
Diesel Exhaust:

A Critical Analysis of Emissions, Exposure, and Health Effects

**A Special Report of the Institute's
Diesel Working Group**

Health Effects Institute

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HEI

HEI HEALTH EFFECTS INSTITUTE

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STATEMENT FROM THE HEI BOARD OF DIRECTORS 1

THE HEI DIESEL WORKING GROUP AND OTHER CONTRIBUTORS 3

EXECUTIVE SUMMARY 5

**PART I: CRITICAL ISSUES IN ASSESSING THE CARCINOGENICITY OF DIESEL EXHAUST:
A SYNTHESIS OF CURRENT KNOWLEDGE 11**
Kathleen M. Nauss and the Diesel Working Group

PART II: BACKGROUND PAPERS

Emissions and Exposure

Diesel Emissions and Control Technology 65
Robert F. Sawyer and John J. Johnson

Atmospheric Transport and Transformation of Diesel Emissions 83
Arthur M. Winer and William F. Busby, Jr.

Assessment of Occupational Exposure to Diesel Emissions 107
Winthrop F. Watts, Jr.

Regional Emissions and Atmospheric Concentrations of Diesel Engine Particulate
Matter: Los Angeles as a Case Study 125
Glen R. Cass and H. Andrew Gray

Biological Responses

Noncancer Effects of Diesel Emissions: Animal Studies 139
Ann Y. Watson and Gareth M. Green

Relation Between Exposure to Diesel Emissions and Dose to the Lung 165
Gareth M. Green and Ann Y. Watson

Diesel Emissions and Other Substances Associated with Animal Carcinogenicity 185
William F. Busby, Jr. and Paul M. Newberne

Genotoxicity of Diesel Emissions

Part I: Mutagenicity and Other Genetic Effects 221
Lata Shirnamé-Moré

Part II: The Possible Role of Dinitropyrenes in Lung Cancer 243
Herbert S. Rosenkranz

Health Effects of Diesel Exhaust: Epidemiology 251
Aaron J. Cohen and Millicent W.P. Higgins

RELATED HEI PUBLICATIONS 293

Statement from the HEI Board of Directors

Since its inception, the Health Effects Institute has participated actively in research on and evaluation of the health effects of diesel exhaust. Starting with our earliest studies on the effects of the organic chemicals adsorbed onto the surfaces of diesel exhaust particles, and including recent studies of the relative carcinogenic potential of diesel exhaust and carbon black particles, HEI has endeavored to understand both the potential health effects of diesel exhaust and the mechanisms that underlie those effects.

Today, there is renewed interest in an emerging generation of high-efficiency, advanced diesel engines; there are new requirements under the Clean Air Act Amendments of 1990 regulating nonroad diesel engines for the first time; and there are continuing questions about the health effects of diesel emissions. State, national, and international agencies are actively considering the risks of diesel exhaust and contemplating further regulations.

Given this high level of interest in diesel emissions, HEI established a Diesel Working Group to review the research that HEI and others have conducted on the health effects of diesel emissions, and to examine what is known, not known, and uncertain about the risks of exposure to them. The Working Group prepared background papers on a number of issues critical to estimating the carcinogenic risks of exposure to diesel exhaust, then met to determine what conclusions could be drawn from the available scientific data.

We have reviewed their report, and believe it represents a responsible summary of the current state of knowledge about the carcinogenic effects of diesel emissions. Although a wealth of information exists about the potential for diesel emissions to cause cancer, the Diesel Working Group's analysis indicates that significant questions remain about the trends in diesel emissions, about the levels of exposure, and about using either current human occupational data or animal bioassay data to develop quantitative estimates of the potential human risk associated with the levels of diesel emissions to which people are exposed in everyday life.

Because of improvements in engine design and emissions control technology, and the use of reformulated diesel fuel, the Diesel Working Group noted that future human exposures to diesel exhaust will generally be lower than past or current exposures. However, reductions in exposure will be gradual because of the long life of existing

heavy-duty diesel engines and the extent to which emission reductions will be offset by growth in vehicle use.

The human occupational data for workers exposed to diesel exhaust during the 1960s and 1970s have been the subject of intense scrutiny and discussion. Studies of men in different occupations suggest that the risk of lung cancer among workers classified as having been exposed to diesel exhaust is approximately 1.2 to 1.5 times the risk in those workers classified as unexposed. Although the data appear consistent, the association is weakened because the reported effects were small and, in a number of studies, the increases in cancer risk were not statistically significant. In addition, the absence of concurrent exposure information limits the interpretation of the epidemiologic studies and the use of these data for quantitative estimates of cancer risk.

The animal studies have shown that diesel exhaust regularly causes lung tumors in laboratory rats, but only with nearly lifetime exposures to very high concentrations of diesel exhaust particulate matter (greater than 2,000 $\mu\text{g}/\text{m}^3$). Diesel exhaust does not produce lung tumors in hamsters; the results in mice are equivocal, suggesting that a species-specific carcinogenic mechanism operates in the rat, and that caution is needed in extrapolating the rat data to humans.

The most likely mechanism for lung tumor induction in the rat involves the animals' response to high concentrations of inhaled particulate matter. High particle exposures impair the ability of the lungs to clear inhaled particles, leading to inflammation and cell proliferation; the exposure threshold for these latter effects in rats ranges from 200 to 500 $\mu\text{g}/\text{m}^3$. This suggests that there may be a threshold for particle-induced tumorigenesis because inflammation and cell proliferation are thought to have important roles in the development of rat lung tumors. If so, and if the mechanism of rat lung carcinogenesis is relevant to humans, then the levels of diesel exhaust particulate matter found in some occupations (greater than 1,000 $\mu\text{g}/\text{m}^3$) might be a cancer hazard for the relatively small number of workers chronically exposed to these levels, and there may be some reason for concern for those exposed to levels one order of magnitude lower. The average levels of diesel exhaust found in most occupational settings, which are below 100 $\mu\text{g}/\text{m}^3$, would not likely be a cancer hazard for these workers, nor would ambient levels (1 to 10 $\mu\text{g}/\text{m}^3$) present a cancer risk for the general population.

Extrapolating data from rats to humans assumes that particle-induced mechanisms of lung cancer operate similarly in rats and humans and that the chemical mutagens in diesel exhaust do not have a role in lung cancer development. Although the latter assumption is consistent with the animal data, it is not entirely consistent with the human data. Some epidemiology studies suggest an increased risk of lung cancer in workers who were exposed to levels of diesel exhaust particulate matter that were retrospectively estimated to be below $100 \mu\text{g}/\text{m}^3$. If these measures reflect actual exposure levels, it is unlikely that the particle-associated mechanism described above would have been responsible for the reported increase in lung cancer. At this time, one cannot exclude the possibility that a mechanism involving direct action between the chemical mutagens in diesel exhaust and DNA might operate in humans exposed to these concentrations; however, the available epidemiologic and animal data are insufficient to support this hypothesis or to be used in quantitative risk assessments.

Beyond the consideration of carcinogenic risk, HEI recognizes that diesel emissions also contribute to overall levels of particulate air pollution, which has recently been suggested to be associated with a number of noncarcinogenic effects. HEI is further pursuing these questions through its Particulate Epidemiology Evaluation Project and its particles research program.

In addition to thanking the entire HEI Diesel Working Group for its efforts in shaping this report, we would particularly like to thank Dr. Gareth M. Green, Chair of the Diesel Working Group, and Drs. Kathleen M. Naus and William Busby, Jr., who served as HEI's project managers.

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Executive Summary

Diesel engine emissions are highly complex mixtures. They consist of a wide range of organic and inorganic compounds distributed among the gaseous and particulate phases. Public health concern has arisen about these emissions for these reasons:

- The particles in diesel emissions are very small (90% are less than 1 μm by mass), making them readily respirable.
- These particles have hundreds of chemicals adsorbed onto their surfaces, including many known or suspected mutagens and carcinogens.
- The gaseous phase contains many irritants and toxic chemicals.
- Oxides of nitrogen, which are ozone precursors, are among the combustion products in the gaseous phase.
- There is a likelihood for humans to be exposed to diesel emissions or their atmospheric transformation products in both ambient and occupational settings.

Diesel emissions have the potential to cause adverse health effects. These effects include cancer and other pulmonary and cardiovascular diseases. However, diesel engines are only one of many sources of ambient particulate matter and gaseous air pollutants. Therefore, it is difficult to measure the exposures from various sources, and to distinguish the potential health risks attributable to exposure to diesel exhaust from those attributable to other air pollutants.

For over a decade, HEI has supported a broad-based research program to evaluate the health risks of diesel emissions, including investigations of carcinogenesis, modeling studies, and emissions characterization. The purpose of this Special Report is to examine what is known, not known, and still uncertain about the health risks of exposure to diesel emissions. The HEI Diesel Working Group, which was appointed by the HEI Review Committee and chaired by Dr. Gareth M. Green, evaluated the research on diesel emissions supported by the Institute and other organizations. The Working Group included members of the HEI Health Research Committee, Health Review Committee, staff, and other scientists.

The HEI Diesel Working Group focused its evaluation on a set of issues that it thought were critical to assessing the carcinogenic risks of exposure to diesel exhaust. As a first step, members of the Working Group prepared background

papers that addressed these issues. These papers underwent external peer review by qualified experts and form Part II of this report. They include in-depth discussions of emissions, exposure, toxicity, carcinogenicity, and dose-response relations.¹

The Working Group then met to:

- evaluate the scientific information relevant to the potential for diesel emissions to cause cancer;
- determine what conclusions could be drawn from the available scientific data; and
- identify important information gaps.

Part I of this report presents the Working Group's conclusions and addresses their implications for risk assessments of diesel engine emissions. The major findings are discussed in this summary.

EMISSIONS

The composition of diesel exhaust varies considerably depending on engine type and operating conditions, fuel, lubricating oil, and whether an emissions control system is present. Diesel engine emissions have changed dramatically over the last 30 years because of improvements in engine technology, emissions controls, and fuel formulation. Emissions of oxides of nitrogen and particulate matter from the diesel engines introduced in the late 1980s and early 1990s are significantly lower than those from older engines. As a result, characterizations of modern-day diesel exhaust cannot be used to estimate past exposures, nor can they be used reliably to project future emission profiles.

EXPOSURE

It is very difficult to assess exposure to diesel emissions because they are highly complex mixtures and constitute only a small portion of a broader mix of air pollutants. For example, combustion of other materials, such as fossil fuels and tobacco, produce many of the same chemical components that are present in diesel emissions; furthermore, both natural and man-made sources of respirable particles are

¹ Although noncancer risks of exposure to diesel emissions are briefly discussed in some of the background papers, they were not a focus of the Diesel Working Group's discussions. A separate HEI analysis, the Particle Epidemiology Evaluation Project, is currently under way to address this issue.

common. No single constituent of diesel exhaust serves as a unique marker of exposure; however, scientists can use the levels of fine particles or elemental carbon (both of which are much higher in diesel emissions than in other combustion products) as surrogate indices of diesel exhaust particulate matter. When estimating exposure to diesel emissions, the following factors need to be considered:

- Because of improvements in engine design and emissions control technology, and the use of reformulated fuels, future human exposures to diesel engine emissions will differ from past and current exposures. However, reductions in exposure to diesel emissions will be gradual because of the long life of heavy-duty diesel engines, and will be offset as the use of diesel engines grows.
- The fact that the chemical and physical characteristics of diesel emissions will change as new technology and fuels are implemented cautions against automatically assuming that a decrease in the amount of emissions will result in a decrease in risk.
- Once emitted, diesel emissions undergo atmospheric transport and transformation processes that may alter the toxic, mutagenic, or carcinogenic properties of the original constituents, creating new products that may be either more or less hazardous than the original emissions.

Exposure to diesel exhaust particulate matter has been assessed in occupational settings and some ambient environments. Although the existing data are limited, some estimates of the range of human exposure to diesel emissions can be made:

- In some occupations, diesel emissions contribute a high proportion of the particulate and gaseous air pollutants. The estimates for workplace exposures to diesel exhaust particulate matter range widely, from approximately 1 to 100 $\mu\text{g}/\text{m}^3$ (eight-hour averages) in some occupations such as trucking or transportation, to 100 to 1,700 $\mu\text{g}/\text{m}^3$ for occupations such as underground mining where equipment powered by diesel engines is often used in enclosed spaces.
- The information on ambient exposures is sparse. In an analysis conducted in the Los Angeles basin in the early 1980s, diesel emissions accounted for approximately 3% of the mass of total particulate matter and 7% of the mass of fine particles emitted into the atmosphere. Average monthly values for ambient levels of diesel exhaust particulate matter ranged from 1 to 3 $\mu\text{g}/\text{m}^3$ in areas with low levels of air pollution. These values are in general agreement with the range of nationwide annual average values derived by the U.S.

Environmental Protection Agency using vehicle emissions factors, sales information, and pollutant exposure models. In the Los Angeles study, the highest monthly average levels of diesel particulate matter were approximately 10 $\mu\text{g}/\text{m}^3$ at the most polluted locations during winter months, the period of highest exposures. Short-term or peak exposures to diesel particulate matter, especially in urban settings such as street canyons, are usually higher than monthly or annual average concentrations.

HUMAN RESPONSES

Given the limited exposure information, it is a challenge to determine the contribution of diesel exhaust to human cancer. The Diesel Working Group developed the following conclusions after reviewing over 30 epidemiologic studies of workers exposed to diesel emissions in occupational settings for the period 1950 through the early 1980s.

- The epidemiologic data are consistent in showing weak associations between exposure to diesel exhaust and lung cancer. The available evidence suggests that long-term exposure to diesel exhaust in a variety of occupational circumstances is associated with a 1.2- to 1.5-fold increase in the relative risk of lung cancer compared with workers classified as unexposed.
- Despite the concern that confounding by cigarette smoke might explain the observed risk elevations, most studies that controlled for smoking found that the association between increased risk of lung cancer and exposure to diesel emissions persisted after such controls were applied, although in some cases, the excess risk was lower. Only a few epidemiologic studies considered other potential confounders such as non-diesel particles, environmental tobacco smoke, asbestos exposure, diet, and socioeconomic factors. At present, there is insufficient evidence to conclude whether confounding by these factors influenced the results.
- As is frequently the case in epidemiologic studies of air pollutants, none of the studies measured exposure to diesel emissions or characterized the actual emissions from the source of exposure for the period of time most relevant to the development of lung cancer. Most investigators classified exposure on the basis of work histories reported by the subjects or their next of kin, or by retirement records. Although these data provide relative rankings of exposure, the absence of concurrent exposure information is the key factor that limits interpreting the epidemiologic findings and using them to make quantitative estimates of cancer risks.

ANIMAL RESPONSES

The carcinogenic activity of diesel emissions has been convincingly demonstrated in rats. Nearly lifetime exposure for 35 hours or more per week to high concentrations of diesel exhaust particulate matter (2,000 to 10,000 $\mu\text{g}/\text{m}^3$) causes an exposure-dependent increase in the incidence of benign and malignant lung tumors in rats. No consistent evidence suggests that diesel emissions induce cancer in rats at sites other than the lung. Prolonged exposure to diesel emissions does not produce lung tumors in hamsters, and the results in mice are equivocal, which suggests that species-specific factors play a critical role in the induction of lung tumors by diesel emissions.

Recent reports from two independent laboratories support the idea that the particle-associated organic chemicals play little or no role in the development of lung tumors in rats exposed to high concentrations of diesel emissions. No significant differences were noted in tumor incidence or histopathologic characteristics between rats exposed to diesel exhaust and those exposed to carbon black (a surrogate for the diesel particles minus the adsorbed organic compounds). These results do not completely eliminate a possible role for the adsorbed chemicals, some of which are potent mutagens and carcinogens. If bioavailable, they could play a role in carcinogenesis that might not be detectable in the rat bioassay because their effect is either too subtle or is masked by the overwhelming response of the rat's lungs to high concentrations of inhaled particles.

