver to make a reevaluation of DE 31 appropriate. Out of consideration of the relevance of (and information lacking on) allergenicity 32 effects associated with DE, and the possibility that the current RfC could change as a 33 consequence of this information becoming available from the scientific community, the database and overall confidence in the current RfC for DE is regarded as medium. 34

35 In the introductory portion of this chapter, DPM is acknowledged as a subfraction of 36 $PM_{2.5}$. It was proposed that apportionment of DPM contributions in relationship to the $PM_{2.5}$

6-16 DRAFT—DO NOT CITE OR QUOTE

- standard and the NAAQS of 15 μ g/m³ could itself conceivably serve both as a general nonspecific 1 2 estimate of a reasonably defensible guideline for DE measured as DPM and as a reasonable 3 bounding estimate for any value(s) derived from any approach taken in formulating a dose-4 response assessment specific for DE. In evaluating the entirety of the disparate DE database, 5 including many chronic studies from several different species, a myriad of possible DE-specific 6 toxicological endpoints, and dose extrapolation models, application of the RfC method produced a value of 14 μ g/m³. As the accuracy of the RfC is part of its definition ("...within an order of 7 8 *magnitude* ..."), this dose-response estimate could be considered to be no different from the apportionment estimate of 1.5-5 μ g/m³ or from the NAAQS of 15 μ g/m³. This congruence of 9 estimates attests to the reasonableness of the data used and the judgments made in the RfC 10 process, as well as enhancing the overall confidence in these estimates regarding the toxicity of 11 12 DE and its potential health risk for the human population.
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14 **6.7. SUMMARY**

15Table 6-3 summarizes the key data and factors used in the dose-response analysis leading16to the derivation of the RfC for DE. The DE RfC of $14 \ \mu g/m^3$ of DPM is a chronic exposure17likely to be without an appreciable risk of adverse human health effects.

18 Given the perspective of RfC values being by definition "within an order of magnitude" of 19 actual values likely to be associated with low probability of adverse health effects occurring with 20 lifetime chronic exposures of sensitive human populations, the DE RfC value of $14 \ \mu g/m^3$ appears 21 to be reasonably concordant with (a) the annual PM_{2.5} NAAQS of 15 $\ \mu g/m^3$ serving as an upper 22 bound for possible allowable DE health risks, and/or (b) the 1.5-5 $\ \mu g/m^3$ apportionment for DE 23 contributions implied to be inherent within the PM_{2.5} NAAQS established to protect against 24 adverse effects of ambient air fine-particle mixes typical of the current U.S. environment.

The estimated air concentration of $14 \ \mu g/m^3$ (the RfC, a lifetime exposure to DE measured as DPM) is well above the ambient air levels that are reported in most rural areas but could be below that reported under short-term conditions in some urban scenarios such as busy intersections or bus stops (see Table 2-23, Chapter 2). Aspects of time-averaging concentrations are also not part of this assessment, although readers and users may wish to consider this in relation to the $14 \ \mu g/m^3$ air level.

Study	Species/sex	Exposure period	Particles (mg/m ³)	NOAEL, AEL, or BMCL ₁₀ (mg/m ³)	Effects
Lewis et al. (1989)	Monkey, Cynomolgus, M	7 h/day 5 days/wk 104 wks	2.0	Ν	AM aggregation; no fibrosis, inflammation, or emphysema
Bhatnagar et al. (1980) Pepelko (1982a)	Rat, F344, M, F	7 h/day 5 days/wk 104 wks	2.0		Multifocal histiocytosis; inflammatory changes; Type II cell proliferation; fibrosis
Pepelko (1982b)	Hamster, Chinese, M	8 h/day 5 days/wk 26 wks	6.0 12.0	А	Inflammatory changes; AM accumulation; thickened alveolar lining; Type II cell hyperplasia; edema; increase in collagen
Heinrich et al. (1982)	Hamster, Syrian, M, F	7-8 h/day 5 days/wk 120 wks	3.9	А	Inflammatory changes, 60% adenomatous cell proliferation
Iwai et al. (1986)	Rat, F344, F	8 h/day 7 days/wk 104 wks	4.9	А	Type II cell proliferation; inflammatory changes; bronchial hyperplasia; fibrosis
Mauderly et al. (1987a) Henderson et al. (1988)	Rat, F344, M, F; Mouse, CD-1, M, F	7 h/day 5 days/wk 130 wks	0.35 3.5 7.1	N A A	Alveolar and bronchiolar epithelial metaplasia in rats at 3.5 and 7.0 mg/m ³ ; fibrosis at 7.0 mg/m ³ in rats and mice; inflammatory changes. Little quantitative data given
Heinrich et al. (1995)	Rat, Wistar, F; Mouse, NMRI, F (7 mg/m ³ only)	18 h/day 5 days/wk 24 mo	0.8 2.5 7.0	A A A	Bronchioalveolar hyperplasia, interstitial fibrosis in all groups. Severity and incidence increase with exposure concentration. Text only given
	Mouse, NMRI, F; C57BL/6N, F	18 h/day 5 days/wk 13.5 mo (NMRI) 24 mo (C57BL/N)	7.0	A	No increase in tumors. Noncancer effects not discussed
Ishnishi et al., (1986, 1988)	Rat, M, F, F344, /Jcl.	16 h/day 6 days/wk 130 wks	0.11^{a} 0.41^{a} 1.08^{a} 2.32^{a} 0.46^{b} 0.96^{b} 1.84^{b}	N N A A A	Inflammatory changes; Type II cell hyperplasia and lung tumors seen at >0.4 mg/m ³ ; shortening and loss of cilia in trachea and bronchi. Data given in text only
			3.72 ^b	A	
Heinrich et al., (1986)	Hamster, Syrian, M, F; Mouse, NMRI, F; Rat, Wistar, F	19 h/day 5 days/wk 120 wks	4.24	А	Inflammatory changes; thickened alveolar septa; bronchioloalveolar hyperplasia; alveolar lipoproteinosis; emphysema (diagnostic methodology not described); hyperplasia; lung tumors

