9. CHARACTERIZATION OF POTENTIAL HUMAN HEALTH EFFECTS OF DIESEL EXHAUST: HAZARD AND DOSE-RESPONSE ASSESSMENTS

9.1. INTRODUCTION

Environmental human health risk assessment entails the evaluation of all pertinent information on the hazardous nature of environmental agents, on the extent of human exposure to them, and on the characterization of the potential risk to the exposed population. Risk assessment consists of four components: hazard assessment, dose-response assessment, exposure assessment, and risk characterization. This document focuses only on hazard and dose-response assessment. The overall objectives of this assessment are:

- to identify and characterize the human health effects that may result from environmental exposure to diesel exhaust (DE); and
- to determine whether there is a quantitative exposure- (or dose-) response relationship for DE exposure and health effects in the range of observation and, if sufficient data are available, to derive toxicity values, estimates of exposure, or dose-specific unit risk for subsequent use in the characterization of potential risk to the general human population and vulnerable subgroups.

This chapter integrates the key findings about the nature and characteristics of environmental exposure to DE (Chapter 2), health hazard information (Chapters 3, 4, 5, and 7), and dose-response analyses (Chapters 6 and 8) that are relevant to the characterization of potential human health effects associated with current-day environmental exposure to DE. It also discusses major uncertainties of this assessment, including critical data and knowledge gaps, key assumptions, and EPA's science policy choices to bridge the data and knowledge gaps.

9.2. PHYSICAL AND CHEMICAL COMPOSITION OF DIESEL EXHAUST

As reviewed in Chapter 2, DE is a complex mixture of hundreds of constituents in gas or particle phases. Gaseous components of DE include carbon dioxide, oxygen, nitrogen, water vapor, carbon monoxide, nitrogen compounds, sulfur compounds, and low-molecular- weight hydrocarbons and their derivatives. The particulate matter of DE, diesel particulate matter (DPM), is composed of elemental carbon, adsorbed organic compounds, and small amounts of sulfate, nitrate, metals, trace elements, water, and unidentified compounds. DPM is either directly emitted from diesel-powered engines (primary particulate matter) or is formed from the gaseous compounds emitted by a diesel engine (secondary particulate matter). Incomplete combustion of

fuel hydrocarbons as well as engine oil and other fuel components such as sulfur leads to the formation of DPM.

After emission from the tailpipe, DE undergoes dilution, chemical and physical transformations, and dispersion and transport in the atmosphere. The atmospheric lifetime for some compounds present in DE ranges from hours to days. In general, secondary pollutants formed in an aged aerosol mass are more oxidized, and therefore have increased polarity and water solubility.

DE emissions vary significantly in chemical composition and particle sizes among different engine types, fuel formulations, and age of emissions. There have been both qualitative and quantitative changes in DE emissions over time as a result of changes in engine technology and fuel reformulation. The following sections identify and characterize the key components of DE that are of special concern in possible health outcomes, and discuss the changes in the composition of DE over time. The latter information is critical for making a scientific judgment about the appropriateness of using epidemiologic and toxicological findings from past DE exposures to assess hazard and risk from current-day environmental exposures. It should be noted that available animal studies are based on exhaust exposures from various model year on-road diesel engines since 1980, whereas many of the epidemiologic studies refer to exposures from on-road and non-road diesel engines in use from the 1950s through the mid-1990s.

9.2.1. Diesel Exhaust Components of Possible Health Concern

The components of DE that are of health concern for this assessment are the particles (elemental carbon core), the organic compounds adsorbed to the particles, and the organic compounds present in the gas phase.

9.2.1.1. *Diesel Particles*

Approximately 80%-95% of DPM mass is in the fine particle size range (0.05-1.0 microns), with a mean particle diameter of about 0.2 microns. Ultrafine particles (0.005-0.05 microns), averaging about 0.02 microns in diameter, account for about 1%-20% of the DPM mass and 50%-90% of the total number of particles in DPM (Section 2.2.8.3).

Particle size is important for a number of reasons. Particles with aerodynamic diameters larger than 2.5 microns (i.e., $>PM_{2.5}$) tend to be retained in the upper portions of the respiratory tract, whereas particles with diameters smaller than 2.5 microns (i.e., $<PM_{2.5}$) are deposited in all areas, but especially into the lower portions of the respiratory tract, including the deep lung. These fine and ultrafine particles have a very large surface area per gram of mass, which make them an excellent carrier for adsorbed inorganic and organic compounds (Chapter 3).

DPM is part of ambient particulate matter (PM). The major characteristics that distinguish DPM from ambient PM are (1) a high portion of elemental carbon, (2) the large surface area associated with carbonaceous particles in the 0.2 micron range; (3) enrichment of certain polycyclic aromatic hydrocarbons (PAHs), and (4) a large percentage of ultrafine particles. The EPA Emissions Trends Report (U.S. EPA, 2000) indicates that annual emissions of diesel $PM_{2.5}$ nationwide in 1998 were 6% of the total $PM_{2.5}$ inventory. Some geographic areas are expected to have a higher percentage of DPM in $PM_{2.5}$ because of variations in the number and types of diesel engines present in the area. For instance, DPM contributions to total $PM_{2.5}$ mass were reported to be about 13%-36% in several urban California regions in 1982. More recent studies in the Phoenix and Denver areas showed diesel $PM_{2.5}$ to be 10%-15% of total $PM_{2.5}$ mass, and in Manhattan, diesel PM was reported to contribute about 50% of ambient PM_{10} (Chapter 2, Section 2.4.2.1).

DPM generally contains a high percentage of elemental carbon per unit mass, which can be used as a distinguishing feature from other combustion and noncombustion sources of $PM_{2.5}$. The DPM elemental carbon content can range from more than 50% to approximately 75% of the DPM mass depending on age of engine, type of engine (heavy-duty versus light-duty), fuel characteristics, and driving conditions. The organic carbon portion of DPM can range approximately from 19% to 43%, although some DPM organic constituents can be higher or lower than these numbers. In comparison, gasoline engine exhaust generally has a lower elemental carbon content and a higher percentage of organics in the particle mass (Table 2-13).

9.2.1.2. *Organic Compounds*

The organic compounds present in the gases and adsorbed onto the particles cover a wide spectrum of compounds related to unburned diesel fuel, lube oil, low levels of partial combustion, and pyrolysis products (Table 2-19). The organic compounds present in the gaseous phase include alkanes, alkenes, aldehydes, monocyclic aromatic compounds, and PAHs. Among the gaseous components of DE, the aldehydes are particularly important because of their potential carcinogenic effects and because they make up an important fraction of the gaseous emissions. Formaldehyde accounts for a majority of the aldehyde emissions (65%-80%) from diesel engines. Acetaldehyde and acrolein are the next most abundant aldehydes. Other gaseous components of DE that are notable for their carcinogenic effects include benzene, 1,3-butadiene, PAHs, and nitro-PAHs (including those with $\leq$4 rings and nitro-PAHs with 2 and 3 rings). A number of the gaseous compounds (e.g., aldehydes, alkanes, alkenes, NO_x, SO_x) are also known to induce respiratory tract irritation given sufficient exposure (see Table 2-21). Very small amounts of dioxins have been measured in diesel truck exhaust. Dioxin emissions from heavy-duty engine

truck exhausts are estimated to represent about 1.2% of the national dioxin inventory; dioxin emissions from non-road exhausts have not been estimated (Section 2.2.7.2).