Even though the evidence strongly suggests that prolonged exposure to high concentrations of diesel exhaust particulate matter induces lung tumors in rats, the Diesel Working Group recommends caution in extrapolating these results to humans for the following reasons:

- The lung tumors observed in rats exposed to high concentrations of diesel emissions may be due to a species-specific response to inhaled particulate matter rather than to a carcinogenic mechanism that also occurs in humans. When rats and other laboratory animals are exposed to high concentrations of diesel exhaust particulate matter or other poorly soluble non-fibrous particles for long time periods, lung clearance mechanisms are impaired and particles gradually accumulate in the lungs; this condition is referred to as lung overload. In the rat, lung overload has a characteristic threshold and initiates a progressive series of cellular responses, including inflammation, alveolar epithelial cell proliferation, and fibrosis. These responses are more severe in rats than in mice or hamsters, and appear to be associated with the subsequent development of lung tumors.

- Although characteristic exposure thresholds for lung overload, as well as for the nonneoplastic and neoplastic responses, have been noted in the rat, extrapolation of no-effect levels for exposure to diesel exhaust from one species to another is problematic because of wide inter- and intraspecies variations in particle clearance rates and in susceptibility to cancer.
- Our knowledge of the mechanisms by which prolonged exposure to high concentrations of diesel emissions produces lung tumors in rats is incomplete. At the high concentrations of diesel emissions used in the rat bioassay, the data imply that the diesel exhaust particulate matter triggers inflammation and cell proliferation. Such responses are thought by many scientists to cause cancer through indirect or "nongenotoxic" mechanisms rather than by direct interaction with DNA, as would be caused by the mutagenic chemicals adsorbed to the particles. At this time, however, only circumstantial evidence supports the hypothesis that diesel emissions induce rat lung tumors by nongenotoxic mechanisms.
- The rat bioassay data do not exclude the possibility that diesel exhaust may induce lung cancer by different mechanisms in different species, or by different mechanisms in the same species at different exposure levels (e.g., predominantly nongenotoxic mechanisms under high-dose exposure conditions and genotoxic mechanisms under low-dose exposure conditions).

The Diesel Working Group cautioned that using the rat bioassay data (obtained at high-dose exposure levels) to make quantitative estimates of the carcinogenic risk of exposure to diesel emissions at environmentally relevant exposure concentrations may overestimate risk if the mathematical models used to extrapolate from high to low doses and from animals to humans do not (1) account for particle overload and associated inflammatory and proliferative processes, (2) recognize the apparent existence of a threshold for particle-induced biologic responses, such as impairment of lung clearance mechanisms, inflammation, cell proliferation, and tumor development, and (3) consider the mechanistic relation of the nongenotoxic injuries to the development of lung tumors in laboratory rats.

INTEGRATING EXPOSURE DATA WITH INFORMATION FROM HUMAN AND ANIMAL STUDIES TO CHARACTERIZE THE POTENTIAL CARCINOGENICITY OF DIESEL EMISSIONS

The Diesel Working Group found that it is not presently possible to base a risk characterization of diesel exhaust solely on either the human or the animal data. Instead, the Working Group evaluated and integrated the available in-

formation from diverse data sets to make the most informed judgments about the potential carcinogenicity of exposure to diesel exhaust.

Key issues concerning the human health risk of diesel exhaust are: Does particle overloading occur in humans under environmental exposure conditions, and if so, does it trigger processes that lead to lung cancer. In the rat, the animal species most sensitive to diesel exhaust, lung tumors are produced after nearly lifetime exposures for 35 hours or more per week to high concentrations of diesel exhaust particulate matter (2,000 to 10,000 $\mu\text{g}/\text{m}^3$). These concentrations are approximately three orders of magnitude higher than current estimates of average atmospheric concentrations of diesel exhaust particulate matter (1 to 10 $\mu\text{g}/\text{m}^3$). One mathematical extrapolation model suggests that lung clearance mechanisms would not be impaired in humans even if they were exposed continuously (24 hours per day) to levels of particulate matter in this ambient range. According to this model, the levels of respirable particles that would be needed to depress lung clearance mechanisms in humans under continuous exposure conditions are greater than 100 to 200 $\mu\text{g}/\text{m}^3$. This, however, is an unlikely exposure scenario, even for most workers. Under more realistic intermittent exposure conditions (eight hours per day, five days per week), the model predicts that the concentration of particulate matter needed to impair lung clearance would be 500 to 1,000 $\mu\text{g}/\text{m}^3$. Only a limited number of workers, primarily miners, are exposed to concentrations of diesel exhaust particulate matter close to this range.

If we assume that particle-induced mechanisms of lung tumorigenesis operate similarly in rats and humans, the analysis above implies that there is some biological rationale for extrapolating the rat bioassay data to the small population of workers who are routinely exposed to high concentrations (greater than 1,000 $\mu\text{g}/\text{m}^3$) of diesel exhaust particulate matter and who may have impaired lung clear-

ance mechanisms. Because of the large interspecies differences in particle clearance, the rat bioassay data also may be relevant to those workers who are exposed to levels of diesel particulate matter one order of magnitude lower (100 to 1,000 $\mu\text{g}/\text{m}^3$). However, the toxicity and modeling data do not support the assumption that exposure to diesel exhaust particulate matter alone at the levels found in most ambient settings (1 to 10 $\mu\text{g}/\text{m}^3$) would be sufficiently high to overwhelm lung clearance processes and, thus, induce lung tumors by a mechanism driven by inflammation and cell proliferation.

SUMMARY

A wealth of information is available about the potential for diesel emissions to cause cancer. However, the lack of definitive exposure data for the occupationally exposed study populations precludes using the available epidemiologic data to develop quantitative estimates of cancer risk. When appropriate human information is not available, some policymakers have relied on the results of animal bioassays to estimate human risk. This document raises questions about the validity of using the rat bioassay data to characterize the potential human risk associated with ambient exposure to diesel emissions. The reason for this uncertainty is that the mechanism of lung tumor induction that appears to operate in rats continuously exposed to high concentrations of diesel exhaust and other particulate matter may not be relevant to most humans, who are exposed intermittently to levels of diesel exhaust particulate matter that are two or three orders of magnitude lower than those used in the rat bioassays. The development of unique markers of exposure to diesel emissions and a better understanding of the mechanisms of carcinogenesis would help to establish scientifically valid links between the lung cancers observed in laboratory animals and the human disease, thus improving the accuracy of cancer risk assessments.

Part I

Critical Issues



Critical Issues in Assessing the Carcinogenicity of Diesel Exhaust: A Synthesis of Current Knowledge

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Introduction 13

Historical Perspective 16

Critical Issues in Understanding the Potential Carcinogenic Hazards of Exposure
to Diesel Engine Emissions 20

Issue 1. *What impact have changes in engine and control technologies had
on the characteristics of diesel engine emissions and, thus, human exposure
to them?* 20

Issue 2. *How do atmospheric changes in diesel exhaust constituents influence
the potential human health effects of diesel emissions?* 26

Issue 3. *What does the current epidemiologic evidence indicate about diesel
emissions and cancer?* 26

Issue 4. *What is the significance of the in vitro mutagenicity of diesel exhaust with
respect to carcinogenic risk in humans from in vivo exposures?* 29

Issue 5. *How strong is the evidence that diesel exhaust is carcinogenic
in laboratory animals?* 31

Issue 6. *What components of diesel emissions cause lung cancer in
laboratory rats?* 34

Issue 7. *How do diesel emissions induce lung tumors in laboratory rats?* 35

(Continued on next page)

* See page 3 for the affiliations of members of the HEI Diesel Working Group.

Critical Issues in Conducting Dose-Response Assessments of Diesel Exhaust 38

Issue 8. *Which species should be used to calculate cancer risk factors for diesel exhaust?* 38

Issue 9. *In what ways do the rat lung tumors induced by diesel emissions resemble human lung tumors?* 39

Issue 10. *What factors need to be considered when extrapolating the rat lung tumor data to humans?* 40

Issue 11. *How can information about mechanisms of action guide the selection of scaling factors, dosimetry models, and extrapolation models for dose-response assessments of diesel emissions?* 44

Critical Issues in Assessing Human Exposure to Diesel Emissions 45

Issue 12. *What do we know about human exposure to diesel exhaust in occupational and ambient settings?* 46

Issue 13. *What do we know about the size and characteristics of the populations exposed to diesel emissions?* 48

Critical Issues in Characterizing the Human Risk of Cancer from Exposure to Diesel Emissions 49

Issue 14. *Considering the currently available data for diesel emissions, how can we best characterize the human cancer risk associated with exposure to diesel exhaust?* 49

Summary 51

Acknowledgments 53

References 53

Appendix A. Risk Assessment: An Evolving Process 58

Abbreviations 61

INTRODUCTION

DEVELOPMENT AND USE OF THE DIESEL ENGINE

It has been over 100 years since Rudolph Diesel patented the two-stroke compression-ignition engine known today as the diesel engine. This new internal-combustion engine was more efficient than Nicholas Otto's spark-ignition engine (which was developed 16 years earlier) and it burned diesel fuel, which was less refined and therefore cheaper than gasoline. Because of their economy and efficiency, diesel engines rapidly replaced gasoline engines in industries that require large engines, such as stationary power plants and the shipping industry. Technological improvements during the 1920s and 1930s reduced the size of diesel engines, and expanded their use to vehicles, locomotives, and mines (Figure 1).

Today, diesel engines still have an efficiency advantage over gasoline engines, and throughout the world, virtually all commercial trucks and buses are powered by diesel engines. In Europe, diesel-powered cars represent a substantial share of the passenger car market. Fifteen years ago, as a result of escalating gasoline prices and fuel shortages,

government and industry analysts estimated that, by the mid-1980s, 10% of all new passenger cars and light-duty trucks sold in the United States would be diesel-powered, and that their market share would reach 25% by 1990 (National Research Council 1981). Once gasoline prices stabilized, however, the American consumer's interest in diesel-powered cars waned; peak sales reached approximately 6% in 1981, and now amount to less than 0.1% of new car sales. In contrast, vehicles with diesel engines represent approximately 25% of current European passenger car sales.

Diesel engines have both advantages and disadvantages relative to gasoline engines. Their chief advantages are fuel economy, durability, and surprisingly, some benefits in emissions. Their disadvantage is that they emit more oxides of nitrogen and particulate matter than gasoline engines.

DIESEL ENGINE EMISSIONS

Both gasoline and diesel engines derive their power from burning a mixture of fuel and air in an enclosed cylinder fitted with a movable piston. The basic difference in the two engines is the way in which the fuel and air are mixed and burned. In a gasoline engine, fuel and air mix in the intake

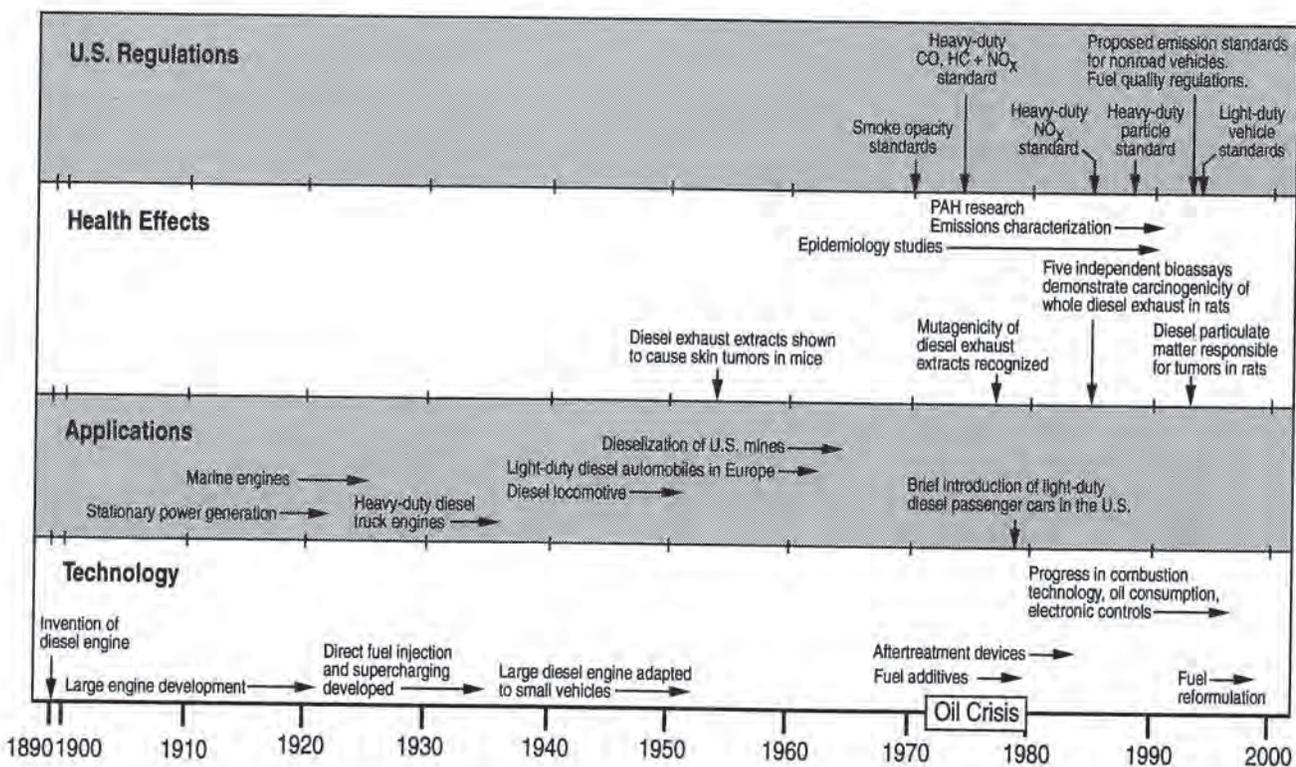


Figure 1. The diesel engine: Milestones in technology, applications, health effects research, and regulations.

flow and are ignited in the cylinder by a spark. In a diesel engine, the air in the cylinder is compressed by a piston. As the piston moves upward on its compression stroke, the temperature of the air in the cylinder increases dramatically and the fuel ignites spontaneously when it is injected into the cylinder. Hence the names "spark-ignition" and "compression-ignition" engines for the gasoline and diesel engines, respectively.

The diesel engine's unique combustion process plays a large role in the output of pollutants. Because diesel engines operate at high temperatures with an excess of air, incomplete combustion products such as carbon monoxide and hydrocarbons are low. Another positive feature is that diesel engines emit approximately 10% to 25% less carbon dioxide than gasoline engines, an important factor when considering global warming trends.

The problem emissions from diesel engines fall into two categories: oxides of nitrogen (precursors of ozone) and particulate matter (or soot). The oxides of nitrogen form when nitrogen in the air is oxidized at the high temperatures in the diesel engines. Early in the combustion process, a low air:fuel ratio (called a "rich burning mixture") in the region of the diesel fuel spray produces solid carbon particles and large organic molecules, which adsorb onto the carbonaceous particles. Most, but not all, of these particles subsequently burn. The remaining particles are particularly troublesome because they are small, readily inhaled, and contain hundreds of organic chemicals, including many known mutagens and carcinogens, adsorbed onto their surfaces. Research has shown that diesel emissions may have both carcinogenic and noncarcinogenic health effects.

WHY ARE DIESEL EMISSIONS A POTENTIAL HEALTH PROBLEM?

