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

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]Environmental equivalent occupational exposure = 0.21 × occupational exposure.

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

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

[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

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