Organic substances adsorbed onto DPM include C_{14-35} hydrocarbon compounds, PAHs with ≥4 rings, and nitro-PAHs. PAHs and their derivatives comprise <1% of the DPM mass (Section 2.2.8). Many of these hydrocarbons are known to have mutagenic and carcinogenic properties. California EPA (Cal EPA, 1998) identified at least 19 hydrocarbons present in DE that are known or suspected carcinogens, according to evaluations by the International Agency for Research on Cancer (IARC).

9.2.2. "Fresh" Versus "Aged" Diesel Exhaust

Newly emitted exhaust is termed "fresh" whereas exhaust that is more than 1 or 2 days old is referred to as "aged" because of alterations caused by sunlight and other chemical-physical conditions of the ambient atmosphere. It is not clear what the overall toxicological consequence of DE aging is because some compounds in the DE mixture are altered during aging to more toxic forms while others are made less toxic. For example, PAHs present in fresh emissions may be nitrated by atmospheric NO_3 to form nitro-PAHs, thus adding to the existing burden of nitro-PAHs present in fresh exhaust. On the other hand, PAHs present in the gas phase can react with hydroxyl radicals present in the ambient air, leading to reduced atmospheric lifetime of the original PAH. Alkanes and alkenes may be converted to aldehydes, and oxides of nitrogen to nitric acid (Section 2.3).

9.2.3. Changes of DE Emissions and Composition Over Time

Chapter 2, with its summary in Section 2.5, provides a full review of emissions trends and a complete characterization of the physical and chemical changes in DE over the years, taking into consideration the lack of consistent analytical and measurement techniques, and the variability in emissions based on vehicle mix, driving cycles, engine deterioration, and other factors. Key findings relevant to the potential health effects of DE are discussed below.

As discussed in Chapter 2, Section 2.2.3, the EPA Emissions Trend Report estimates that DPM_{10} on-road emissions decreased 27% between 1980 and 1998. DPM emission factors (g/mile by model year) from new on-road diesel vehicles decreased on average by a factor of six in the period from the mid-1970s to the mid-1990s. These significant reductions are largely attributable to reductions in three PM components: elemental carbon, organic carbon, and sulfate. Limited data are available to assess the changes in emission rates from locomotive, marine, or other non-road diesel sources over time. It is estimated that DPM_{10} (≤ 10 μm) emissions from non-road diesel engines increased 17% between 1980 and 1998. Despite significant reductions in DPM from diesel vehicles, combined non-road and on-road diesel engines still contributed

approximately 23% of $DPM_{2.5}$ ($\leq$2.5 μm) emissions to the 1998 inventory (not including the contribution of natural and miscellaneous sources) (Section 2.2.5).

Because of changes in engine technology and fuel composition, the chemical composition of DPM from on-road vehicles has also changed over time. The percentage of soluble organic material associated with DPM from new on-road vehicles decreased by model year from the 1980s to the 1990s, and the proportion of elemental carbon is correspondingly higher. PAHs and nitro-PAHs are present in DPM from both new and older diesel engine exhaust. There are insufficient data to provide insight into the potential for changes in total PAH emissions over time or specific organic constituents such as benzo[a]pyrene and 1-nitropyrene. It should be noted that the chemical composition of DPM to which people are currently exposed is determined by a combination of older and newer technology on-road and non-road engines. Consequently, the decrease in the soluble organic fraction of DPM by model year does not directly translate into a proportional decrease in DPM-associated organic material to which people are currently exposed. In addition, the impact from high-emitting and/or smoking diesel engines has not been quantified (Section 2.5.2).

Because of these uncertainties, changes in DPM composition over time cannot be confidently quantified. Available data clearly indicate that toxicologically significant organic components of DE (e.g., PAHs, PAH derivatives, nitro-PAHs) were present in DPM and DE in the 1970s and are still present. Even though a significant fraction of ambient DPM (possibly more than 50%) is also emitted by non-road equipment, there are no data available to characterize changes in the chemical composition of DPM from non-road equipment over time. Given the variation in fuel, engine technology, and in-use operational factors over the years, caution should be exercised in presuming that a decrease in the amount of emissions or emission constituents will result in a decrease in risk.

9.3. AMBIENT CONCENTRATIONS AND EXPOSURE TO DIESEL EXHAUST

Section 2.4 provides some information on ambient concentrations of DE, and on occupational and environmental exposures to DE, in order to provide a context for hazard assessment and dose-response analysis. Highlights of available information are discussed below.

DE is emitted from a variety of sources, both on-road (e.g., motor vehicles, construction equipment) and non-road (e.g., farm equipment, railway locomotives, marine diesel engines). Environmental exposure to DE is generally higher in urban areas than in rural areas. The concentration of DE constituents in the air is also expected to vary within any geographic area depending on the number and types of diesel engines in the area, the atmospheric patterns of dispersal, and the proximity of the exposed individuals to the DE source. Certain occupational

populations (e.g., transportation and garage workers, heavy equipment operators) can be exposed to much higher levels of DE than is the general population.

As DE is a complex mixture of a great variety of compounds, "exposure levels" are difficult to define. Even though the environmental levels of a number of individual constituents are generally known, it is difficult to quantify the portion that directly or indirectly comes from diesel engine emissions. Moreover, there is still incomplete knowledge about the relative roles of the relevant DE constituents in mediating the potential health effects of DE. Accordingly, exposure levels to DPM have historically been measured using surrogate markers for whole DE. Although considerable uncertainty exists as to whether DPM mass (expressed as $\mu g/m^3$ of DPM) is the most appropriate dosimeter, it is considered to be a reasonable choice on the basis of available data until more definitive information about the mechanisms or mode(s) of action of DE becomes available.

Several techniques exist for estimating ambient concentrations of DPM, including chemical mass balance (CMB) source apportionment, dispersion modeling, and using elemental carbon as a surrogate for DPM. DPM concentrations reported from CMB and dispersion modeling studies in the 1980s suggest that in urban and suburban areas (Phoenix and Southern California), the annual average DPM concentration ranged from 2 to 13 $\mu g/m^3$. In the 1990s, annual or seasonal average DPM concentrations in suburban or urban locations have ranged from 1.2 to 4.5 $\mu g/m^3$. DPM concentrations at a major bus stop in downtown Manhattan ranged from 13.2 to 46.7 $\mu g/m^3$ over a 3-day period in 1993. In nonurban and rural areas in the 1980s, DPM concentrations were reported to range from 1.4 to 5 $\mu g/m^3$. In the 1990s, nonurban air basins in California were reported to have DPM concentrations ranging from 0.2 to 2.6 $\mu g/m^3$ (Section 2.4.2).

A comprehensive exposure assessment cannot be currently conducted because of lack of data. Interim exposure estimation based on EPA's Hazardous Air Pollutant Exposure Model (HAPEM-MS3 model), for on-road sources only, suggests that in 1996 annual average DPM exposure in urban areas from only on-road engines was 0.7 $\mu g/m^3$, while in rural areas exposure was 0.3 $\mu g/m^3$. A high-end exposure estimate for 1996 is not yet available. Among 10 urban areas, the 1996 annual average estimated exposure ranged from 0.5 to 1.2 $\mu g/m^3$. Comparable 1990 exposure estimates for on-road sources ranged from 0.9 $\mu g/m^3$ for urban areas and from 0.5 $\mu g/m^3$ for rural areas. Exposure estimates for the most highly exposed individuals (e.g., outdoor workers and children who spend large amounts of time outdoors) for 1990 had DPM exposures up to 4.0 $\mu g/m^3$ (Section 2.4.3.2, Table 2-29). Based on the national inventory, DPM exposure that includes non-road emission sources could at least double the on-road exposure.