Diesel engine emissions are highly complex mixtures. Public health concern has arisen about these emissions for the following reasons:

- The particles in diesel emissions are very small (90% are less than 1 μm by mass), making them readily respirable.
- These particles have hundreds of chemicals adsorbed onto their surfaces, including many known or suspected mutagens and carcinogens.
- The gaseous phase contains many irritants and toxic chemicals.
- Oxides of nitrogen, which are ozone precursors, are among the combustion products in the gaseous phase.

- Because of their contribution to indoor and outdoor air pollution, people are exposed to some level of diesel emissions (or their atmospheric transformation products) in both ambient and occupational settings.

Diesel emissions have the potential to cause adverse health effects. These effects include cancer as well as other pulmonary and cardiovascular diseases. The noncancer risks have come under increased scrutiny because of the contribution diesel emissions make to particulate air pollution and the recent epidemiologic evidence that relatively small elevations in the levels of ambient particles are associated with increases in mortality (reviewed by Dockery and Pope 1994). The biologic mechanism for the reported noncarcinogenic effects of ambient particles has not been elucidated, and there is an active debate as to whether particles or other factors are responsible; however, these results have increased the concerns about particulate air pollution. Although this report focuses on lung cancer, noncancer risks of exposure to diesel exhaust are considered in some of the background papers (Watson and Green, this report; Cohen and Higgins, this report). Other HEI efforts, including the Particle Epidemiology Evaluation Project and a recently initiated research program, currently are under way to address the issue of particulate air pollution.

It is important to note that diesel engines are only one of many sources of ambient particulate matter and gaseous air pollutants. Because no unique biologic tracers for diesel emissions have been identified, it is difficult to measure the actual dose absorbed by the body, and, therefore, to distinguish the potential health risks associated with exposure to diesel exhaust constituents from the potential risks associated with exposure to other air pollutants.

DEVELOPMENT OF THIS REPORT

When the Health Effects Institute began operations in 1980, a major part of its initial research program was directed toward diesel emissions, particularly the potential for diesel exhaust constituents to cause cancer. Since that time, HEI has supported investigations of the carcinogenicity of diesel exhaust, as well as modeling studies, emissions characterizations, and a recently completed animal bioassay. In the early 1990s, the Institute decided to step back and examine what progress has been made. The HEI Review Committee, which routinely evaluates the results of HEI-funded research, organized a Diesel Working Group to review what is presently known, not known, and still uncertain about the risks of exposure to diesel emissions. The HEI Diesel Working Group was composed of members of the HEI Health Research Committee, Health Review

Committee, staff, and outside experts, under the chairmanship of Dr. Gareth M. Green. Members had expertise that included automotive engineering, atmospheric chemistry, toxicology, pathology, molecular biology, epidemiology, and environmental sciences.

The HEI Diesel Working Group organized its efforts around issues that it thought were critical to evaluating the carcinogenic risks associated with exposure to diesel emissions (Table 1). As a first step, individual writing teams developed background papers that addressed these issues. The background papers, which include in-depth discussions of emissions, exposure, toxicity, carcinogenicity, and dose-response relations, were discussed by the Working Group, and submitted for outside peer review. The Working Group then met to

- evaluate the scientific information relevant to the potential for emissions from diesel engines to cause cancer,
- determine what conclusions could be drawn on the basis of available scientific information, and
- identify important information gaps.

The results of these efforts, which are documented in this report, are intended for use by policymakers and others involved in assessing the carcinogenic risk of diesel exhaust. For example, a number of organizations, including the U.S. Environmental Protection Agency (EPA)*, the State of California EPA, and the World Health Organization, are currently evaluating the potential for diesel exhaust to cause cancer. These evaluations or risk assessments will have a direct impact on regulations for diesel engines and diesel fuel, and therefore will have far-reaching economic and societal impacts. The best policy choices are those based on sound scientific information. The HEI Diesel Working Group thought that the issues discussed in this report warranted consideration when conducting risk assessments of diesel exhaust and reporting the results to the public.

ORGANIZATION OF THIS REPORT

This report has two parts. Part II contains four background papers that address emissions and exposure issues and five background papers that consider biological responses to diesel engine emissions. Part I presents consensus views of the HEI Diesel Working Group; it

- summarizes and synthesizes the key conclusions of background papers,
- places the conclusions into the larger context of recent developments in the areas of carcinogenesis and risk assessment, and

- discusses critical issues that impact evaluations of the carcinogenicity of diesel exhaust.

Table 1. Critical Issues in Assessing the Carcinogenicity of Diesel Exhaust

Hazard Identification

Issue 1. *What impact have changes in engine and control technologies had on the characteristics of diesel engine emissions and, thus, human exposure to them?*

Issue 2. *How do atmospheric changes in diesel exhaust constituents influence the potential human health effects of diesel emissions?*

Issue 3. *What does the current epidemiologic evidence indicate about diesel emissions and cancer?*

Issue 4. *What is the significance of the in vitro mutagenicity of diesel exhaust with respect to carcinogenic risk in humans from in vivo exposures?*

Issue 5. *How strong is the evidence that diesel exhaust is carcinogenic in laboratory animals?*

Issue 6. *What components of diesel emissions cause lung cancer in laboratory rats?*

Issue 7. *How do diesel emissions induce lung tumors in laboratory rats?*

Dose-Response Assessment

Issue 8. *Which species should be used to calculate cancer risk factors for diesel exhaust?*

Issue 9. *In what ways do the rat lung tumors induced by diesel emissions resemble human lung tumors?*

Issue 10. *What factors need to be considered when extrapolating the rat lung tumor data to humans?*

Issue 11. *How can information about mechanisms of action guide the selection of scaling factors, dosimetry models, and extrapolation models for dose-response assessments of diesel emissions?*

Exposure Assessment

Issue 12. *What do we know about human exposure to diesel exhaust in occupational and ambient settings?*

Issue 13. *What do we know about the size and characteristics of the populations exposed to diesel emissions?*

Risk Characterization

Issue 14. *Considering the currently available data for diesel emissions, how can we best characterize the human cancer risk associated with exposure to diesel exhaust?*

* A list of abbreviations appears at the end of this paper.

Part I is organized according to the four steps in the risk assessment process (hazard identification, dose-response assessment, exposure assessment, and risk characterization) proposed by the National Research Council (1983, 1994). For each step, we discuss critical issues relevant to evaluating the carcinogenicity of diesel emissions and offer conclusions based on our current understanding of the available scientific information as documented in Part II. The Diesel Working Group did not conduct a quantitative risk assessment; however, in the Risk Characterization section of this chapter, the Working Group integrates information on emissions and exposure with the toxicologic and epidemiologic data to make some judgments about the carcinogenic risks associated with different levels of exposure to diesel emissions.

HISTORICAL PERSPECTIVE

One of the first reports of the carcinogenic potential of diesel emissions came from a series of investigations of hydrocarbon pollution in the Los Angeles area in the early 1950s. Kotin and coworkers (1955) demonstrated that skin papillomas and cancers developed when acetone extracts of the particulate matter found in diesel engine emissions were painted onto the skin of mice. These findings did not receive much attention, however. Only in the late 1970s, when domestic and foreign motor vehicle manufacturers announced that they would be introducing diesel-powered passenger cars into the United States, did the research and regulatory communities become concerned about the carcinogenic potential of diesel exhaust.

RESEARCH APPROACHES

At about this time, Ames and colleagues (1975) introduced the *Salmonella typhimurium* assay—a short-term bacterial mutagenicity assay—that was quickly adopted by scientists as a tool to predict carcinogenicity. Using this assay, researchers reported that organic solvent extracts of diesel exhaust particulate matter produced mutations in bacteria (Huisingh et al. 1978; Wang et al. 1978). This finding was a turning point on three fronts:

- First, government agencies and diesel engine manufacturers launched multimillion-dollar research programs to study diesel exhaust.
- Second, industry committed substantial resources to improve diesel engine technology, with the goal of reducing emissions of particulate matter and oxides of nitrogen.

- Third, the EPA proposed the first diesel emissions particulate standards for cars and light-duty trucks.¹

During the 1980s, scientists made substantial progress in identifying the potentially hazardous constituents of diesel exhaust. Using a method called bioassay-directed fractionation, which combines analytical chemistry techniques and mutagenicity bioassays, researchers identified hundreds of chemicals in diesel exhaust, including many known mutagens and carcinogens. Of these, polycyclic aromatic hydrocarbons (PAHs) and their nitro-derivatives (nitro-PAHs) attracted particular attention because they are among the most potent mutagens and carcinogens (International Agency for Research on Cancer 1989).

Two other developments also had an impact on scientists' thinking about the potential carcinogenicity of diesel exhaust. The first was the evolution of formal risk assessment procedures for estimating the human risk of exposure to environmental pollutants. The second was basic research on the molecular mechanisms of carcinogenesis that led to the conceptual paradigm of carcinogenesis as a multistage process controlled by multiple genes and gene products. Recently, some scientists have put forth the theory that, although some carcinogens act directly on these genes, others appear to exert their effect indirectly through processes that involve cytotoxicity and cell proliferation. The latter mechanism has important implications for risk assessment because it suggests that some carcinogens may have thresholds; in other words, they may not pose significant cancer risks at doses below the levels needed to cause cell proliferation or cytotoxicity.

In 1981, when the EPA convened a public meeting to review research on the toxicologic effects of emissions from diesel engines, the participants focused on the effects of diesel exhaust constituents in short-term carcinogenesis assays and in vitro mutagenicity studies (Lewtas 1982). The paradigm that guided most of the research at that time was that diesel emissions were a carcinogenic hazard because they contained potent mutagens and carcinogens adsorbed onto the surfaces of particles. These particles were in a size range that allowed them to be inhaled into the deep regions of the lungs, bringing the adsorbed chemicals into close contact with the respiratory epithelium, where they could interact with DNA and initiate carcinogenesis. Scientists were uncertain, however, whether the organic compounds were actually bioavailable; that is, under physiological conditions, would sufficient amounts of the carcinogens be desorbed from the particles and activated to chemical spe-

¹ Regulations for heavy-duty vehicles lagged behind those for light-duty engines, but were implemented in the late 1980s. Recently, some nonroad vehicles such as agricultural and construction equipment have come under the regulatory umbrella (see Box 2), and new regulations have been directed at the composition of diesel fuels.

cies that would react with DNA. Studies of the organic chemical constituents of diesel exhaust particulate matter dominated research on diesel emissions until recently, when attention shifted to the particle itself.

Epidemiologic studies generally provide the strongest evidence about the presence or absence of a relation between exposure to environmental substances and the risk of human disease. Only recently have epidemiologists had a sufficient number of subjects to examine the prevalence of cancer in populations exposed to diesel emissions; diesel engines were not introduced into many industries until the middle part of the century (Figure 1), and any cancers resulting from these exposures would have taken many years to develop. Prior to 1980, only two studies of workers exposed to diesel exhaust had been published, prompting a National Research Council panel to conclude that the available data did not indicate an excess risk of cancer in the population groups studied (National Research Council 1981). During the 1980s, a number of epidemiologic studies were published indicating a small increase in the risk of developing lung cancer in workers classified as having been exposed to diesel exhaust. These findings were interpreted cautiously because of inevitable limitations in study design and because, even in the best studies, exposure to diesel exhaust had not been documented.

Over the last decade, a number of expert groups and individuals have reviewed the information from epidemiologic studies of diesel emissions (National Research Council 1981; McClellan 1986; National Institute for Occupational Safety and Health 1988; International Agency for Research on Cancer 1989; U.S. Environmental Protection Agency 1990, 1994b; Mauderly 1992; California Environmental Protection Agency 1994; Cohen and Higgins, this report). Not surprisingly, the scientists' views of the strength of the evidence for a causal relationship between exposure to diesel exhaust and lung cancer differ, and have changed as the results from multiple studies involving different populations and using different investigative approaches have been published.

Animal bioassays conducted in the 1980s by groups in the United States, Europe, and Japan provided information about the effects of well-defined exposures to diesel exhaust in the absence of confounding factors (reviewed by Mauderly 1992; Busby and Newberne, this report). Considering the differences among laboratories in the animal strains and exposure regimens used, the results were quite consistent: diesel exhaust, when inhaled at high concentrations for prolonged periods of time (24 months or longer), produced lung tumors in rats. Some studies compared whole engine exhaust to filtered exhaust and found no tumorigenic effect from the vapor phase, thus implicating

one or more components of the particulate phase as the causative agents. At that time, the most likely agents were the chemical carcinogens adsorbed onto the particle surfaces. Consequently, most research efforts were directed toward studies of the mutagenicity and metabolism of the PAHs and nitro-PAHs.

When the results of the animal bioassays were first reported, Vostal (1986) pointed out the similarity between the lung tumors induced by diesel exhaust and those caused by titanium dioxide and other particulate materials. He suggested that the tumors produced in rats by exposure to high concentrations of diesel emissions were caused by a non-specific reaction related to an excessive lung burden of particles rather than by the chemical carcinogens. At the same time, Kawabata and colleagues (1986) reported that instillation of either diesel exhaust particles or activated carbon particles (a surrogate for the carbonaceous diesel particles minus the adsorbed organic chemicals) into the lungs of rats produced tumors. The possibility that the diesel particle might be more than a passive carrier of carcinogenic compounds set the stage for the next generation of inhalation bioassays.

Two research groups set out to evaluate the contribution of the particles in diesel exhaust to the rat tumorigenic response. By the early 1990s, preliminary data from both laboratories indicated that, when inhaled at high concentrations for prolonged periods of time, diesel exhaust particulate matter and carbon black were equally carcinogenic in rats (Heinrich et al. 1992; Mauderly et al. 1992). These results were surprising, not only because they implied that under certain conditions a supposedly inert physical agent (carbon black) could produce lung tumors in rats, but also because the carcinogens associated with the diesel exhaust particulate matter did not appear to enhance tumorigenicity.

Scientists have long known that many types of particles, such as silica, asbestos fibers, and coal dust, accumulate in the lungs and can cause respiratory diseases in humans. However, the ability of different types of particles to produce toxic effects is highly variable, and many particles were thought to be relatively inert because they produced no lung damage in short-term studies. During the late 1980s, new studies of inhaled particles were conducted and some of the older literature on inhaled dusts and particles was reexamined. This work showed that even particulate material generally regarded as benign or inert (e.g., titanium dioxide) caused lung inflammation, fibrosis, and sometimes tumors when rats inhaled high concentrations for two or more years (Lee et al. 1985). Morrow (1988, 1992) noted a phenomenon that was common to a number of diverse types of particles; namely, lung clearance mechanisms in the rat were impaired at high exposure rates, leading to a

progressive accumulation of particles—a condition termed "lung overload" or "dust overload"—and damage to the surrounding tissue.

By the early 1990s, a significant paradigm shift had occurred in scientists' views about the carcinogenicity of diesel emissions. No longer was the diesel exhaust particle thought to be simply a carrier of chemical carcinogens. The most reasonable interpretation of the Mauderly and Heinrich studies was that the respirable particulate matter in diesel exhaust was primarily responsible for the development of lung cancer in rats exposed to high concentrations of diesel emissions, and that the mutagenic compounds played a lesser role, if any, in tumor development in this species. The key questions are:

- Can these findings be extrapolated to low doses (where lung clearance is not impaired); and
- Can they be extrapolated to humans?

The answers to these questions have far-reaching implications because they have a direct impact on risk assessments of diesel exhaust and ultimately on federal and state regulations.