Table 6-1. Histopathological effects of diesel exhaust in the lungs of laboratory animals

Study	Species/sex	Exposure period	Particles (mg/m ³)	NOAEL, AEL, or BMCL ₁₀ (mg/m ³)	Effects
Barnhart et al. (1981.	Guinea pig.	20 h/day	0.25	Ν	Minimal response at 0.25 and
1982): Vostal et al.	Hartley, M	5.5 days/wk	0.75	А	ultrastructural changes at 0.75 mg/m^3 :
(1981)	, , , , , , , , , , , , , , , , , , ,	104 wks	1.5	А	thickened alveolar membranes; cell
			6.0	А	proliferation; fibrosis at 6.0 mg/m ³ ; increase in PMN at 0.75 mg/m ³ and 1.5 mg/m ³
Plopper et al. (1983)	Cat, inbred, M	8 h/day	6.0°	А	Inflammatory changes; AM
Hyde et al. (1985)		7 days/wk 124 wks	12.0 ^d	А	aggregation; bronchiolar epithelial metaplasia; Type II cell hyperplasia; peribronchiolar fibrosis
Nikula et al. (1995)	Rat, F344, M	16 h/day	2.44	А	AM hyperplasia, epithelial hyperplasia,
		5 days/wk	6.33	А	inflammation, septal fibrosis,
		-		BMCL ₁₀ ^e	bronchoalveolar metaplasia
		23 mo		10	1

Table 6-1. Histopathological effects of diesel exhaust in the lungs of laboratory animals (continued)

^aLight-duty engine. ^bHeavy-duty engine.

°1 to 61 weeks exposure.

^d62 to 124 weeks of exposure. ^eSee Appendix C.

AM = Alveolar macrophage.PMN = Polymorphonuclear leukocyte.

histopathology and inflammation as reported in the individual studies					
Study	Exposure concentration (mg/m ³)	Effect level ^a	HEC (mg/m ³)		
Ishinishi et al. (1988) (LD ^c)	0.11	NOAEL	0.032		
Mauderly et al. (1987a)	0.35	NOAEL	0.038		
Ishinishi et al. (1988) (LD)	0.41	NOAEL	0.128		
Ishinishi et al. (1988) (HD)	0.46	NOAEL	0.144		
Heinrich et al. (1995)	0.84	LOAEL	0.33		
Nikula et al. (1995)	2.44 & 6.3	BMCL ₁₀ -inflam	0.37		
Ishinishi et al. (1988) (HD)	0.96	LOAEL	0.883		
Ishinishi et al. (1988) (LD)	1.18	LOAEL	1.25		
Nikula et al. (1995)	2.44 & 6.3	BMCL ₁₀ - fibrosis	1.3		
Mauderly et al. (1987a)	3.47	LOAEL	1.375		
Nikula et al. (1995)	2.44	LOAEL	1.95		
Ishinishi et al. (1988) (HD)	1.84	AEL	2.15		
Heinrich et al. (1995)	2.5	AEL	2.35		
Ishinishi et al. (1988) (LD)	2.32	AEL	2.75		
Mauderly et al. (1987a)	7.08	AEL	3.05		
Ishinishi et al. (1988) (HD)	3.72	AEL	4.4		

Table 6-2. Human equivalent continuous concentrations (HECs) calculated with
the model of Yu et al. (1991) from long-term repeated exposure rat studies of DPM
exposure. Effect levels are based on the critical effects of pulmonary
histopathology and inflammation as reported in the individual studies

^aNOAEL: no-observed-adverse-effect level; LOAEL: lowest-observed-adverse-effect level; AEL: adverse-effect level; BMCL₁₀; lower 95% confidence estimate of the concentration of DPM associated with a 10% incidence of chronic pulmonary inflammation (inflam) or fibrosis (see Appendices A and C for more specifics). ^bThe duration-adjusted value from the laboratory animal exposure concentrations from hours/day, days/week to

a

continuous 24 hr/day, 7 day/week exposure concentration.

^cL/HD = light/heavy duty diesel engine.

Quantitative assessment for noncancer effects from lifetime exposure to DPM	14 μ g/m ³
Critical effect	Pulmonary inflammation and histopathology in rats
Principal study	Array of 4 chronic rat studies
Designated basis for quantitation (in laboratory animals)	0.46 mg/m ³ , a NOAEL
NOAEL _{HEC} (Human Equivalent Concentration)	0.144 mg/m ³
Adjustments for human-to-sensitive-human (Uncertainty Factor, UF)	10
NOAEL _{HEC} /UF	$0.144 \text{ mg/m}^3 / 10 = 14 \ \mu \text{g/m}^3$

Table 6-3. Decision summary for the quantitative noncancer RfC assessment for continuous exposure to diesel particulate matter (DPM)

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