Estimates for occupational exposures to DE as DPM mass have been generally higher than environmental exposures. The Health Effects Institute (HEI, 1995) reported that mean air

concentrations of DPM in the workplace as shown in the available literature ranged from 4 to 1,740 $\mu g/m^3$. Tables 2-27 and 2-28 provide some exposure estimates for specific worker categories. Available information indicates that DPM exposure estimates range up to 1,280 $\mu g/m^3$ for miners, with lower exposures for railroad workers (39-191 $\mu g/m^3$), firefighters (4-748 $\mu g/m^3$), public transit workers who work with diesel equipment (7-98 $\mu g/m^3$), mechanics and dock workers (5-65 $\mu g/m^3$), truck drivers (2-7 $\mu g/m^3$), and bus drivers (1-3 $\mu g/m^3$).

For direct comparison of lifetime exposures between an occupational setting (8 hours per day, 5 days per week, for 45 years) and environmental exposure (continuous exposure for 70 years), the occupational estimates are converted to an equivalent environmental lifetime estimate,[1] which is also shown in Table 2-28. A conversion of EC-based measurements to total DPM may also be needed for some estimates. The estimated 70-year lifetime exposures equivalent to those for the occupational groups discussed above range from 0.4 to 2 $\mu g/m^3$ on the low end to 2 to 269 on the high end. These data indicate that some lower-end occupational estimates of DPM, when converted to environmental equivalents, overlap the range of estimated environmental exposures to DPM (national average in 1990 of 0.8 $\mu g/m^3$, with high-end exposures up to 4 $\mu g/m^3$).

9.4. HAZARD CHARACTERIZATION

With DE being a component of ambient particles in the general environment, it may partly contribute to the range of health effects associated with ambient PM. However, the spectrum of health effects associated with DE exposure are somewhat different, though not entirely inconsistent, with those reported for ambient PM. The primary health effects of concern from environmental exposure to DE, on the basis of combined human and experimental evidence, are lung cancer and noncancer respiratory effects resulting from chronic exposure, and possibly immunologic and allergenic effects from acute and repeated exposures. On the other hand, a wide range of noncancer health effects has been associated with acute, short-term, and long-term exposure to ambient PM. Community epidemiologic studies have shown that ambient PM exposure is statistically associated with increased mortality (especially among people over 65 years of age with preexisting cardiopulmonary conditions) and morbidity as measured by increases in hospital admissions, respiratory symptom rates, and decrements in lung function. A cancer hazard has not been characterized for ambient PM, although there is some indication of a possible association between particle air pollution and increased lung cancer risk (U.S. EPA, 1996a,b; also see Chapter 7, Section 7.1.2).

[1]Environmental equivalent occupational exposure = 0.21 × occupational exposure.

9.4.1. Acute and Short-Term Exposures

The combined human and animal evidence indicates that DE can induce irritation to the eye, nose, and throat, as well as inflammatory responses in the airways and the lung following acute and/or short-term exposure to high concentrations. There is also suggestive evidence for possible immunological and allergenic effects of DE.

9.4.1.1. *Acute Irritation*

DE contains various respiratory irritants in the gas phase and in the particulate phase (e.g., SO_x, NO_x, aldehydes). Acute exposure to DE has been associated with irritation of the eye, nose, and throat, respiratory symptoms (cough and phlegm), and neurophysiological symptoms such as headache, lightheadedness, nausea, vomiting, and numbness or tingling of the extremities. Such symptoms have been described mainly in reports of individuals exposed to DE in the workplace, or in clinical studies in humans exposed acutely to high concentrations of DE. Because of the general lack of exposure information in available reports, the exact role of DE in causing these effects is not known. An exposure-response relationship for these acute irritation and respiratory symptoms has not been demonstrated (Chapter 5, Section 5.1.1.1).

9.4.1.2. *Respiratory Effects*

Available studies of occupational exposure to DE have not provided evidence for significant decrements of lung function in workers over a work shift or after a short-term exposure period. Short-term and subchronic inhalation studies of DE in animals (rats, mice, hamsters, cats, guinea pigs) showed inflammation of the airways and minimal or no lung function changes. These effects were associated with high DE exposures (up to 6 mg/m^3). Exposure-response relationships have not been established for these responses (Chapter 5, Sections 5.1.2.2 and 5.1.1.1).

9.4.1.3. *Immunological Effects*

Recent human and animal studies show that acute DE exposure episodes may exacerbate immunological reactions to other allergens or initiate a DE-specific allergenic reaction. The effects seem to be associated with both the organic and carbon core fraction of DPM. In human subjects, intranasal administration of DPM has resulted in measurable increases of IgE antibody production and increased nasal mRNA for the proinflammatory cytokines. The ability of DPM to act as an adjuvant to other allergens has been demonstrated in human subjects. For example, co-exposure to DPM and ragweed pollen was reported to significantly enhance the IgE antibody response and cytokine expression relative to ragweed pollen alone. Available animal studies also demonstrate the potential adjuvant effects of DPM with model allergens. For instance, DPM has

been shown to enhance IgE antibody production and cytokine production response to several model allergens (ovalbumin, Japanese cedar pollen) in mice (Chapter 5, Sections 5.1.1.1.3, 5.1.1.1.4, 5.1.2.3.5, and 5.1.2.3.6). Additional research is needed to further characterize possible immunological effects of DE and to determine whether or not the immunological effects constitute a low-exposure hazard. This health endpoint is of considerable public health concern, given the increases in allergic hypersensitivity in the U.S. population (Section 5.6.2.6).

9.4.2. Chronic Exposure

9.4.2.1. *Noncancer Effects*

Available long-term and cross-sectional studies have provided evidence for an association between respiratory symptoms (cough and phlegm) and DE exposure, but there was no consistent effect on lung function. DE has been shown in many animal studies of several species to induce lung injury (chronic inflammation and histopathologic changes) following long-term inhalation exposure. DE has also been tested in laboratory animals for other health effects, and no significant effects have been found. Overall, available data support the conclusion of a potential chronic respiratory hazard to humans from long-term exposure to DE.

9.4.2.1.1. ***Respiratory effects.*** A few human studies in various diesel occupational settings suggest that DE exposure may impair pulmonary function, as evidenced by increases in respiratory symptoms and some reductions in baseline pulmonary function consistent with restrictive airway disease. Other studies found no particular effects. The methodologic limitations in available human studies limit their usefulness in drawing any firm conclusions about DE exposure and noncancer respiratory effects (Chapter 5, Section 5.1.1.2).

Available studies in animals, however, provide a considerable body of evidence demonstrating that prolonged inhalation exposure to DE can result in pulmonary injury. A number of long-term laboratory studies in rats, mice, hamsters, cats, and monkeys found varying degrees of adverse lung pathology including focal thickening of the alveolar walls, replacement of Type I alveolar cells by type II cells, and fibrosis. The rat is the most sensitive animal species to DE-induced pulmonary toxicity (Chapter 5, Sections 5.1.2.3 and 5.4).