RISK ASSESSMENT: AN EVOLVING METHODOLOGY

Risk assessment is a systematic process for evaluating the scientific information on the hazardous properties of a substance, estimating the extent of human exposure to it, and characterizing the resulting risk. The key features, as defined by the National Research Council, are illustrated in Figure 2. They include the following four steps: (1) hazard identification, (2) dose-response assessment, (3) exposure assessment, and (4) risk characterization (National Research Council 1983, 1994). The following four sections of this Summary use the risk assessment model as a frame-

work for discussing the health effects of diesel emissions; readers who are not familiar with risk assessment can find more details on its nature and limitations in Appendix A.

Federal and state agencies charged with protecting public health are required to make judgments, based on the best scientific evidence, about the potential carcinogenic risks of exposure to diesel exhaust and other environmental pollutants. Regulators must then make the best public policy decisions about how to control those risks without increasing other hazards. As noted in Figure 2, the National Research Council made a clear conceptual distinction between risk assessment (the process of evaluating risk) and risk management (integrating risk assessment results with other information to make policy decisions). In response to these regulations, manufacturers and fuel suppliers must make costly technological decisions. Thus, as a key input into risk management, risk assessments for suspected carcinogens can influence the expenditure of billions of dollars by government and industry and impact the life style of average citizens.

In the last decade, the National Research Council risk framework has been widely adopted by regulatory agencies in the United States. During that time, procedures for conducting risk assessments have evolved and become increasingly sophisticated. However, as applied in developing federal and state regulations for hazardous substances, they also have been criticized for being too rigid and unresponsive to new scientific knowledge, and for sometimes failing to capture the uncertainties that are inherent in the process and in the underlying scientific data base. Recently, two committees of the National Research Council (1993, 1994) reviewed risk assessment procedures and the International Agency for Research on Cancer examined how mechanistic information could contribute to the evaluation of cancer risks (Vainio et al. 1992). Neither National Research Council committee advocated a radical departure from current procedures; however, both recognized a need to analyze the assumptions underlying risk assessment procedures and to provide a clear explanation of the uncertainties. The International Agency for Research on Cancer concluded that information on mechanisms of carcinogenesis could be used to either upgrade or downgrade the classification of a suspected carcinogen (Vainio et al. 1992).

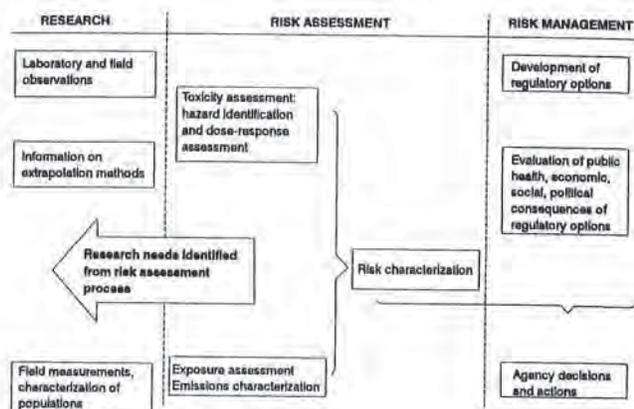


Figure 2. NAS/NRC risk assessment and risk management paradigm. (Reprinted from NRC 1994.)

EVOLUTION OF RISK ASSESSMENTS FOR DIESEL EMISSIONS

Risk assessments for suspected carcinogens are ongoing efforts and depend not only on the available scientific information but also on the judgment of the group making

the classification. Table 2 provides an overview of the carcinogen classifications that have been made for diesel emissions over the last 15 years. (Those designated as "draft" should be considered preliminary judgments that may change before the risk assessment document is formally released.)

The first quantitative estimates of risk from diesel exhaust exposure, some of which were developed before epidemiologic or animal bioassay data were available, used comparative potency methods (Albert et al. 1983; Harris 1983; Cuddihy and McClellan 1983). For example, using the results of *in vitro* and short-term animal bioassays, Albert and colleagues (1983) compared the carcinogenic and mutagenic potencies of the extracts of particle-bound organic compounds collected from diesel emissions with those of other combustion products (coke oven emissions, roofing tar, and cigarette smoke condensate). Epidemiologic data were available for the reference compounds, which had been shown to cause lung cancer in humans. They then combined the potency factors derived from the epidemiologic data and the mutagenicity bioassays to develop estimates of lung cancer risk for diesel exhaust. The early risk estimates calculated using comparative potency methods for a lifetime exposure to $1 \mu\text{g}/\text{m}^3$ of diesel exhaust ranged from 1.8×10^{-6} to 3.5×10^{-5} depending on the engine

and duty cycle used to generate the diesel particulate matter (Albert et al. 1983; Cuddihy and McClellan 1983). The comparative potency method has many limitations. It assumes, for example, that (1) the same factors in the known carcinogenic mixtures and in diesel exhaust cause cancer and (2) short-term tests reflect carcinogenicity both qualitatively and quantitatively. Also, uncertainties about the composition and bioavailability of the different materials, and the potency factors derived from the epidemiologic studies, have not been resolved.

The animal bioassays reported in the mid-1980s provide a better basis for dose-response assessment than the comparative potency method. In fact, at present, the animal bioassay data for diesel emissions are probably better than for most other environmental pollutants. How these data have been used in risk assessments illustrates how research on diesel emissions has impacted the risk assessment process.

In 1990, most scientists thought that the organic constituents in diesel exhaust particulate matter were responsible for the observed carcinogenicity in rats; the Environmental Protection Agency in a draft risk assessment of diesel exhaust, based its risk calculations on benzo[a]pyrene, one of the PAHs in diesel emissions (U.S. Environmental Protection Agency 1990). However, when preliminary data be-

Table 2. Risk Assessments of Diesel Exhaust

Organization and Year ^a	Human Evidence	Animal Evidence	Classification
National Research Council 1981	Not convincingly demonstrated	Negative	—
National Institute for Occupational Safety and Health 1988	Limited	Confirmatory	Potential occupational carcinogen
International Agency for Research on Cancer 1989	Sufficient	Limited	Probable human carcinogen
U.S. Environmental Protection Agency (Draft Risk Assessment) 1990	Limited	Sufficient	Probable human carcinogen
U.S. Environmental Protection Agency (Draft Risk Assessment) 1994b	Limited	Sufficient	Probable human carcinogen
California Environmental Protection Agency (Draft Risk Assessment) 1994	Sufficient	Sufficient	Human carcinogen

^aAssessments noted as "draft" include preliminary judgments of classifications that may change before the document is officially released.

came available showing that carbon black and diesel exhaust particulate matter were equally effective in inducing lung tumors in rats (Heinrich et al. 1992; Mauderly et al. 1992), the EPA abandoned this approach in favor of using the nonorganic carbonaceous particle core as the basis of potency factor calculations. The recent draft risk assessments for diesel exhaust, which are now under review, use either the cumulative exposure to diesel exhaust particulate matter (California Environmental Protection Agency 1994), the mass of elemental carbon in the lungs (California Environmental Protection Agency 1994), or the particle concentration per unit of lung surface area (U.S. Environmental Protection Agency 1994b) as comparative dose terms when extrapolating from animals to humans.

The unit risk estimates for diesel exhaust that have been made on the basis of the same animal bioassays vary considerably—by as much as two orders of magnitude—depending on the assumptions made about the exposure term and the extrapolation models selected. This variability is illustrated in the figure prepared by the State of California EPA (Figure 3). Risk estimates based on an epidemiologic study of railroad workers vary by more than one order of magnitude; although they are within the range of the animal-based risk estimates, they tend to be higher (California Environmental Protection Agency 1994).

Assessing the cancer risk of diesel emissions is a dynamic process that likely will evolve for some time as research provides new data and new perspectives on existing data. The following four sections provide an analysis, based on current knowledge, of key critical issues associated with hazard identification, dose-response assessment, exposure assessment, and risk characterization.

CRITICAL ISSUES IN IDENTIFYING THE POTENTIAL CARCINOGENIC HAZARDS OF EXPOSURE TO DIESEL EXHAUST

Hazard identification, the first step in the risk assessment process, is a qualitative evaluation of what is known about the adverse health effects of a substance in animals and humans. Four types of research provide information for identifying the potential hazards of exposure to diesel emissions: physicochemical characterization of emissions, epidemiologic studies of exposures and health effects in human populations, toxicologic research on dose-response relations, and basic biological research on mechanisms of activity that help link the animal and human data. The Diesel Working Group considered the following critical issues related to the hazard identification step of health risk assessments of diesel exhaust:

- the changing nature of diesel engine emissions,
- atmospheric transformation of diesel exhaust constituents,
- epidemiologic data,
- in vitro mutagenicity data,
- animal bioassay data, and
- mechanisms of lung carcinogenesis.

The major findings of the group, based on its literature review (Part II of this report), are summarized below.

ISSUE 1: *What impact have changes in engine and control technologies had on the characteristics of diesel engine emissions and, thus, on human exposure to them?*

CHARACTERISTICS OF DIESEL EMISSIONS

Characterizing diesel emissions for risk assessment purposes is complicated by a lack of data on heavy-duty engines, which are the primary users of diesel fuel. The extensive analytical work that was conducted in the 1970s and 1980s focused on light-duty vehicles. Comparing heavy-duty and light-duty emissions data is difficult because of differences in the test procedures for the two types of engines and differences in how the emissions data are expressed. In this report, Sawyer and Johnson summarize the results of characterization work on diesel emissions conducted from the 1970s through the 1990s; they also review the control technology developed or under consideration to meet new emissions standards (see Boxes 1 and 2, and Sawyer and Johnson, this report). Additional information on characterization of diesel emissions can be found in reviews by the International Agency for Research on Cancer (1989), Volkswagen (1989), and Scheepers and Bos (1992), and in a paper by Gallagher and coworkers (1994).

Diesel emissions, which are derived from the complete and incomplete combustion of fuel and lubricating oil, are a complex mixture of relatively low-molecular-weight gases and carbonaceous particles to which higher-molecular-weight organic compounds are adsorbed. Both the gaseous and the particulate phases of diesel engine exhaust contain components that are of public health concern. Figure 4 lists the major constituents of diesel emissions, their atmospheric reaction products, and potential biological impacts.

The vapor phase of diesel exhaust contains typical combustion gases (e.g., carbon monoxide, sulfur dioxide, and oxides of nitrogen) and low-molecular-weight hydrocarbons; the latter include aldehydes, organic acids, monocyclic aromatic compounds, and some PAHs and their

derivatives. Emissions of carbon monoxide and hydrocarbons from diesel engines are generally comparable with or slightly lower than those from gasoline engines. Carbon dioxide emissions are approximately 10% to 25% lower; emissions of oxides of nitrogen, however, are higher.

The particle phase of diesel emissions consists of aggregates of spherical carbonaceous particles (about 0.2 μm in mass median aerodynamic diameter), to which significant amounts of higher-molecular-weight organic compounds become adsorbed as the hot engine exhaust is cooled to ambient temperature (Figure 5). The particles in diesel emissions are unique because they have large surface areas that allow for adsorption of organic compounds. Typically, 10% to 40% of the diesel particle mass consists of organic chemicals. These include high-molecular-weight hydrocarbons, most notably the PAHs and their derivatives. The particulate matter also contains a sulfate component, which is largely in the form of sulfuric acid. The sulfate level varies with the sulfur content of fuel. In this paper, the term

diesel exhaust particulate matter refers to the solid elemental carbon particles plus the adsorbed organic and inorganic chemicals.

A recent finding of elevated levels of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans in a Norwegian traffic tunnel has raised concerns that heavy-duty diesel engines may be contributors to nationwide ambient dioxin levels (Oehme et al. 1991; Jones 1993). Efforts to obtain dioxin emissions data are now under way. At present, the data are inadequate to assess whether diesel engine emissions play a role in the public's exposure to dioxin.

IMPACT OF CHANGES IN DIESEL ENGINE DESIGN ON EMISSIONS

As engine manufacturers have responded to increasingly stringent federal and state regulations with improved en-

Box 1

CONTROLLING DIESEL ENGINE EMISSIONS

Engine Technology

Early diesel engines were designed for optimum fuel economy and performance. However, over the last decade, engine manufacturers have substantially reduced gaseous and particulate matter emissions without decreasing performance in response to increasingly stringent emissions standards (see Sawyer and Johnson, this report; Hammerle et al. 1994b). First, they improved the engine itself by modifying the fuel injection system (so that the fuel would be more completely burned), the combustion chamber, and engine controls. When research showed that much of the diesel exhaust particulate matter consisted of oil-derived hydrocarbons, manufacturers modified the engine seals and rings, which greatly reduced the oil contribution to particulate matter. Electronic control systems added in the late 1980s allowed more precise control of fuel injection.

Exhaust Treatment and Fuel Modification

Industry researchers are exploring two other approaches to reducing emissions to meet the increasingly stringent standards for heavy-duty diesel engines: exhaust-treatment devices (e.g., catalysts and particle traps) and fuel modifications. The petroleum industry has already developed fuel additives that improve engine performance. Engine designers are interested in lowering the sulfur content of diesel fuel because sulfur combustion produces sulfates that contribute to the mass of the particulate matter in diesel emissions and interfere with the function of the catalysts. As of 1993, sulfur levels for diesel fuel used in on-highway applications were limited to 0.05% by weight. The low-sulfur fuel required by the 1993 regulations has resulted in substantial reductions in sulfur emissions and made the use of oxidation catalytic converters feasible in 1994 medium-duty trucks. Several metal-based fuel additives have been shown to reduce emissions of particulate matter; however, none has been approved for use because of concerns about the production of metallic aerosols. Alternative fuels, such as natural gas, methanol, and dimethyl ether, are being investigated for diesel engines and their use could further reduce diesel engine particulate matter emissions.

Box 2**FEDERAL REGULATIONS FOR DIESEL ENGINE EMISSIONS**

The Clean Air Act authorizes the EPA to regulate emissions from all types of motor vehicles, including diesel-powered vehicles. It also allows the State of California to establish more stringent diesel fuel quality and vehicle emissions standards in order to achieve federal ambient air quality standards in that state.

Diesel Light-Duty Vehicles and Trucks

In the United States, diesel light-duty vehicles and trucks account for only 0.1% of passenger car and 2% of truck sales. Between 1970 and 1991, the hydrocarbon, carbon monoxide, and oxides of nitrogen standards for diesel light-duty passenger cars were identical to those for gasoline-powered vehicles. Now there are separate emissions standards for oxides of nitrogen and a particulate matter standard for diesel-powered light-duty vehicles. After the 1990 Amendments to the Clean Air Act, the EPA promulgated separate emissions standards (total hydrocarbons, nonmethane hydrocarbons, carbon monoxide, oxides of nitrogen, and particulate matter) for diesel-powered light-duty vehicles and trucks. These standards, which take the form of grams of pollutant per mile traveled, are being phased in from 1994 through 1997.

Diesel Heavy-Duty Vehicles

Emissions standards for heavy-duty diesel engines have lagged behind those for light-duty vehicles and trucks. Between 1974 and 1985, the EPA required manufacturers of heavy-duty diesel engines used in motor vehicles to meet a combined standard for hydrocarbons and oxides of nitrogen and a separate standard for carbon monoxide. Beginning in 1985, the EPA established separate standards for hydrocarbons and oxides of nitrogen. It was not until 1988 that manufacturers of heavy-duty vehicles had to meet a particulate matter standard. Since 1988, the federal particulate matter standard has been dropped from 0.60 g/bhp-hr to the 1994 level of 0.1 g/bhp-hr; the particulate matter standard for bus engines will be reduced further in 1996. The federal standards for hydrocarbons and carbon monoxide (1.3 and 15.5 g/bhp-hr, respectively) have not changed since 1985.