Available mechanistic data, mainly in rats, indicate that the DPM fraction of DE is primarily involved in the etiology of pulmonary toxicity, although a role for the adsorbed organic compounds on the particles and in the gaseous phase cannot be ruled out. The lung injury appears to be mediated by an invasion of alveolar macrophages that release chemotactic factors that attract neutrophils and additional alveolar macrophages, which in turn release mediators (e.g., cytokines, growth factors) and oxygen radicals. These mediators result in persistent inflammation, cytotoxicity, impaired phagocytosis and clearance of particles, and eventually

deposition of collagen by activated fibroblasts. This postulated mode of action seems to be operative for a variety of poorly soluble particles in addition to DPM (ILSI, 2000). Because long-term exposure to DE has been shown to induce exposure-dependent chronic respiratory effects in a wide range of animal species, and the postulated mode of action is deemed relevant to humans, there is a sufficient scientific basis to support a conclusion that humans could also be at hazard for these effects under a chronic exposure condition. This inference is deemed reasonable in the absence of information to the contrary.

9.4.2.1.2. ***Other noncancer effects***. The negative results from available studies in several animal species (rats, mice, hamsters, rabbits, monkeys) indicate that DE is not likely to pose a reproductive or developmental hazard to humans. There has been some evidence from animal studies indicating possible neurological and behavioral effects, as well as liver effects. These effects, however, are seen at exposures higher than the respiratory effects. Overall, there is inadequate evidence for a low-exposure human hazard for these health endpoints (Chapter 5, Sections 5.1.2.3.7, 5.1.2.3.11, and 5.1.2.3.12).

9.4.2.2. ***Carcinogenic Effects***

Many epidemiologic and toxicologic studies have been conducted to examine the potential for DE to cause or contribute to the development of cancer in humans and animals, respectively. In addition, there have been extensive mechanistic studies that provide an improved understanding about the underlying carcinogenic process and the likelihood of hazard to humans. The available evidence indicates that chronic inhalation of DE has the potential to induce lung cancer in humans. There is insufficient information for an evaluation of the potential cancer hazard of DE by oral and dermal routes of exposure.

9.4.2.2.1. ***Epidemiologic studies.*** Twenty-two epidemiologic studies about the carcinogenicity of workers exposed to DE in various occupations are reviewed in Chapter 7, Section 7.2. Exposure to DE has typically been inferred on the basis of job classification within an industry, with cumulative exposure based on duration of employment or age. Increased lung cancer risk, although not always statistically significant, has been observed in 8 out of 10 cohort studies and 10 of 12 case-control studies within several industries, including railroad workers, truck drivers, heavy equipment operators, and professional drivers. The increased lung cancer relative risks generally range from 1.2 to 1.5, although a few studies show relative risks as high as 2.6. Statistically significant increases in pooled relative risk estimates (1.33 to 1.47) from two independent meta-analyses further support a positive relationship between DE exposure and lung cancer in a variety of DE-exposed occupations.

The generally small increased lung cancer relative risk (less than 2) observed in the epidemiologic studies potentially weakens the evidence of causality. This is because with a relative risk of less than 2, if confounders (e.g., smoking, asbestos exposure) were having an effect on the observed risk increases, it could be enough to account for the increased risk. With the strongest risk factor for lung cancer being smoking, there is a concern that smoking effects may be influencing the magnitude of the observed increased relative risks. However, in studies in which the effects of smoking were accounted for, increased relative risks for lung cancer prevailed. Although some studies did not have information on smoking, confounding by smoking is unlikely because the comparison populations were from the same socioeconomic class. Moreover, when the meta-analysis focused only on the smoking-controlled studies, the relative risks tended to increase.

As evaluated in Chapter 7 (Section 7.2.4.5), application of the criteria for causality provides evidence that the increased risks observed in available epidemiologic studies are consistent with a causal association between exposure to DE and occurrence of lung cancer. Overall, the human evidence for potential carcinogenicity for DE is judged to be strong but less than sufficient to be considered as a human carcinogen because of exposure uncertainties (lack of historical exposure of workers to DE) and uncertainty as to whether all confounders have been satisfactorily accounted for. The epidemiologic evidence for DE being associated with other forms of cancer is inconclusive.

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

In several intratracheal instillation studies, DPM, DPM organic extracts, and carbon black, which is virtually devoid of PAHs, have been found to produce increased lung tumors in rats. When directly implanted into the rat lung, DPM condensate containing mainly four- to seven-ring PAHs induced increases in lung tumors. DPM extracts have also been shown to cause skin tumors in several dermal studies in mice, and sarcomas in mice following subcutaneous injection.

Overall, there is sufficient evidence for the potential carcinogenicity of whole DE in the rat at high exposure concentration or administered dose, both by inhalation and intratracheal instillation. Available data indicate that both the carbon core and the adsorbed organics have

potential roles in inducing lung tumors in the rat, although their relative contribution to the carcinogenic response remains to be determined. The gaseous phase of DE, however, does not have any observable role in the DE-induced lung cancer response in the rat.

Available data also indicate that among the traditional animal test species, the rat is the most sensitive species to DE. As reviewed in Chapter 7, Section 7.4, the lung cancer responses in rats from high-concentration exposures to DE appear to be mediated by impairment of lung clearance mechanisms owing to particle overload, resulting in persistent chronic inflammation and subsequent pathologic and neoplastic changes in the lung. Overload conditions are not expected to occur in humans as a result of environmental or most occupational exposures to DE. Thus, the animal evidence (i.e., increased lung tumors in the rat) provides additional support for identifying a potential cancer hazard to humans, but is considered not suitable for subsequent dose-response analysis and estimation of human risk with DE.

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

9.4.2.2.3. ***Other key data.*** Other key data, while not as extensive as the human and animal carcinogenicity data, are judged to be supportive of potential carcinogenicity of DE. As discussed above, DE is a complex mixture of hundreds of constituents in either gaseous phase or particle phase. Although present in small amounts, several organic compounds in the gaseous phase (e.g., PAHs, formaldehyde, acetaldehyde, benzene, 1,3-butadiene) are known to exhibit mutagenic and/or carcinogenic activities. PAHs and PAH derivatives, including nitro-PAHs present on the diesel particle, are also known to be mutagenic and carcinogenic. As reviewed in Chapter 4, DPM and DPM organic extracts have been shown to induce gene mutations in a variety of bacteria and mammalian cell test systems. DPM and DPM organic extracts have also been shown to induce chromosomal aberrations, aneuploidy, and sister chromatid exchange in vitro tests using rodent cells as well as human cells.

There is also suggestive evidence for the bioavailability of the organic compounds from DE. Elevated levels of DNA adducts in lymphocytes have been reported in workers exposed to DE. In addition, inhalation studies of animals using radio-labeled materials indicate some elution of organic compounds from DE after deposition in the lung, as measured by their presence in biological tissue and fluids (Chapter 3, Section 3.5).

9.4.2.2.4. ***Modes of carcinogenic action.*** As discussed above, there is an adequate understanding of the modes of action of DE-induced lung tumors in the rat. However, the modes of action by which DE increases lung cancer risks in humans are not fully known. The term

"mode of action" refers to a series of key biological events and processes that are critical to the development of cancer. This is contrasted with "mechanisms of action," which is defined as a more detailed description of the complete sequence of biological events at the molecular level that must occur to produce a carcinogenic response.

As discussed in Section 7.4, it is likely that multiple modes of action are involved in mediating the carcinogenic effect of DE. These may include (a) mutagenic and genotoxic events (e.g., direct and indirect effects on DNA and effects on chromosomes) by organic compounds in the gas and particle phase, (b) indirect DNA damage via the production of reactive oxygen species (ROS) induced by particle-associated organics, and (c) particle-induced chronic inflammatory response leading to oxidative DNA damage through the release of cytokines, ROS, etc., and an increase in cell proliferation.

The particulate phase appears to have the greatest contribution to the carcinogenic effects, and both the particle core and the associated organic compounds have demonstrated carcinogenic properties, although a role for the gas-phase components cannot be ruled out. The carcinogenic activity of DE also appears to be related to the small size of the particles. Moreover, the relative contribution of the various modes of action may be different at different exposure levels. Available evidence from animal studies indicates the importance of the role of DE particles in mediating lung tumor response at high exposure levels. Thus, the role of the adsorbed organic compounds may take on increasing importance at lower exposure levels.

9.4.2.2.5. ***Weight-of-evidence evaluation.*** Section 7.5 provides an evaluation of the overall weight of evidence for potential human carcinogenicity in accordance with EPA's Carcinogen Risk Assessment Guidelines (U.S. EPA, 1986, 1996a). The totality of evidence supports the conclusion that DE is a *probable human carcinogen (Group B1)* using the criteria as laid out in the 1986 guidelines. A cancer hazard narrative for DE is also provided in accordance with the proposed revised guidelines, which concludes that DE *is likely to be carcinogenic to humans* by inhalation at any exposure condition. The common bases for either conclusion include the following lines of evidence:

- strong but less than sufficient evidence for a causal association between DE exposure and increased lung cancer risk among workers of different occupations;
- sufficient animal evidence for the induction of lung cancer in the rat from inhalation exposure to high concentrations of DE, DPM, and the elemental carbon core;
- supporting evidence of carcinogenicity of DPM and the associated organic compounds in rats and mice by noninhalation routes of exposure;

- extensive evidence for mutagenic effects of the organic constituents in both particulate matter and gaseous phase, and chromosomal effects of DE, DPM and DPM organics;
- suggestive evidence for the bioavailability of DE organics from DE in humans and animals; and
- the known mutagenic and carcinogenic activity of a number of individual organic compounds present on the particles (PAHs and their derivatives) and in the gaseous phase (e.g., formaldehyde, acetaldehyde, benzene, 1,3-butadiene, PAHs).

A major uncertainty in the characterization of the potential cancer hazard of DE at low levels of environmental exposure is the incomplete understanding of its mode of action for the induction of lung cancer in humans. Available data indicate that DE-induced lung carcinogenicity appears to be mediated by mutagenic and nonmutagenic events by both the particles and the associated organic compounds, and that a role for the organics in the gaseous phase cannot be ruled out. Given that there is some evidence for a mutagenic mode of action, a cancer hazard is presumed at any exposure level. This is consistent with EPA's science policy position that assumes a nonthreshold effect for carcinogens in the absence of definitive data demonstrating a nonlinear or threshold mechanism. Because of insufficient information, the human carcinogenic potential of DE by oral and dermal exposures cannot be determined.

Several organizations have previously reviewed available relevant data and evaluated the potential human carcinogenicity of DE or the particulate component of DE. Similar conclusions were reached by various organizations (see Table 7-9). For example, some organizations have concluded that DE is probably carcinogenic to humans (IARC, 1989; IPCS, 1996), or reasonably anticipated to be a carcinogen (U.S. DHHS, 2000).

Overall, the weight of evidence for potential human carcinogenicity for DE is considered strong, even though inferences are involved in the overall assessment. Major uncertainties of the cancer hazard assessment include the following unresolved issues.

First, there has been a considerable scientific debate about the significance of the available human evidence for a causal association between occupational exposure and increased lung cancer risk. Many experts view the evidence as weak, while others consider the evidence as strong. This is due to a lack of consensus about whether the effects of smoking have been adequately accounted for in key studies, and the lack of historical DE exposure data for the available studies.

Second, while the mode of action for DE-induced lung tumors in rats from high exposure is sufficiently understood, the mode of action for lung cancer risk in humans is not fully known. To date, available evidence for the role of both the adsorbed organics and the carbon core particle has been shown to be associated with high-exposure conditions. There is virtually no information

about the relative role of DE constituents in mediating carcinogenic effects at the low-exposure levels. Furthermore, there is only a limited understanding regarding the relationship between particle size and carcinogenicity.

Third, DE is present in ambient PM (e.g., $PM_{2.5}$ or PM_{10}); however, examination of the available PM data has not resulted in the identification of a cancer hazard for ambient PM, although there is some evidence indicating a possible association between ambient PM and lung cancer. Additional research is needed to address these issues to reduce the uncertainty associated with the potential cancer hazard of exposure to DE.

9.5. DOSE-RESPONSE ASSESSMENT

For agents that are known to cause adverse health effects to humans at the exposure of interest, such as the general environment (e.g., air pollutants regulated under the National Ambient Air Quality Standards [ambient PM, ozone, carbon monoxide, sulfur dioxide, nitrogen oxide, lead, environmental tobacco smoke, etc.]), estimates of human health risks are based on exposure-/dose-response data of the affected populations. However, for most environmental agents, available health effects information is generally limited to high exposures in studies of humans (e.g., workers) or laboratory animals. For these agents, dose-response assessment is performed in two steps: assessment of observed data to derive a point of departure (which usually is the lowest exposure or dose that induces some, minimal, or no apparent effects), followed by extrapolation to lower exposures to the extent necessary. Human data are always preferred over animal data, if available, as their use obviates the need for extrapolation across species. Extrapolation to low dose is based on the understanding of mode of toxic action of the agent. In the absence of sufficient data that would allow the development of biologically based dose-response models, default methods are generally used to derive toxicity values for estimation of human risks at low doses.

For DE, there is sufficient evidence to conclude that acute or short-term inhalation exposure at relatively high levels can cause irritant effects to the eye and upper respiratory tract and inflammation of the lung; however, no quantitative data are available to derive an estimate of human exposure that is not likely to elicit irritant and inflammatory effects in humans.

There is also adequate evidence to support the conclusion that DE has the potential to cause cancer and noncancer effects of the lung from long-term inhalation exposure. Chapters 6 and 8 provide dose-response information and analyses related to the noncancer and cancer hazards to humans, respectively, from lifetime exposure to DE. The results of the analyses are discussed below.

9.5.1. Evaluation of Risk for Noncancer Health Effects

As discussed above (Section 9.4), the evidence for potential chronic noncancer health effects of DE is based primarily on findings from chronic animal inhalation studies showing a spectrum of dose-dependent chronic inflammation and histopathological changes in the lung in several animal species including rats, mice, hamsters, and monkeys. On the other hand, available epidemiologic studies of workers exposed to DE, although considered limited because of the lack of exposure information and short exposure duration, have not provided evidence of significant chronic health effects associated with DE exposure, and respiratory symptoms were the only effects reported in a few studies.

One approach to derive an estimation of an exposure air level of DE to which humans may be exposed throughout their lifetime without experiencing any untoward or adverse noncancer health effects is to derive a reference concentration (RfC) for DE based on available animal studies. This approach assumes that humans would respond to DE similarly to the tested animals under similar exposure conditions. A major uncertainty of this approach is that animal studies have generally used high DE exposures, and the potential chronic health effects of DE in humans at environmental exposure levels could not be ascertained with available human data. In addition, as DPM is a component of ambient PM, it is conceivable that DPM may partly contribute to the adverse health effects of ambient PM. Ambient PM has been shown to be statistically associated with increased mortality (especially among people over 65 years of age with preexisting cardiopulmonary conditions) and morbidity, as measured by increases in hospital admissions, respiratory symptoms rates, and decrements in lung function.