Table 2.1. Federal Emissions Standards for Oxides of Nitrogen and Particulate Matter for Vehicles Powered by Heavy-Duty Diesel Engines

Engine Year	Oxides of Nitrogen (g/bhp-hr)	Particulate Matter ^a (g/bhp-hr)	
	Truck and Bus	Truck	Bus
1985	10.7	NA	NA
1988	10.7	0.6	0.6
1990	6.0	0.6	0.6
1991	5.0	0.25	0.25
1993	5.0	0.25	0.10
1994	5.0	0.10	0.07
1996	5.0	0.10	0.05
1998	4.0	0.10	(0.07 in use) 0.05/0.07

^a NA = no federal standards were applied during this period.

Diesel Nonroad Vehicles

In 1994, the EPA promulgated emissions standards for diesel nonroad vehicles. These include construction and agricultural equipment, and auxiliary engines that power equipment transported by any means. Engines used in mines, aircraft, locomotives, and marine vessels were excluded.

Diesel Fuel

The formulation of diesel fuel impacts emissions. In 1993, federal regulations went into effect limiting the sulfur content of diesel fuel to no more than 0.05% by weight, and the content of aromatic hydrocarbons to no more than 35% by volume.

gine design, better emissions control technology, and new fuels, the levels of solid carbonaceous particles, associated organic compounds, and the sulfates in diesel emissions have substantially decreased (Figure 6). As a result, new

heavy-duty diesel engines emit approximately 90% less particulate matter than old uncontrolled diesel engines, and most manufacturers were able to meet the 1991 federal emissions standards for particulate matter. (Further details

Emission Component	Atmospheric Reaction Products	Biological Impact ^a
A. Vapor-Phase Emissions		
Carbon dioxide	—	Major contributor to global warming.
Carbon monoxide	—	Highly toxic to humans; blocks oxygen uptake.
Oxides of nitrogen	Nitric acid, ozone	Nitrogen dioxide is a respiratory tract irritant and major ozone precursor. Nitric acid contributes to acid rain.
Sulfur dioxide	Sulfuric acid	Respiratory tract irritation. Contributor to acid rain.
Hydrocarbons		
Alkanes ($\leq C_{18}$)	Aldehydes, alkyl nitrates, ketones	Respiratory tract irritation. Reaction products are ozone precursors (in the presence of NO_x).
Alkenes ($\leq C_4$) (e.g., 1,3-butadiene)	Aldehydes, ketones	Respiratory tract irritation. Some alkenes are mutagenic and carcinogenic. Reaction products are ozone precursors (in the presence of NO_x).
Aldehydes		
Formaldehyde	Carbon monoxide, hydroperoxyl radicals	Formaldehyde is a probable human carcinogen and an ozone precursor (in the presence of NO_x).
Higher aldehydes (e.g., acrolein)	Peroxyacyl nitrates	Respiratory tract and eye irritation; causes plant damage.
Monocyclic aromatic compounds (e.g., benzene, toluene)	Hydroxylated and hydroxylated-nitro derivatives ^b	Benzene is toxic and carcinogenic in humans. Some reaction products are mutagenic in bacteria (Ames assay).
PAHs (≤ 4 rings) ^c (e.g., phenanthrene, fluoranthene)	Nitro-PAHs (≤ 4 rings) ^d	Some of these PAHs and nitro-PAHs are known mutagens and carcinogens.
Nitro-PAHs (2 and 3 rings) (e.g., nitronaphthalenes)	Quinones and hydroxylated-nitro derivatives	Some reaction products are mutagenic in bacteria (Ames assay).
B. Particle-Phase Emissions		
Elemental carbon	—	Nuclei adsorb organic compounds; size permits transport deep into the lungs (alveoli).
Inorganic sulfate	—	Respiratory tract irritation.
Hydrocarbons (C_{14} - C_{35})	Little information; possibly aldehydes, ketones, and alkyl nitrates	Unknown
PAHs (≥ 4 rings) (e.g., pyrene, benzo[a]pyrene)	Nitro-PAHs (≥ 4 rings) ^d Nitro-PAH lactones	Larger PAHs are major contributors of carcinogens in combustion emissions. Many nitro-PAHs are potent mutagens and carcinogens.
Nitro-PAHs (≥ 3 rings) (e.g., nitropyrenes)	Hydroxylated-nitro derivatives	Many nitro-PAHs are potent mutagens and carcinogens. Some reaction products are mutagenic in bacteria (Ames assay).

^a Unless otherwise stated, the impact results from both the emissions components and the atmospheric reaction products.

^b Some reaction products expected to partition into the particle phase.

^c PAHs containing 4 rings are usually present in both the vapor and particle phases.

^d Nitro-PAHs with more than 2 rings will partition into the particle phase.

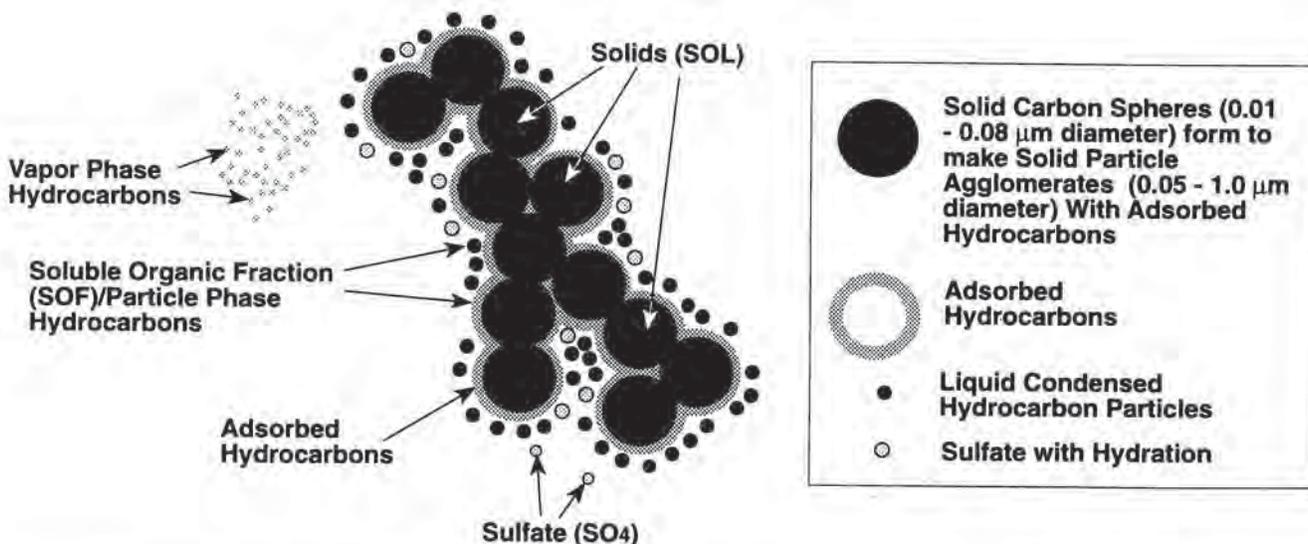


Figure 5. Schematic drawing of diesel particles and vapor-phase compounds. (Sawyer and Johnson, this report.)

on historical trends of particulate and gaseous emissions for different types of heavy-duty diesel engines can be found in Tables 3 through 8 of the background paper by Sawyer and Johnson.) A recent European study indicated that some emissions (hydrocarbons, carbon monoxide, carbon dioxide, methane, nonmethane organic gases, benzene, and 1,3-butadiene) from current light-duty diesel passenger vehicles are lower than those from gasoline cars, although other emissions (oxides of nitrogen, particulate matter, formaldehyde, and acetaldehyde) are higher (Hammerle et al. 1994a). Only limited information is available on the composition of emissions emitted from either heavy-duty or light-duty diesel engines operating under real-world conditions.

TRADE-OFF BETWEEN PARTICLES AND OXIDES OF NITROGEN

One of the problems with controlling diesel emissions is the tradeoff between emissions of particulate matter and emissions of oxides of nitrogen. The particulate matter forms as a result of incomplete combustion, a problem unique to diesel engines because the fuel and air are not thoroughly mixed before they start burning. The oxides of nitrogen form when nitrogen in the air is oxidized at the high temperatures in diesel engines. Generally speaking, the control strategies that decrease particulate matter and hydrocarbon emissions (higher combustion temperature and increased injection pressure) increase emissions of oxides of nitrogen; lowering the combustion temperature reduces oxides of nitrogen, but increases particulate matter and hydrocarbon emissions, and decreases fuel economy.

CONCLUSIONS

- The composition of diesel exhaust varies considerably and depends on engine type, fuel, engine operating conditions, type of lubricating oil, and the emission control system.

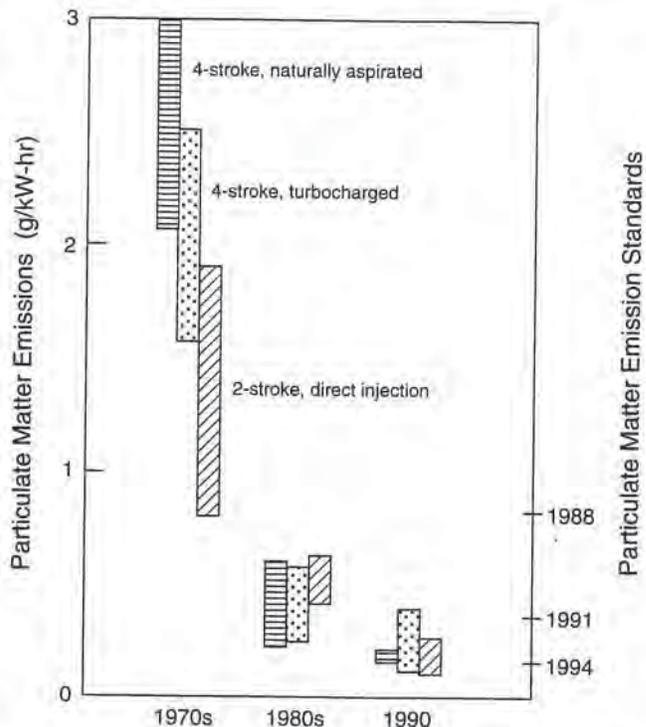


Figure 6. Range of heavy-duty diesel engine particulate emissions for the period 1970 through 1994. (Sawyer and Johnson, this report.)

- Diesel emissions have changed dramatically over the last 30 years. Emissions of oxides of nitrogen, and particulate matter from new diesel engines decreased significantly during the past decade and future reductions are expected.
- Future human exposure to diesel engine emissions will be less than past and current exposures. However, this reduction will be gradual because of the long life of heavy-duty diesel engines, and will be offset as the use of diesel engines grows.
- The fact that the physical and chemical characteristics of diesel emissions will change as new technology and fuels are implemented cautions against automatically assuming that a decrease in the amount of emissions will result in a decrease in risk.
- The currently available analyses of diesel engine exhaust do not adequately characterize historical emissions, nor can they be used reliably to project future emission profiles. Because of expected changes in engine technology and fuel composition, continued characterization of the gaseous and particulate constituents of diesel emissions is necessary to assess human exposures adequately.
- Future diesel engine emissions will be shaped by a dynamic interaction involving the requirements of health-based regulations (to control both oxides of nitrogen and particulate matter), changes in engine technology and diesel fuel formulation, and the inherent trade-off of controlling particles versus oxides of nitrogen.

ISSUE 2: *How do atmospheric changes in diesel exhaust constituents influence the potential human health effects of diesel emissions?*

Ambient air contains diesel emission constituents and additional chemical species produced by physical and chemical reactions with atmospheric components, including sunlight, ozone, hydroxyl radicals, and nitrate radicals. These reactions may increase the toxic and carcinogenic activity of certain constituents of diesel emissions and alter their residence time in ambient air (Winer and Busby, this report). For example, in the atmosphere, PAHs react with hydroxyl radicals (in the presence of oxides of nitrogen), to form secondary nitro-PAHs and oxygenated nitro-PAHs. The nitro-PAHs are often more mutagenic and carcinogenic than the original PAHs, and transformation products would be more water-soluble than the parent molecules. This could translate into greater bioavailability. As much as 30% of the mutagenicity of ambient particles appears to be due to the atmospheric transformation products of PAHs. Thus,

health risk assessments for diesel emissions should account for both the primary pollutants present in diesel emissions and the secondary pollutants produced by atmospheric transformation.

CONCLUSION

- A comprehensive characterization of diesel exhaust needs to consider that diesel emissions undergo atmospheric transport and transformation processes that alter the toxic, mutagenic, and carcinogenic properties of the original emission constituents, creating new products that may be more or less hazardous than the original emissions.

ISSUE 3: *What does current epidemiologic evidence indicate about diesel emissions and cancer?*

Epidemiologic studies that offer definitive data can provide the most relevant information for hazard identification because they study effects in humans rather than laboratory animals. However, the observational, and often retrospective, nature of these studies imposes limitations on the quality of the data, especially information on exposure to the pollutant of interest and other potential confounders. As of 1995, no prospective epidemiologic study of populations exposed to diesel exhaust have been conducted. As summarized below, numerous retrospective studies of the relation of lung cancer to occupational exposure to diesel exhaust have been conducted and their interpretation is limited to varying degrees by the problems just noted. Nevertheless, careful review of these studies can yield insights into whether diesel exhaust is a human carcinogen (see Cohen and Higgins, this report).

OCCUPATIONAL STUDIES

Epidemiologic studies have focused exclusively on male workers exposed to diesel emissions after 1950, when the railroad, trucking, and public mass transit industries widely converted to diesel engines (Figure 1). Two types of studies have been conducted: (1) studies of occupational cohorts exposed to relatively high concentrations of diesel emissions, and (2) studies that used interviews or questionnaires to identify individuals from the general population who had received occupational exposures to diesel exhaust. The occupational cohorts studied most extensively include railroad, dock, trucking industry, and bus garage workers. Underground miners are also exposed to diesel exhaust; however, they have not generally been targeted for epidemiologic studies of diesel emissions because they are often exposed to other pollutants such as radon progeny,

asbestos, dusts, and metals. No data are available on the effects of diesel exhaust exposures on women, children, or individuals with cardiovascular or respiratory disorders.

The results of the occupational cohort and case-control studies of diesel exhaust, especially those published in the last 15 years, are generally consistent in showing a weak association between exposure to diesel exhaust and lung cancer. They suggest that prolonged exposure to diesel exhaust over many years is associated with a 1.2 to 1.5 times increase in the relative risk of lung cancer incidence or mortality in male workers. Figures 7 and 8 summarize the relative risks and confidence intervals for railroad workers and truckers respectively. In all studies, the incidence rate for lung cancer was higher in workers classified as "exposed to diesel exhaust" than in workers classified as "unexposed." However, as illustrated in Figures 7 and 8, the increase in the relative risk of lung cancer was generally small and many of the measurements were imprecise; thus, the results of most of the studies were not statistically significant. However, the results of the more robustly designed studies were statistically significant, which increases confidence in interpreting the positive lung cancer data in occupational cohorts. Moreover, in some studies, the largest relative risks were seen in the categories expected to have the greatest cumulative exposure to diesel exhaust (Garshick et al. 1987, 1988; Gustavsson et al. 1990; Steenland et al. 1992; Emmelin et al. 1993). The general population studies also indicate small elevations in lung cancer rates among workers in similar occupational groups such as truckers, railroad workers, mechanics, and dock workers; however, these estimates are based on small numbers of exposed subjects.

In addition to lung cancer, some epidemiologic studies suggest that an elevated risk of bladder cancer may be linked to diesel exhaust exposure in occupational settings. The evidence for bladder cancer, however, is not as consistent as that for lung cancer. Cohort studies suggest that diesel exhaust exposures create little or no increase in bladder cancer risk in railroad workers; in contrast, the general population studies generally show a small increased risk of bladder cancer in workers exposed to diesel exhaust, especially in truck drivers. Silverman and coworkers (1986) proposed that urinary stasis, which prolongs exposure of the bladder mucosa to mutagenic metabolites of the organic constituents of diesel exhaust and is common among professional truck drivers, could be a factor contributing to the observed elevation in bladder cancer risk in this population.