To address these uncertainties, this assessment also provides two additional approaches for estimating noncancer risk from environmental exposure to DE as bounding estimates. The first approach is to assume that quantitative estimates of risk derived for ambient fine particles ($PM_{2.5}$) would represent a plausible upper bound for persons potentially exposed to DPM as one of the numerous constituents of ambient $PM_{2.5}$. Another alternative approach would be to assume equal potency of DPM with other constituents comprising ambient $PM_{2.5}$. The support for this approach is that DPM has been shown to have comparable capacity in inducing lung injury in a variety of animal species, as do other poorly soluble particles (ILSI, 2000). Thus, estimation of DE noncancer risks could be based on apportionment of DPM contributions in relationship to the ambient $PM_{2.5}$.

9.5.1.1. *Chronic Reference Concentrations for Diesel Exhaust*

EPA's Inhalation Reference Concentration Methodology (U.S. EPA, 1994) for the evaluation of human risks for health effects other than cancer assumes that there is an exposure threshold below which effects will not occur. The RfC can be derived on the basis of either

human or animal data. A chronic RfC is defined as *"an estimate of a continuous inhalation exposure to the human population, including sensitive subgroups, with uncertainty spanning perhaps an order of magnitude, that is likely to be without appreciable risks of deleterious noncancer effects during a lifetime."* The RfC is not a bright line; rather, as the human exposure increases above the RfC, the margin of protection decreases.

In the absence of exposure-response data in humans, this assessment derives an RfC for DE based on dose-response data from four chronic inhalation studies in rats (Mauderly et al., 1987; Ishinishi et al., 1988; Heinrich et al., 1995; Nikula et al., 1995). All of these four studies used DPM (expressed as $\mu g/m^3$) as a measure of DE exposure. The pulmonary effects, including inflamation and histopathologic lesions, were considered to be the critical noncancer effects. As shown in Table 6-2, the no-observable-adverse-effects levels (NOAELs), the lowest-observable-adverse-effects levels (LOAELs), and the adverse effects levels (AELs) for lung inflammation and histopathologic changes were identified for the first three studies. Lower 95% confidence estimates of the concentrations of DPM associated with a 10% incidence ($BMCL_{10}$) of chronic pulmonary inflammation and fibrosis were derived for the Nikula et al. study. Human equivalent concentrations (HECs) corresponding to the animal exposure levels (NOAEL, LOAEL, AEL, $BMCL_{10}$) were then computed by using a dosimetry model developed by Yu et al. (1991) as described in Chapter 6, Section 6.5.2, and Appendix A. The dosimetry model accounts for species differences (rat to human) in respiratory exchange rates, particle deposition efficiency, differences in particle clearance rates at high and low doses, and transport of particles to lymph nodes.

The highest HEC value associated with no apparent effects, i.e., a NOAEL of 0.14 $\mu g/m^3$ was selected as the point of departure for deriving an RfC. To obtain the RfC, this point of departure was then divided by an uncertainty factor (UF) of 10 to account for inter-individual variation. In the absence of mechanistic or specific data, a default value of 10 is considered appropriate to account for possible human variability in sensitivity, particularly for children and people with preexisting respiratory conditions. The resulting RfC for DE is 14 $\mu g/m^3$ of DPM.

Overall, the confidence level of the RfC assessment for DE is considered medium. A principal uncertainty of the assessment is the reliance on animal data to predict human risk. The critical effects, chronic inflammation and pathologic changes, which are well characterized in four animal species, are considered relevant to humans. Collective evidence for all poorly soluble particles indicates that the rat is the most sensitive laboratory animal species tested to date and appears to be more sensitive to lung injury induced by any solid particles (including DE) than the human (ILSI, 2000). In addition, differences in particle deposition, retention, and clearance mechanisms have been addressed to some extent by the use of the rat-to-human dosimetry model. Thus, the use of rat data is not likely to underestimate human risk for noncancer health effects. In

addition, available toxicologic information for DE is relatively complete, as it has been extensively tested in standard toxicologic studies. Still, some uncertainties remain given that there is growing evidence suggesting the potential for DE to cause immunological effects and/or to exacerbate allergenic effects to known sensitizers. The potential relevance for these health endpoints to public health is significant because of increases in the number of individuals with preexisting respiratory conditions and possible interactions with other air pollutants.

9.5.1.2. *Risks Based on Ambient $PM_{2.5}$*

As discussed in Chapter 6 (Section 6.3), the EPA has promulgated a long-term $PM_{2.5}$ NAAQS of 15 $\mu g/m^3$ as an acceptable level for annual-average fine particles to protect against effects from chronic exposure. The standard is based on combined findings of excess daily mortality and morbidity from short-term exposures and findings from long-term fine PM studies (e.g., Harvard Six City and ACS studies) showing increases in mortality around or above the annual average level of 15 $\mu g/m^3$. If one assumes that the adverse health effects of ambient fine particles are due entirely to DPM, i.e., that DPM is exceptionally toxic, then any characterization of health effects attributable to ambient fine particles could therefore represent an upper-limit estimate for DPM. Accordingly, the upper-limit for DE would be 15 $\mu g/m^3$.

9.5.1.3. *Apportionment Method Based on Ambient $PM_{2.5}$*

As discussed in Chapters 2 and 6, DPM is a component of ambient PM. In some urban areas, the fraction of $PM_{2.5}$ attributable to DPM from DE sources may exceed 30%, although the proportion appears to be more typically in the range of 10%. If one assumes that DPM is as toxic as other constituents of ambient $PM_{2.5}$, then ambient concentration to DPM needs to be below the range of 1.5 to 5.0 $\mu g/m^3$ (i.e., 10% × 15 $\mu g/m^3$ to 30% × 15 $\mu g/m^3$) to achieve the same protection for the annual average standard for ambient fine particles of 15 $\mu g/m^3$.

9.5.1.4. *Conclusions*

Three approaches are used to estimate an exposure air level of DE (as measured by DPM) to which humans may be exposed throughout their lifetime without experiencing any untoward or adverse noncancer health effects. The RfC method produces an RfC of 14 $\mu g/m^3$ of DPM on the basis of four chronic inhalation studies of DE in rats. This value is almost the same as the long-term $PM_{2.5}$ NAAQS of 15 $\mu g/m^3$, and close to the 1.5 to 5.0 $\mu g/m^3$ derived from the apportionment of the $PM_{2.5}$ standard. As the accuracy of the RfC is part of the definition (*"within an order of magnitude"*), this dose-response estimate could be considered not to be substantially different from the other two approaches. This congruence of estimates attests to the reasonableness of the data used and the judgments made in the RfC process, as well as tending to

support the accuracy of the estimates of DPM within ambient $PM_{2.5}$. This congruence of independent methods should also increase overall confidence in these estimates regarding toxicity of DE and its potential health risks for the human population.

9.5.2. Evaluation of Cancer Risks

As discussed above (Section 9.4.3), the combined weight of evidence indicates that DE has the potential to pose a cancer hazard to humans at anticipated levels of environmental exposure. The critical target organ of DE-induced carcinogenicity is the lung. Strong but less than sufficient evidence exists for a causal relationship between risk for lung cancer and occupational exposure to DE in certain occupational workers such as railroad workers, truck drivers, heavy equipment operators, transit workers, etc. In addition, it has been shown unequivocally in several studies that DE can cause benign and malignant lung tumors in rats in a dose-related manner following chronic inhalation exposure to high concentrations. The mechanism(s) by which DE induces lung cancer in humans has not been established, but available data indicate that mutagenic and nonmutagenic modes of action are possible. Hence, for estimating DE cancer risk at low environmental exposures, linear low-dose extrapolation is considered most appropriate, which is consistent with EPA's science policy position that in the absence of an understanding of modes of carcinogenic action, a nonthreshold effect is to be presumed (U.S. EPA, 1986, 1996a). This approach is consistent with the approaches taken by other organizations or individuals who have previously used either linear risk extrapolation models or mechanistically based models to estimate cancer risk from environmental exposure to DE (e.g., IPCS, 1996; Cal EPA, 1998; also see Appendix D).