Some epidemiologic studies of diesel emissions have compared disease rates in exposed workers with those in national or regional populations. Estimates of relative risk in these studies might reflect differences associated with socioeconomic circumstances (including smoking habits)

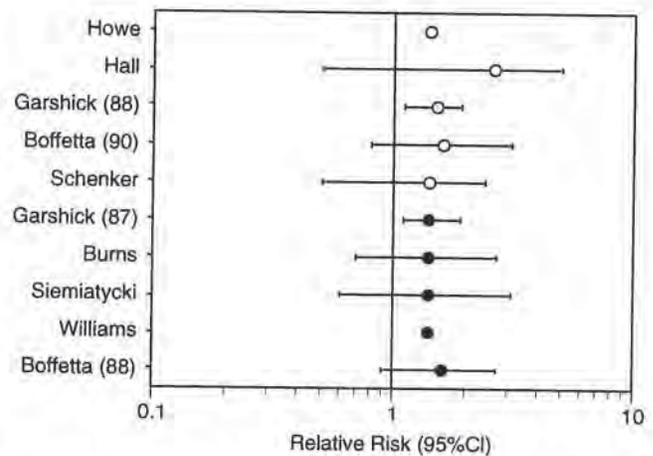


Figure 7. Lung cancer and exposure to diesel exhaust in railroad workers. ● = Relative risk adjusted for cigarette smoking; ○ = relative risk not adjusted for cigarette smoking. For the two studies by Howe and Williams, confidence intervals were not reported and could not be calculated. (Cohen and Higgins, this report.)

as well as differences related to exposure to diesel exhaust, or they might be influenced by the fact that workers in some occupations have a lower mortality rate than the general population (i.e., the healthy worker effect).

LIMITATIONS

The epidemiologic studies of diesel exhaust have been criticized on two fronts. First, many of the studies did not control for confounding factors, such as cigarette smoking, environmental tobacco smoke, nondiesel particulate matter, diet, socioeconomic factors, or exposures to other air

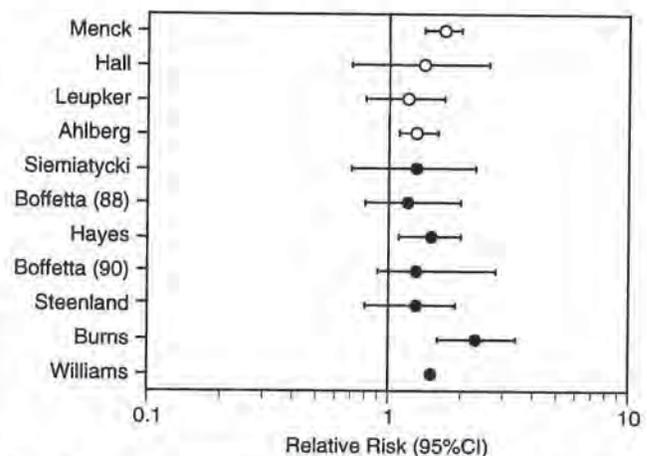


Figure 8. Lung cancer and exposure to diesel exhaust in truck drivers. ● = Relative risk adjusted for cigarette smoking; ○ = Relative risk not adjusted for cigarette smoking. For the study by Williams, confidence intervals were not reported and could not be calculated. For the Steenland study, the data were gathered from union reports of long-haul truck drivers; for the Boffetta (1988) study, the data were self-reported by diesel truck drivers; and for the Siemiatycki study, they were self-reported by heavy-duty truck drivers (personal communication). (Cohen and Higgins, this report.)

pollutants. Controlling for such factors is a common methodologic challenge for epidemiologists. Cigarette smoking is a particular problem because it is the dominant cause of lung cancer, and failure to control for its effects can seriously compromise any epidemiologic study of lung cancer risks. An analysis by Cohen and Higgins (Part II of this report) indicates that controlling for smoking, which reduces the relative risks in some studies, could not fully explain the associations between exposure to diesel exhaust and lung cancer. Also, when Cohen and Higgins estimated the impact of hypothetical differences in cigarette smoking prevalence on the lung cancer rates observed in two studies of emissions that did not control for smoking, their estimate supports the idea that cigarette smoking cannot fully explain the observed increases in lung cancer in railroad workers (Garshick et al. 1987) or bus garage workers (Gustavsson et al. 1990).

Only a few epidemiologic studies considered other potential confounders such as asbestos exposure, environmental tobacco smoke, diet, and socioeconomic factors. No study has addressed possible confounding due to exposure to nondiesel particles, which are possibly important in light of the recent animal studies that demonstrate that, at high concentrations, many poorly soluble particles cause lung tumors in rats (discussed under Issue 5).

The second criticism of the epidemiologic studies of diesel exhaust is that none included measurements of any constituent of diesel emissions during the time the study population was actually exposed. Instead, exposure classification was based on self-reported work histories or company records and on the investigators' or the industrial hygienists' opinions about whether the reported job or occupation entailed exposure to diesel exhaust. Although these approaches are probably sensitive to diesel exhaust exposure (i.e., they tend to identify most truly exposed subjects), they are not specific (i.e., they tend to classify some unexposed subjects as exposed). Misclassification of exposures can cause spurious increases or decreases in estimates of effects depending on whether the misclassification differs between subjects with and without disease.

Another complicating factor is that the diesel exhaust to which the populations were actually exposed was never characterized. This information gap cannot be filled by using later characterizations of diesel exhaust because the characteristics of emissions depend greatly on factors such as the type of engine, how it is operated, and the specific fuel used. For example, diesel fuel for locomotives has a higher content of aromatic hydrocarbons than the diesel fuel used in truck engines (see Sawyer and Johnson, this report). Therefore, the PAH content of locomotive exhaust is probably higher than that of exhaust from trucks and other diesel engines that use conventional fuels—a factor that needs to be considered if data obtained in railroad

worker studies are extrapolated to the general population. Furthermore, both the particulate and the PAH content of diesel emissions have decreased dramatically over the last two decades (Figure 6). Therefore, large uncertainties are associated with applying emissions or exposure data from one type of engine during a specific time period to risk assessments for other populations and time periods. These uncertainties limit the use of the epidemiologic data for quantitative risk assessments.

To reach the conclusions listed below, the Diesel Working Group evaluated the available epidemiologic evidence for diesel exhaust exposure and considered the classic criteria for causality; the consistency of the responses, the strength of the statistical association, the relation (if any) between the amount of exposure and the incidence of cancer, and the absence of other causative factors. Biological plausibility is addressed in the section on Risk Characterization.

CONCLUSIONS

- The epidemiological data show that long-term exposure to diesel exhaust in a variety of occupational circumstances is associated with small increases (in the 1.2- to 1.5-fold range) in the relative risk of lung cancer occurrence, or mortality, or both. The epidemiologic studies are consistent in showing weak associations between exposure to diesel exhaust and lung cancer, but vary in the strength of the statistical association; only a few studies showed elevated relative risks that were statistically significant.
- The absence of exposure measurements in the study populations is the main methodologic problem limiting interpretation of the epidemiologic data and its use in quantitative risk assessments. None of the published studies measured actual levels of exposure to diesel exhaust or characterized the actual emissions from the exposure source.
- The issue of confounding is difficult to address. Cigarette smoke, is a major potential confounder in lung cancer studies. Most studies that controlled for cigarette smoking found that the association of lung cancer with exposure to diesel exhaust persisted after such controls were applied, although in some cases, the excess risk was lower. Only a few epidemiologic studies considered other potential confounders such as nondiesel particles, environmental tobacco smoke, asbestos exposure, diet, and socioeconomic factors. At present there is insufficient evidence to conclude whether confounding by these factors influenced the results.
- The above conclusions are based on studies of male workers. None of the thirty or more epidemiologic studies conducted to date examined the risk of diesel

exhaust exposure for women or potentially susceptible populations such as infants, children, or people with health disorders.

ISSUE 4: What is the significance of the *in vitro* mutagenicity of diesel exhaust with respect to carcinogenic risk in humans from *in vivo* exposures?

A wealth of data from different short-term *in vitro* and *in vivo* test systems demonstrate that whole diesel engine exhaust, the particulate matter in diesel emissions, and organic solvent extracts of the particulate matter are mutagenic. Some studies also indicate that diesel exhaust constituents cause chromosomal damage and neoplastic cell transformation. The results of these assays are reviewed by Shirnamé-Moré in this report, and are summarized in Table 3. Although these results provide convincing evidence of the mutagenic potential of diesel exhaust, it is not clear what fraction of the genotoxic material is bioavailable (that is, the amount of the chemical actually available for biological interactions, which is likely to be different from the exposure concentration), or whether the mutagenic potency demonstrated *in vitro* extends to the more complex *in vivo* environment.

BIOAVAILABILITY

In vitro studies provide conflicting evidence about the bioavailability of the genotoxic material adsorbed onto diesel particles. On the one hand, this material generally appears to be less genotoxic in *in vitro* studies when it is extracted from the diesel particles by physiological fluids

(such as saline, serum albumin, or lung lavage fluid) than when extracted by the harsher, nonphysiological organic solvents generally used to prepare bioassay samples (Brooks et al. 1980; Siak et al. 1981). These results suggest that the genotoxic fraction in diesel exhaust may not be as mutagenic *in vivo* as it is in the *in vitro* studies. In contrast, material extracted from diesel particulate matter by Keane and coworkers (1991) using an aqueous mixture containing dipalmitoyl phosphatidylcholine (a major component of pulmonary surfactant) was highly mutagenic.

Several factors determine the bioavailability of the organic compounds adsorbed to the surface of diesel particles (Green and Watson, this report). These include the surface structure of the particle, the composition of the adsorbed organic chemicals, the composition of the extra- and intracellular fluids, the balance of the molecular binding forces between the particle and the adsorbed organic molecules on the one hand and the extracting biological fluids on the other, and the metabolism of the desorbed compound. The binding energies of the adsorbed organic chemicals also depend on their concentration on the particle surface; organic molecules are more tightly bound at low concentrations (as occurs in emissions from today's well-controlled diesel engines) than at high concentrations (as occurs in emissions from older engines).

An additional factor controlling bioavailability is the degree of agglomeration of free and intracellular particles (Gerde et al. 1991). Agglomeration, which occurs with tracheal instillation (Sun et al. 1989) and high exposure levels (such as those used to produce lung tumors in animals), appears to retard the release of organic compounds and prolongs the dose administration to the lung cells.

Table 3. Spectrum of Genetic Effects of Diesel Exhaust and Its Constituents^a

Assay	Whole Exhaust	Diesel Particles	Particle Extracts	Gas Phase	Benzo[a]pyrene	1,6-Dinitropyrene
Mutagenicity (bacteria)	ND	+	+	+	+	+
Mutagenicity (mammalian cells)	ND	+	+	ND	+	+
Chromosomal damage	±	±	±	ND	+	+
Cell transformation	ND	ND	+	ND	+	+
DNA adducts	±	±	+	ND	+	+

^a + = positive in most studies; - = negative in most studies; ± = equivocal data; ND = not determined, or only limited data are available. (Adapted from Shirnamé-Moré, this report.)

DNA ADDUCTS

One way to evaluate whether the genotoxic chemicals adsorbed onto diesel exhaust particles are bioavailable is to determine whether *in vivo* exposures to diesel exhaust result in the formation of DNA or protein adducts. Many of the individual PAHs and nitro-PAHs in diesel exhaust form characteristic DNA adducts *in vitro* and *in vivo*. Aromatic-DNA adducts have been detected in target and nontarget tissues of cigarette smokers and workers exposed to some combustion products; however, scientists have not yet established whether specific PAH or nitro-PAH adducts form in animals or humans exposed to diesel emissions.

Only one study has examined DNA adducts in humans exposed to diesel emissions. Hemminki and Pershagen (1994) reported elevated levels of aromatic-DNA adducts in lymphocytes from nonsmoking bus maintenance and truck terminal workers. The researchers did not identify the adducts, but they did establish that the main adducts were not similar to benzo[*a*]pyrene-DNA or other PAH-DNA adducts. Because they did not measure the levels of diesel emissions, they could not establish dose-response relations.

The results of animal studies that examined DNA adducts are difficult to interpret. Some report small increases in total DNA adduct levels in lung tissues from rats exposed to high concentrations of diesel exhaust compared with control animals (Wong et al. 1986; Bond et al. 1988, 1990a,b; Mauderly et al. 1994). One study found the highest adduct levels in peripheral lung tissue, the target region for diesel exhaust-induced lung tumors in rats (Bond et al. 1988). However, the levels of DNA adducts were independent of the concentration of diesel exhaust (Bond et al. 1990b), and other investigators found either no increase in total DNA adduct levels in diesel exhaust-exposed animals (Gallagher et al. 1994), or small and somewhat variable differences between test and control animals (Randerath et al. 1995).

Two groups of investigators looked for specific carcinogen-DNA adducts in rats exposed to diesel emissions by inhalation. Randerath and coworkers (1995) found no indication that typical PAH- or nitro-PAH-DNA adducts formed in the lungs of rats exposed to high concentrations of diesel exhaust or carbon black. However, when these investigators applied an extract of the same diesel exhaust particulate matter to mouse skin, DNA adducts formed in both skin and lung tissue, demonstrating that the particulate matter clearly contained organic chemicals capable of reacting with DNA. Although these findings support the idea that the particle-associated organic compounds in inhaled diesel emissions may not be sufficiently bioavailable to initiate carcinogenesis in rats continuously exposed to high levels of diesel emissions, the rate of DNA repair also could be a factor.

In contrast, Gallagher and coworkers (1994) found low levels of an adduct, which they postulated was a nitro-PAH-DNA adduct, in peripheral lung tissue isolated from rats exposed to high concentrations of diesel exhaust, but not in rats exposed to carbon black or titanium dioxide. However, the identity of this adduct requires further confirmation because it was not characterized by comparing it with authentic nitro-PAH standards. In agreement with Randerath and associates (1995), Gallagher and coworkers (1994) did not detect any PAH-derived DNA adducts in lung tissue from rats exposed to diesel exhaust.

There are several reasons why DNA adducts, generally regarded as good biomarkers for carcinogen exposure, have been difficult to detect in animals exposed to diesel exhaust. First, the amount of bioavailable PAHs and nitro-PAHs in diesel emissions may be so low that any DNA adducts that are formed are below detection limits. Second, because most DNA adducts have a finite lifetime (due to DNA repair and cell turnover), they are generally biomarkers of recent rather than past exposures, and therefore cannot indicate whether the levels of exogenous DNA adducts were high earlier in the exposure period. Third, in the animal bioassays, DNA adducts may have been diluted by particle-induced cell proliferation. Finally, the high concentrations of diesel exhaust required to induce lung tumors in rats may affect carcinogen metabolism and, as suggested by Rosenkranz (this report), may prevent the activation of procarcinogens to species that react with DNA.

COMPARATIVE POTENCY ANALYSES

Scientists have used short-term bioassays, such as the mouse skin tumor assay, the rat lung implantation assay, and the preweanling mouse assay, to evaluate the relative tumorigenic potency of the individual carcinogens found in diesel exhaust (Busby and Newberne, this report). The mouse skin tumor assay showed a rough correlation between the mutagenic potency of organic compounds extracted from diesel exhaust particles and the concentration of one of the PAHs, benzo[*a*]pyrene. Benzo[*a*]pyrene represented approximately 10% to 20% of the total tumorigenic burden in the preweanling mouse assay, and 20% to 35% in the mouse skin-painting assay. In the rat lung implantation assay, most of the carcinogenic activity was associated with the PAH-containing fraction; only low carcinogenic activity was associated with the fraction containing nitro-PAHs. 1-Nitropyrene was not carcinogenic in any of the three short-term *in vivo* bioassays. 1,6-Dinitropyrene, a minor but highly mutagenic constituent of diesel exhaust, was 4.5-fold more potent than benzo[*a*]pyrene in the rat lung implantation assay, a finding consistent with its potent carcinogenicity in other animal species. Based on the inactivity of 1-nitropyrene in three short-term animal assays and the low concentrations of dinitropyrenes in diesel

emissions, Busby and Newberne question whether the nitropyrenes contribute significantly to the tumorigenic potency of diesel emissions. They note that the few instances in which it was analyzed, dibenzanthracene contributed a larger proportion of total tumorigenic potency than did other PAHs. Based on the carcinogenic potency of dibenzanthracene and dibenzopyrene in animal bioassays and their concentrations in diesel particle extracts, these compounds or their isomers may have greater carcinogenic potency than some of the more well-studied PAHs.

The results of these short-term bioassays are interesting; however, their utility for risk assessment is limited for several reasons. First, the data needed to make potency comparisons are available presently for only a few PAHs and some alkyl- and nitro-PAH derivatives. Second, short-term bioassay data are available for only a few of the many compounds in diesel emissions. Third, almost no information is available on the possible synergistic or inhibitory effects that occur when chemical mixtures react in a complex cellular environment. Finally, as discussed earlier, extrapolating short-term results to humans presumes that the same carcinogenic mechanisms operate in animals and humans.

CONCLUSIONS

- Adsorption of mutagenic organic compounds to the carbonaceous particles in diesel exhaust enhances their penetration into the respiratory portions of the lungs. However, adsorption also diminishes the bioavailability of the mutagens in proportion to the binding energy of the chemical and the agglomeration of the particle.
- There is limited evidence that the adsorbed mutagens and other organic molecules are actually bioavailable. Their prolonged presence in the lungs may or may not be biologically significant as long as they adhere to the particle surface.
- The chemicals in diesel emissions have the potential to induce mutations in humans, and therefore, could conceivably play a role in both genotoxic and nongenotoxic carcinogenesis. However, no consistent relation between mutagenic potency and carcinogenic potency has been demonstrated.

ISSUE 5: *How strong is the evidence that diesel exhaust is carcinogenic in laboratory animals?*

As discussed earlier, in the 1980s, several independent investigators conducted long-term inhalation bioassays of diesel exhaust using different species (rat, mouse, and hamster). (See Box 3 for a discussion of animal bioassays.)

Busby and Newberne (this report) review these results, and Green and Watson (this report) summarize dose-response considerations.

Box 3

ANIMAL BIOASSAYS

Two-year or lifetime animal bioassays are the traditional tests used to detect carcinogens. Their results form the basis of most risk assessments. Long-term bioassays are more relevant to human risk assessment than short-term bioassays, like the mouse skin-tumor assay, because they more closely approximate human exposure. Furthermore, in contrast to epidemiologic studies, bioassays allow investigators to control the characteristics and concentration of the test material, and to examine dose-response relations over a range of concentrations.

Animal bioassays are, however, blunt tools; because of statistical considerations, they have limited ability to detect small increases in cancer incidence. For this reason, they are generally conducted under conditions designed to maximize the researcher's ability to observe a response in an animal population of reasonable size. This usually means using the maximum dose that the animals will tolerate as one of the exposure concentrations. Long-term bioassays have been criticized because the outcomes obtained at such high doses may not be relevant to humans exposed to much lower concentrations (Abelson 1994). The National Research Council Committee on Risk Assessment Methodology did not reach a consensus about using the maximum tolerated dose in animal bioassays for carcinogenesis (National Research Council 1993). Most Committee members recommended that the maximum tolerated dose continue to be used as one of the doses in carcinogenicity bioassays, and that additional information be provided for determining human relevance.

What constitutes a maximum tolerated dose for inhalation studies is not clearly defined. A National Toxicology Program Workshop on Maximal Aerosol Exposure Concentrations in Inhalation Studies (Lewis et al. 1989) recommended that prolonged exposure studies not be performed at the highest technologically feasible aerosol concentration, but that three concentrations be used, only one of which interferes with lung defense mechanisms.

indices of inflammation become evident, including the presence of macrophages, neutrophils, and alveolar epithelial cell hyperplasia. Fibrotic changes (i.e., increases in the number of fibroblasts, interstitial macrophages, and collagen fibers) become apparent after six to twelve months of exposure. After 18 to 24 months of exposure, bronchiolar-alveolar epithelial cells undergo metaplasia (i.e., one cell type replaces another), and particle-containing macrophages aggregate in the interstitium where focal fibrosis develops. Around this time, tumors begin to appear. Also, debris composed of dead macrophages accumulates in the focal lesions. These macrophages appear to have disintegrated and released particulate matter, thus exposing local tissues to both the particles and to the degradation products of the disintegrating macrophages.

In rats, the above events occur when the animals are exposed to high doses of poorly soluble, nonfibrous particles, such as carbon black (Mauderly et al. 1994; Heinrich et al. 1995), titanium dioxide (Lee et al. 1985), and talc (National Toxicology Program 1994), and are associated with a pathophysiologic process referred to as "lung overload" or "particle overload." Lung overload occurs when the dose rate for particulate matter is so high that it overwhelms the long-term pulmonary clearance processes, causing lung burdens greater than those predicted by deposition kinetics at low exposure concentrations. One theory to explain how

high particle lung burdens impair long-term clearance is that the massive intracellular particle load prevents the alveolar macrophages from effectively phagocytizing and removing the inhaled particulate material (Morrow 1992). As a result, particles accumulate in the alveolar spaces and, ultimately, move into the pulmonary interstitium.

Investigators have observed impaired particle clearance due to lung overload in rats, mice, hamsters, and dogs (see Green and Watson, this report); however, the effects of impaired clearance differ markedly among these species (see Watson and Green, this report) (Figure 10). In rats, macrophages aggregate earlier and at lower exposure concentrations than in hamsters. Mice have less marked fibrotic (Henderson et al. 1988) and proliferative responses (Heinrich et al. 1986) to lung overload than rats. Investigators do not know why particle overload is associated with alveolar epithelial cell hyperplasia, metaplasia, and neoplasia in one species (rat) but not another (hamster). The answer may lie in differences in macrophage responses or antioxidant defense systems (Oberdörster 1994).

CONCLUSIONS

- Nearly lifetime exposures to high concentrations of diesel exhaust induce a dose-dependent increase in benign and malignant pulmonary neoplasms in rats.

Table 4. Progression of Nonneoplastic and Neoplastic Lung Lesions in F344/N Rats Exposed to Diesel Exhaust or Carbon Black^a

Lesions	Time of Observation ^b (months)					
	3	6	12	18	23	More than 23
Macrophage hyperplasia	+	+	+	+	+	+
Alveolar epithelial cell hyperplasia	+	+	+	+	+	+
Chronic active inflammation	+	+	+	+	+	+
Septal fibrosis	0	+	+	+	+	+
Alveolar proteinosis	0	+	+	+	+	+
Bronchiolar-alveolar metaplasia (alveolar bronchiolarization)	0	0	+	+	+	+
Interstitial aggregation of macrophages containing particles	0	0	0	+	+	+
Focal fibrosis	0	0	0	0	+	+
Squamous metaplasia	0	0	0	0	+	+
Squamous cyst	0	0	0	0	+	+
Neoplasms	0	0	0	+ ^c	+	+

^a Reprinted from the HEI Review Committee Commentary for Mauderly et al. 1994, and Busby and Newberne, this report.

^b A + indicates the presence of lesions and a 0 indicates their absence.

^c First tumor appeared at 15 months.

Response	Rats	Mice	Hamsters
Clearance overload	+++	+++	++++
Inflammation	+++	+	+
Cell proliferation	+++	+	+
Fibrosis	+++	+	+
Lung cancer	+++	+/-	-

Figure 10. Species differences in pulmonary responses to inhaled diesel emissions.

The tumorigenic response of rats to diesel exhaust is similar to that seen in response to other poorly soluble, nonfibrous particles. There is no consistent evidence to suggest that diesel exhaust induces neoplasms at sites other than the lung.

- In contrast, prolonged exposure to diesel emissions does not produce lung tumors in hamsters, and the results in mice are equivocal, pointing to a critical role for host factors in the induction of lung tumors by diesel emissions.
- Diesel exhaust-induced lung cancer develops in rats under conditions of depressed alveolar particle clearance associated with inflammation and alveolar epithelial cell hyperplasia. The presence of a particle burden sufficient to produce these effects appears to be a significant risk factor for this species.
- Scientists do not know which animal species (the rat, the mouse, or the hamster) is the most relevant model for extrapolating animal results to humans.

ISSUE 6: What components of diesel emissions cause lung cancer in laboratory rats?

Having established that diesel emissions are carcinogenic in rats, the next step was to identify which agent or agents in diesel exhaust cause the tumors. Such information might, in turn, enable investigators to elucidate the mechanism of carcinogenesis and to obtain more precise dose-response data, which would improve the accuracy of health risk assessments for diesel exhaust.

Studies in rats exposed to either whole diesel exhaust or filtered exhaust (from which the particles had been removed) revealed no lung tumors in rats exposed to filtered diesel exhaust, and significant increases in lung tumors in all treatment groups exposed to unfiltered exhaust (Hein-

rich et al. 1986; Iwai et al. 1986; Brightwell et al. 1989). These findings demonstrate the primary importance of the particulate matter in causing lung tumors in rats, but do not establish whether the organic compounds bound to the carbonaceous particles, the particles themselves, or a combination of the particles and the bound chemicals play a role in tumor induction.

Recent studies (Mauderly et al. 1994; Heinrich et al. 1995; Nikula et al. 1995) have confirmed that the particulate matter is primarily responsible for the rat lung response to high concentrations of diesel exhaust. These studies also shifted attention away from the genotoxic chemicals and changed scientists' thinking about how diesel exhaust causes lung cancer in rats. In these studies, researchers exposed rats to either clean air, diesel exhaust from a light-duty automotive diesel engine, or carbon black. The carbon black particles were similar to the diesel exhaust particles; however, they contained approximately 100 times less adsorbed organic material than the diesel exhaust particulate matter and, unlike the organic solvent extracts of the diesel particles, carbon black extracts produced little or no response in bacterial mutagenicity assays. Thus, in these studies, the carbon black served as a surrogate for diesel exhaust particles that were relatively free of mutagenic organic compounds.

Mauderly and coworkers (1994; Nikula et al. 1995) found no significant differences in tumor incidence or lung histopathology between male and female F344/N rats exposed to diesel exhaust and those rats exposed to carbon black (Figure 11). These findings agree with those of Heinrich and colleagues (1995) who reported that long-term exposures to diesel exhaust, carbon black, or titanium dioxide (another poorly soluble nonfibrous particle) all caused lung tumors in female Wistar rats at a rate proportional to the cumulative exposure.

CONCLUSIONS

- The particulate matter in diesel exhaust appears to cause the lung tumors in rats exposed to high concentrations of diesel emissions. Under the conditions of the animal bioassay, the mutagenic compounds adsorbed onto the particles do not appear to play a role in tumor development in this species.
- The results do not completely exclude a role for the mutagenic organic compounds found in diesel exhaust. The possibility exists that these compounds have a low degree of potency that is not detectable within the rat bioassays in which lung cancer development is dominated by the particle effect.

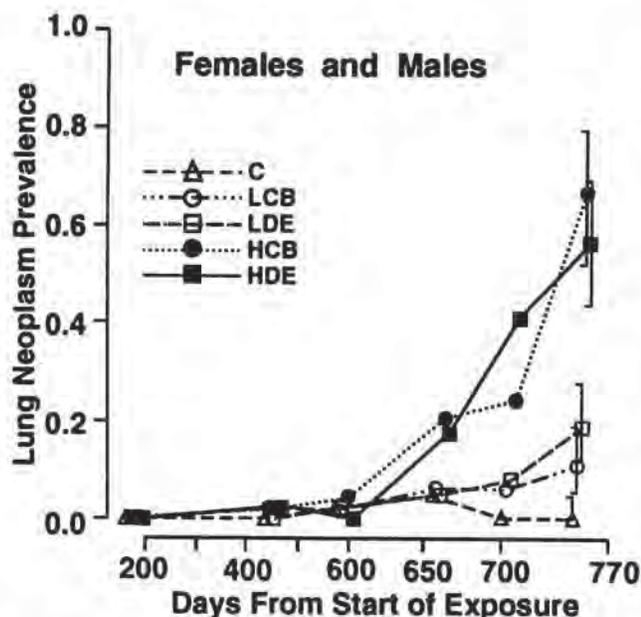


Figure 11. The prevalence of (male and female) rats observed to have malignant or benign lung neoplasms during various intervals after exposure to diesel exhaust or carbon black. C = control; LCB = low carbon black (2.5 mg/m^3); LDE = low diesel exhaust (2.5 mg/m^3); HDE = high diesel exhaust (6.5 mg/m^3); HCB = high carbon black (6.5 mg/m^3). (Reprinted from Mauderly et al. 1994a.)

ISSUE 7: How do diesel emissions induce lung tumors in laboratory rats?

GENOTOXIC AND NONGENOTOXIC MECHANISMS OF CARCINOGENESIS

Genotoxic and nongenotoxic mechanisms are both biologically plausible alternatives to explain the development of lung cancer in animals exposed to diesel emissions. (See Box 4 for a discussion of mechanisms of carcinogenesis.) These mechanisms, as they apply to diesel emissions, are depicted in Figure 12 as separate pathways. However, they are not mutually exclusive because (1) biologic processes that are not directly genotoxic can ultimately cause genetic damage, (2) different pathways may operate in different species, (3) different pathways may operate in the same species depending, for example, on exposure conditions, and (4) both pathways may operate in the same species but at different stages of carcinogenesis.

Scientists generally agree that, because of their high mutagenic potency, the chemicals in diesel exhaust have the potential to act through direct genotoxic mechanisms. However, recent findings from the studies described in Issue 6 do not support the hypothesis that this mechanism operates in rats exposed to high concentrations of diesel exhaust or other particulate matter. These studies showed that, at equivalent exposure concentrations, carbon black

particles (which contain greatly reduced levels of adsorbed organic mutagens) induced tumors similar in frequency and type to those induced by diesel emissions. In addition, tumors induced by diesel exhaust and carbon black have a relatively long latency period (approximately two years) compared with the latency period (approximately 0.8 years) of tumors induced by pure chemicals, such as benzo[a]pyrene and the dinitropyrenes (Iwagawa et al. 1989), which are among the organic chemicals adsorbed onto the surface of the particles in diesel exhaust.

These results suggest that the lung tumors induced in rats by diesel emissions do not result from direct genotoxic activity of the particle-associated mutagens. Several scientists have proposed that some agents, especially when administered at high concentrations, induce tumors by nongenotoxic (or indirectly genotoxic) mechanisms associated with inflammation and cell proliferation (Ames and Gold 1990; Butterworth 1990; Cohen and Ellwein 1990; Preston-Martin et al. 1990; Butterworth et al. 1992; International Agency for Research on Cancer 1992; Vainio et al. 1992). This alternative mechanism may apply to diesel emissions because rats exposed to diesel exhaust develop lung tumors only at particle concentrations sufficiently high to cause reduced pulmonary clearance accompanied by inflammation and fibrosis (Vostal 1986; McClellan 1990). It is possible that the initial response to inhaled diesel exhaust is not the formation of chemical-DNA adducts, but rather a cellular response to the prolonged presence of high concentrations of particles. Scientists have proposed several hypotheses about how particle-induced responses might lead to carcinogenesis; however, no definitive data are currently available to support the validity of one hypothesis or another.