Dose-response assessment is generally based on either human or animal data, although human data are always preferred if available. Many quantitative assessments have been conducted by several organizations and investigators on the basis of both occupational data and rat data (see Appendix D). However, more recent cumulative evidence indicates that DE causes tumors in the rat via a mode of action that involves impairment of lung clearance mechanisms (referred to as "lung overload response") associated with high exposures. Although the dose-response for increases in lung tumors in rats is supportive for identifying a cancer hazard in humans, the mode of action in the rat is not expected to be operative at environmental exposure conditions. Therefore, the rat lung tumor dose-response data are not considered suitable for predicting human risk at low environmental exposures. Given that the rat data are not appropriate for estimating cancer risk to humans, this assessment focuses on the use of occupational data for estimating environmental risk of DE to humans.

Even though occupational data are considered most relevant for use in dose-response assessment, considerable uncertainties exist, including the following issues:

- the use of DPM (expressed as $\mu g/m^3$) as a surrogate dosimeter for DE exposure, given that the relative roles of various constituents in mediating carcinogenic effects and the mode of carcinogenic action are still not fully known;
- the representativeness of occupational populations for the general population and vulnerable subgroups, including infants and children and individuals with preexisting diseases, particularly respiratory conditions;
- the lack of actual DE workers' exposure data in available epidemiologic studies;
- possible confounders (smoking and asbestos exposure) that could contribute to the observed lung cancer risk in occupational studies of DE; and
- whether or not exposure-response relationships for lung cancer risks have been demonstrated for available occupational studies of DE.

Chapter 8, Section 8.3 provides a discussion of these uncertainties, along with an evaluation of the suitability of available occupational studies for a derivation of a cancer unit risk estimate for DE. Unit risk 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 $\mu g/m^3$ of DPM).

Among the occupational studies, the railroad worker studies (Garshick et al., 1987, 1988) and the Teamsters Union truck driver studies (Steenland et al., 1990, 1998) are considered to have the best available exposure data for possible use in establishing exposure-response relationships and deriving a cancer unit risk. There have been different views on the suitability of either set of studies for estimating environmental cancer risks (e.g., Cal EPA, 1998; HEI, 1995, 1999). Given the equivocal evidence for the presence or absence of an exposure-response relationship for the studies of railroad workers, and exposure uncertainties for the studies of truck drivers, it is judged that available data are too uncertain at this time for a confident quantitative dose-response analysis and subsequent derivation of cancer unit risk for DE.

In the absence of a cancer unit risk to assess environmental cancer risk, this assessment provides some perspective about the possible magnitude of risk from environmental exposure to DE. One approach involves examining the differences between the levels of occupational and ambient environmental exposures by (1) using a nationwide average and upper limit environmental exposures of 0.8 $\mu g/m^3$ and 4 $\mu g/m^3$, respectively, and (2) assuming that cancer risk to DE is linearly proportional with cumulative lifetime exposure. Risks to the general public would be low in comparison with occupational risk, if the differences in exposure are large. On the other hand, if the differences are small, the environmental risks would approach the workers' risk observed in studies of past occupational exposures. The comparative exposure analysis indicates that for certain occupations, there is a potential for overlap between environmental

exposure and environmental equivalent of occupational exposure, having exposure margins of less than 1 to about 460 (see Table 8-1). When environmental exposure is at the high end, the resultant cancer risk may approach that of workers in certain occupations.

A second approach is to derive a rough estimate of lung cancer risks from occupational exposures to DE, and then take into account the exposure margins between occupational and environmental exposures to derive an upper limit range of possible lung cancer risks from lifetime environmental exposure to DE. Given the range of observed relative risks or odds ratios of lung cancer in a number of occupational studies (1.2 to 2.6) and the pooled relative risk estimates from two independent meta-analyses (1.35 and 1.47), a relative risk of 1.4 is selected as a reasonable estimate for the purpose of this analysis. The relative risk of 1.4 means that the workers faced an extra risk that is 40% higher than the approximately 5% background lifetime lung cancer risk in the U.S. population.[2] Thus, using the relationship [*excess risk = (relative risk-1) × background risk*], 2% (10^{-2}) of these DE-exposed workers would have been at risk (and developed lung cancer) attributable to occupational exposure to DE [(1.4 -1) × 0.05) = 0.02].

Using a nationwide average environmental exposure (0.8 $\mu g/m^3$ DPM), and assuming (a) the excess lung cancer risk from occupational exposure is about 10^{-2}; (b) the risks fall proportionally with reduced exposure; and (c) the past occupational exposures were at the high end of the range (about 1740 $\mu g/m^3$ which corresponds to an environmental equivalent exposure of 365 $\mu g/m^3$, resulting in an exposure margin of 457), then the environmental cancer risk could be between 10^{-4} to 10^{-5}. On the other hand, if occupational exposures for some groups were lower, e.g., closer to 100 $\mu g/m^3$, (i.e., an equivalent environmental exposure of 21 $\mu g/m^3$ with an exposure margin of 25), the environmental risk would approach 10^{-3}.

The analyses presented above are not intended to be precise, but are useful in gauging the possible range of risk based on applying scientific judgment and simple risk exploration methods to the relative risk findings from the epidemiologic studies. The analyses provide a sense of where an upper limit (or "upper bound") of the risk may be. The simple methodologies used are generic in that they are valid for any increased relative risk data, and thus are not unique to the DE data. It should be pointed out that these analyses are subject to considerable uncertainties, particularly

[2] 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 × 10E-5/8.8 × 10E-3 = 6.8 × 10E-2, where 59.8 × 10E-5 and 8.8 × 10E-3 are, respectively, the crude estimates of lung cancer deaths (including intrathoracic organs, estimated to be fewer than 105 of the total cases) and total deaths for 1996 reported in the Statistical Abstract of the U.S. Bureau of the Census (1998, 118th Edition), and (2) 156,900/270,000,000 × 76 = 0.045, where 156,900 is the projected number of lung cancer deaths for the year 2000 as reported in Cancer Statistics 9J of the American Cancer Society, Jan/Feb 2000; 270,000,000 is the current U.S. population; and age 76 is the expected lifespan.

the lack of actual exposure information and the underlying assumption that cancer risk is linearly proportional to cumulative exposure. Nevertheless, these analyses, which include the use of public health conservative assumptions, indicate that environmental exposure to DE may pose a lifetime cancer risk that could range from 10^{-5} to 10^{-3}. These findings are general indicators of the potential significance of the lung cancer hazard, and should not be viewed as a definitive quantitative characterization of risk. Further research is needed to more accurately assess and characterize environmental cancer risks from DE.

9.6. SUMMARY AND CONCLUSIONS

Adverse human health effects may result from current-day environmental exposure to DE. DE may cause acute and chronic respiratory effects and has the potential to cause lung cancer in humans.

DE may cause acute irritation to the eye and upper respiratory airways, and mild respiratory symptoms at relatively high exposures. DE may also have immunological properties and may induce allergic responses and/or exacerbate existing respiratory allergies. Quantitative dose-response estimates for these effects could not be developed because of the lack of exposure-response information for these acute and short-term effects.

Long-term exposure to low levels of DE may cause chronic inflammation and pathological changes in the lung. The RfC for chronic respiratory effects is estimated to be 14 $\mu g/m^3$ of DPM. This value is almost the same as the long-term $PM_{2.5}$ NAAQS of 15 $\mu g/m^3$, and close to the 1.5 to 5.0 $\mu g/m^3$ derived from an apportionment of DPM from the $PM_{2.5}$ standard. The congruence of these estimates supports the reasonableness of the data used and the accuracy of the risk estimates of DPM within ambient $PM_{2.5}$. This congruence should also increase the overall confidence that these estimates identify a protective exposure level for the chronic toxicity of DE and its potential health risks for the human population.

DE is considered to be a probable human carcinogen, or is likely to be carcinogenic in humans, by inhalation under any exposure condition. Because of considerable uncertainty in the available exposure-response data, a cancer unit risk for DE has not been derived at this time. Simple analyses using conservative assumptions provide a perspective of the possible range of lung cancer risk from environmental exposure to DE. These analyses indicate that lifetime cancer risk could range from 10^{-5} to 10^{-3}. These analyses are subject to considerable uncertainties, particularly the lack of actual exposure information and the underlying assumption that cancer risk is linearly proportional to cumulative exposure. Nevertheless, these findings are general indicators of the potential significance of the lung cancer hazard, although they should not be viewed as a definitive quantitative characterization of risk.

Even though the evidence for potential human health effects of DE is convincing and persuasive, uncertainties exist because of the use of many assumptions to bridge data and knowledge gaps about human exposures to DE and the underlying mechanisms by which DE causes observed toxicities in humans and animals. As discussed in Section 9.2, a major uncertainty of this assessment is how the physical and chemical nature of past exposures to DE compares with present-day exposures, and how the DE exposure-response data from occupational and toxicological studies can be used for the characterization of possible hazard and risk from present-day environmental exposures. Available data are not sufficient to provide definitive answers to these questions, as the modes of action for DE toxicity and carcinogenicity are still not known. Clearly, there have been qualitative and quantitative differences in DE emissions and their physical and chemical composition. Given that the changes in DE (e.g., DPM) over time cannot be quantified, and that the mode of action for DE toxicity is unknown, this assessment assumes that prior-year toxicologic and epidemiologic findings can be applied to more current exposures, both of which use DPM mass as the dosimeter.

Other uncertainties include the assumptions that health effects observed at high doses may be applicable to low doses, and that toxicologic findings in laboratory animals are predictive of human responses. Available data are not sufficient to demonstrate the presence or absence of an exposure-dose-response threshold for DE toxicity and carcinogenicity. This is due to the lack of complete understanding of how DE may cause adverse health effects in exposed humans and laboratory animals. Although there are hypotheses about the specific mechanisms by which DE might cause cancer and other toxicities, no specific biological pathways or specific constituents of DE have been firmly established as the responsible agents for low-dose effects. The assumptions used in this assessment, i.e., a biological threshold for chronic respiratory effects and the absence of a threshold for lung cancer, are considered prudent and reasonable.

The assessment assumes that the potential DE health hazards are for average healthy adults. There is no DE-specific information that provides direct insight into the question of variable susceptibility within the general human population and vulnerable subgroups. Although default approaches to account for uncertainty in interindividual variation have been included in the derivation of the RfC (i.e., use of an uncertainty factor of 10), they may not be adequately protective for certain vulnerable subgroups. For example, adults who predispose their lungs to increased particle retention (e.g., smoking, high particulate burdens from nondiesel sources), have existing respiratory or lung inflammation or repeated respiratory infections, or have chronic bronchitis or asthma could be more susceptible to adverse impacts from DE exposure. Infants and children could also have a greater susceptibility to the acute/chronic toxicity of $PM_{2.5}$, of which DPM is a part, because of a greater breathing frequency, resulting in greater respiratory tract particle deposition. Increased respiratory symptoms and decreased lung function in children

have been associated with ambient PM levels (U.S. EPA, 1996b). Despite these uncertainties, the default approach for using a UF of 10 to account for possible interindividual variation in reaction to DE is appropriate and reasonable given the lack of DE-specific data.

Variation in DE exposure is another source of uncertainty. Because of variation in activity patterns, different population subgroups could potentially receive higher or lower exposure to DE depending on their proximity to DE sources. The highest exposed are clearly occupational subgroups whose job brings them very close to diesel emission sources, such as trucking industry workers, engine mechanics, some types of transit operators, railroad workers, diesel powered machinery operators, underground miners, etc. High exposures in the general population would be to those living very near or having time outdoors in proximity to diesel engine exhaust sources. For example, children with outdoor playtime adjacent to roadways where diesel-engine vehicles are in use are likely to have higher DE exposures. Accordingly, DE exposure estimates used in this assessment have included possible high-end exposures as bounding estimates.

Lastly, this assessment considers only potential heath effects from exposures to DE alone. DE exposure could be additive or synergistic to concurrent exposures to many other air pollutants. For example, there is suggestive evidence that DPM that has been altered by being in the presence of ambient ozone may significantly increase the rat lung inflammatory effect compared to DPM that was not subjected to ozone (Madden et al., 2000). It would follow then that DPM in areas with ambient ozone present could be more potent in causing noncancer inflammatory effects. Other concerns include the possible impacts for children and adults on the potentiation of allergenicity from DE exposure. However, in the absence of more definitive data demonstrating interactive effects from combined exposures to DE and other pollutants, it is not possible to further address these issues at this time.

9.7. REFERENCES

Cal EPA (California Environmental Protection Agency-OEHHA). (1998) Part B: Health risk assessment for diesel exhaust, Public and Scientific Review Draft. February 1998.

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

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

Health Effects Institute (HEI). (1995) Diesel exhaust: a critical analysis of emissions, exposure, and health effects. Cambridge, MA: Health Effects Institute.

HEI. (1999) Diesel emissions and lung cancer: epidemiology and quantitative risk assessment. A special report of the Institute's Diesel Epidemiology Expert Panel. Cambridge, MA: Health Effects Institute.

Heinrich, U; Fuhst, R; Rittinghausen, S; et al. (1995) Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide. Inhal Toxicol 7:553-556.

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

International Life Sciences Institute (ILSI). (2000) ILSI Risk Science Institute workshop: the relevance of the rat lung response to particle overload for human risk assessment. Gardner, DE, ed. Inhal Toxicol 12(1-2).

International Programme on Chemical Safety (IPCS), World Health Organization. (1996) Diesel fuel and exhaust emissions. Environmental Health Criteria 171. Geneva: World Health Organization.

Ishinishi, N; Kuwabara, N; Takaki, Y; et al. (1988) Long-term inhalation experiments on diesel exhaust. In: Diesel exhaust and health risks. Results of the HERP studies. Ibaraki, Japan: Research Committee for HERP Studies; pp. 11-84.

Madden, M; Richards, J; Dailey, L; et al. (2000) Effect of ozone on diesel exhaust toxicity in rat lung. Toxicol Appl Pharmacol: in press.

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

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

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

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

U.S. Department of Health and Human Services (DHHS). (2000) 9th report on carcinogens. National Toxicology Program, Research Triangle Park, NC. http://ntp-server.niehs.nih.gov.res.

U.S. Environmental Protection Agency (U.S. EPA). (1986) Guidelines for carcinogen risk assessment. Federal Register 51(185):33992-34003.

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Research Triangle Park, NC: Office of Research and Development, National Center for Environmental Assessment; EPA/600/8-90/066F.

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

U.S. EPA. (1996b) Air quality criteria for particulate matter. National Center for Environmental Assessment; Research Triangle Park, NC: EPA/600/P-95/001aF.

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