One hypothesis is that the inflammatory cells, which are recruited to the lungs in response to high particle burdens, produce factors that directly or indirectly cause genetic damage (Figure 12) (Sibelle and Reynolds 1990; Driscoll et al. 1994, 1995). For example, when macrophages and neutrophils are stimulated, they release reactive oxygen species that can produce DNA strand breaks and DNA-protein cross-links. Such DNA lesions can lead to mutations that affect the activities of protooncogenes and tumor suppressor genes (Cerutti and Trump 1991). Reactive oxygen species also can act as transduction signals, which could alter gene expression, growth, and differentiation (Cerutti and Trump 1991; Maki et al. 1992; Daniel 1993).

Although many scientists think that oxidative mechanisms are important in the development of particle-induced lung tumors, no experimental evidence that oxidative DNA damage occurs in the lungs of animals exposed to diesel exhaust is presently available. The DNA adduct studies

Box 4

MECHANISMS OF CARCINOGENESIS

Carcinogenesis in animals and humans is a multistage, multifactorial process that involves alterations in the genes that control cell proliferation, cell growth, and programmed cell death (reviewed by IARC 1992, and by Harris 1991). It is usually divided into at least three steps: initiation, promotion, and progression.

Tumor initiation, the first step, results from irreversible genetic damage caused by chemical, physical, or microbial carcinogens to one or more individual cells. The genetic change conferred on the initiated cells gives them a growth advantage. During promotion, selective clonal expansion of the altered cells occurs, and additional genetic damage may result. Tumor promoters are chemicals that can disproportionately increase the proliferative rate of initiated cells, and thus, expand the subpopulation of tumor cells. During progression, a series of genetic and other biologic events causes the malignant tumor to develop increasingly aggressive properties, such as invasion, metastasis, and drug resistance.

The genes that regulate cellular proliferation, differentiation, and communication are known as protooncogenes and tumor suppressor genes. Protooncogenes are normal cellular genes that stimulate proliferation. When abnormally activated, they are called oncogenes and lead to unregulated growth and malignancy. Tumor suppressor genes normally inhibit proliferation. When they are inactivated, unregulated growth results. Environmental agents can influence carcinogenesis at any stage of the process; they not only initiate carcinogenesis, but also can cause mutations in the genes that control cell proliferation and malignancy.

Currently, there is an active debate about the relative contribution of genotoxic and nongenotoxic events to carcinogenesis (Ames and Gold 1990; Cohen and Ellwein 1990; Preston-Martin et al. 1991). Genotoxic carcinogens are generally regarded as carcinogens for which the primary biological activity is altering the information encoded in DNA (Butterworth 1990). They cause genetic changes (mutations, insertions, deletions, or changes in chromosome

structure) leading to initiation, activation of protooncogenes, or inactivation of tumor suppressor genes. As a group, they are relatively potent carcinogens that can cause cancer in multiple species (Ashby and Tennant 1988; Gold et al. 1989; Rosenkranz and Ennever 1990). Most known human carcinogens act through genotoxic mechanisms (Ennever et al. 1987; Shelby 1988; Bartsch and Malaveille 1989). However, some chemicals that cause tumors in rodents appear to do so by nongenotoxic mechanisms, either by killing cells and inducing compensatory cell proliferation, or by increasing rates of cell proliferation through mitogenesis (Ames and Gold 1990). In either case, the increase in cell division associated with internal or external stimulation is thought to increase the risk of genetic errors of various kinds, leading to neoplasms. Some carcinogens may act through both genotoxic and nongenotoxic mechanisms.

Our understanding of cancer mechanisms has advanced considerably over the last 15 years, prompting discussions among scientists and regulators about how to incorporate this information into cancer risk assessments. Both the EPA (1994a) and the International Agency for Research on Cancer (1992) are revising their procedures for determining whether a chemical is a carcinogen. Their proposed guidelines recommend that the hazard identification step include a discussion of possible mechanisms when appropriate data are available.

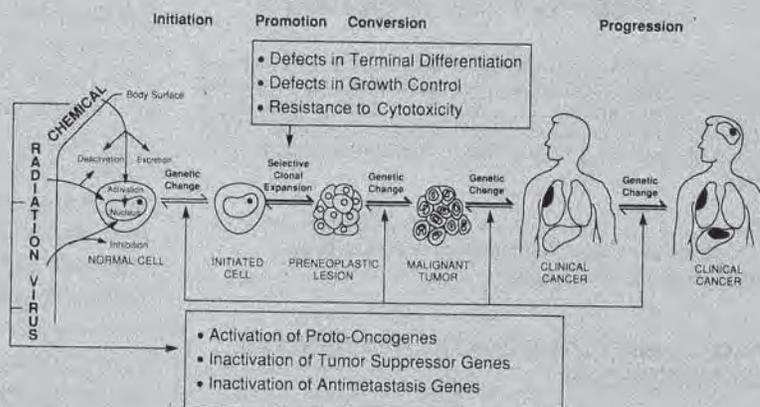


Figure 4.1. Carcinogenesis is a multistage process involving multiple genetic and epigenetic events in protooncogenes, tumor suppressor genes, and antimetastasis genes. (Reprinted with permission from Harris 1991.)

conducted to date have focused on analyzing PAH-DNA adducts and used techniques that could not have detected oxidative DNA adducts. A recent preliminary report of rats exposed to high levels of carbon black (7 or 50 mg/m³) demonstrated exposure-dependent increases in the levels of neutrophils in bronchoalveolar lavage fluid and an increase in hypoxanthine-guanine phosphoribosyltransferase (HPRT) mutations in lung epithelial cells (Driscoll et al. 1995); this study provides the first experimental evidence that inflammatory cells may have a role in the development of particle-induced lung tumors.

Alternatively, cell proliferation could be the driving force behind lung tumor development in rats exposed to high concentrations of diesel emissions. Either the particles themselves or factors released by the inflammatory cells

(such as growth factors or cytokines) may stimulate proliferation of alveolar epithelial cells or fibroblasts, causing them, in turn, to release mediators that further stimulate cell division (Driscoll et al. 1994). Cell proliferation might lead to tumor formation either by increasing the frequency of spontaneous mutations during cell replication or by allowing more opportunity for exogenous chemicals to damage DNA (Ames and Gold 1990).

Even if we understood how diesel exhaust particulate matter causes rat lung tumors, we would still be uncertain whether the rat bioassay is relevant to the human situation. Although the bioassay results suggest that the organic chemicals in diesel emissions are not involved in either initiation or promotion of lung tumors in rats, they do not exclude the possibility that such events may (1) be too low

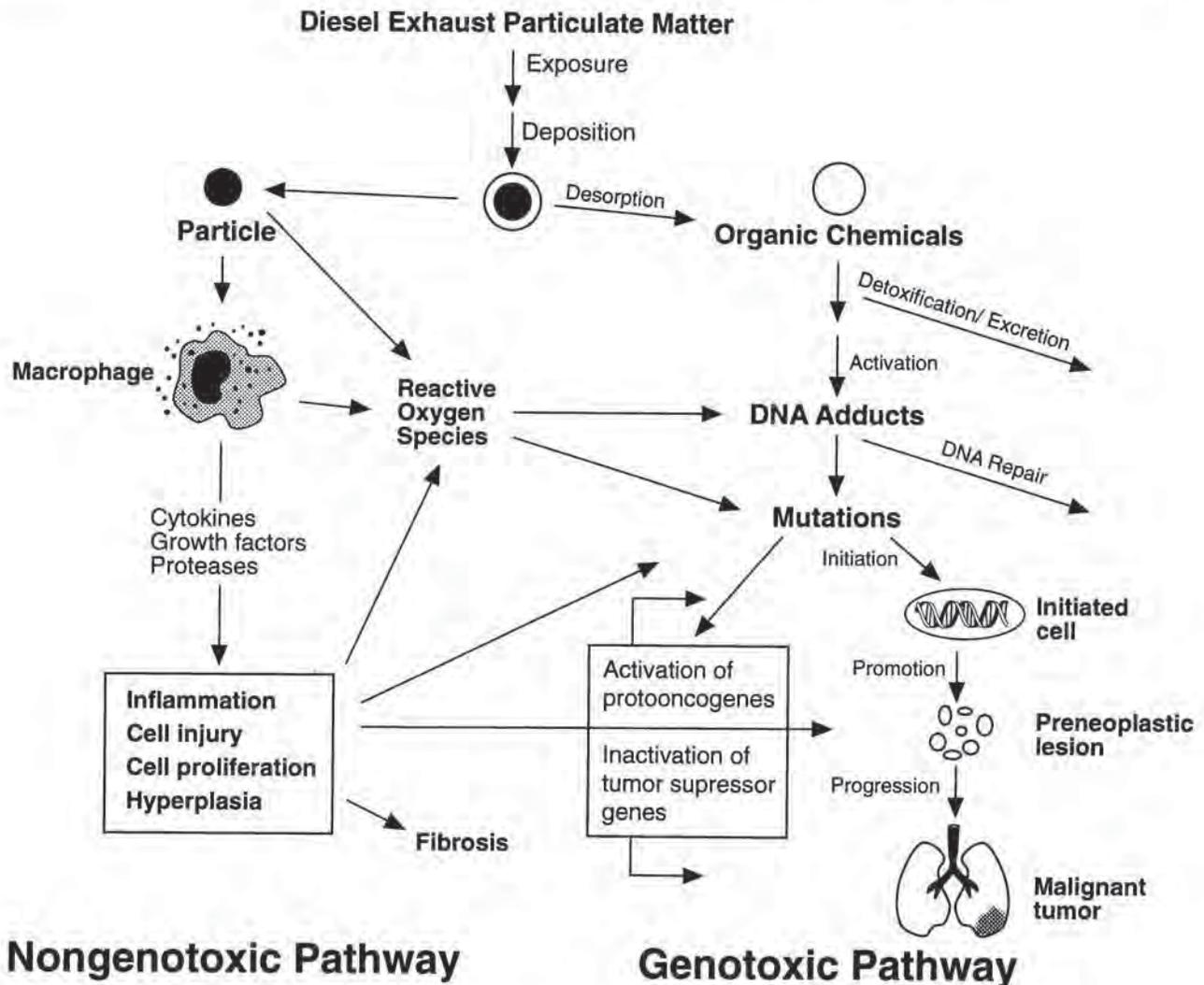


Figure 12. Possible mechanisms for diesel exhaust-induced carcinogenesis.

to detect in the rat bioassay, or (2) operate in either humans or rats under exposure conditions that do not lead to a massive inflammatory and proliferative response.

CONCLUSIONS

- The mechanism or mechanisms by which prolonged exposure to high concentrations of diesel emissions produces lung tumors in rats appear to be related to impaired lung clearance, inflammation, and alveolar epithelial cell proliferation. The available data are consistent with nongenotoxic mechanisms that do not involve direct interaction with DNA.
- Although definitive information is not available, the toxicologic data imply that nongenotoxic mechanisms of lung carcinogenesis may not be relevant to other species or to low-level exposure conditions.
- The PAHs and nitro-PAHs are potent mutagens and, if bioavailable, could play a role in carcinogenesis that might not be detectable in the rat bioassay, either because their effect is too subtle to be detected at low concentrations of diesel exhaust exposure, or is masked by the overwhelming inflammatory and proliferative responses of the rat lung to high concentrations of inhaled particles.
- Different mechanisms of diesel exhaust-induced carcinogenesis may operate under different exposure conditions; for example, nongenotoxic mechanisms under high-level exposure conditions and genotoxic mechanisms under low-level exposure conditions.

CRITICAL ISSUES IN CONDUCTING DOSE-RESPONSE ASSESSMENTS OF DIESEL EXHAUST

Developing quantitative estimates of the likely relation between the dose of a suspected carcinogen and the incidence of cancer (dose-response assessment, the third step in risk assessment) is the most uncertain and contentious aspect of risk assessment. This is because the data for dose-response assessments are generally obtained at high exposure concentrations of the test material. In addition, the choices of scaling factors and extrapolation models to be used profoundly affect the risk assessment outcome. This section discusses the following critical issues concerning dose-response assessments for diesel exhaust:

- which species to use for dose-response extrapolation,
- whether the rat lung tumors induced by diesel emissions resemble human lung tumors,

- whether dose-response assessments should be based on the organic or particulate constituents of diesel emissions,
- lung overload and threshold levels, and
- scaling factors and extrapolation models.

ISSUE 8: Which species should be used to calculate cancer risk factors for diesel exhaust?

Ideally, cancer risk factor calculations would be based on epidemiologic studies of industrial workers or other special groups for whom well-characterized exposure information was available. Unfortunately, such information is not fully available for diesel exhaust (or for most air pollutants). None of the epidemiologic studies published to date monitored exposure to diesel exhaust. Rather they assigned subjects to exposed or nonexposed categories based on their job classification.

There are estimates of diesel exhaust exposure for some occupational cohorts for whom epidemiologic data are also available. This information, however, was not obtained during the time period when the subjects of the epidemiologic studies were being exposed. For example, Garshick and coworkers (1987, 1988) published two studies of railroad workers observed from 1952 through 1980 to evaluate whether an association between exposure to diesel emissions from locomotives and lung cancer mortality could be ascertained. In a related study conducted in the early 1980s, Woskie and colleagues (1988a,b) assessed diesel exhaust exposure (respirable particulate matter adjusted for cigarette smoke particles) in four small railroads in the northern part of the United States. Although these measurements provided estimates of the relative dose of diesel emissions for the job groups analyzed in the epidemiologic studies, their applicability to dose-response assessments of the general population, or even to railroad workers from all regions of the country (who represent the population examined in the epidemiologic studies) is questionable because:

- exposures to locomotive diesel emissions in the 1950s and 1960s (the likely period of cancer initiation) were probably quite different from those in the 1980s due to changes in engine technology and industrial hygiene,
- exposures differed among railroad yards across the United States,
- climate was found to have a major effect on exposure in some job groups (Woskie et al. 1988a), and
- subsequent analyses have not supported a dose-response relation for the railroad workers (Crump et al. 1991; Valberg et al. 1995).

In the absence of reliable human exposure data, risk assessments are based on animal bioassay results. As discussed in Issue 5, the animal data base for diesel exhaust is robust compared with many suspected carcinogens. Rats exposed to diesel exhaust developed lung tumors in at least eight independent studies. The findings have been equivocal in mice and negative in hamsters. We do not know how diesel emissions exert their effects in humans or rodents. When mechanistic information is not available to suggest which species is the most suitable model for estimating human responses, the EPA's default assumption is to base risk assessments on the most sensitive of the responding species. This is a policy decision in keeping with the Agency's mandate to protect human health. For diesel exhaust, the most sensitive species clearly is the rat. The validity of basing estimates of human cancer risk for diesel exhaust on the rat bioassay data would be strengthened if scientists could establish that prolonged exposure to respirable particulate matter also causes lung cancer in humans.

Because mice respond to diesel exhaust with either small or no increases in lung tumors, this species has not been used for quantitative risk assessments. If diesel exhaust causes lung tumors in the mouse, the mechanism may well differ from the particle-related mechanisms that appear to operate in the rat. In contrast to the rat, exposure of mice to particle-free, filtered diesel exhaust appeared to cause increases in lung tumor incidence that either were not statistically significant (Heinrich et al. 1995) or of questionable significance because the tumor rate in the control animals was lower than historical values (Heinrich et al. 1986).

Because of the uncertainty of the data from mouse studies, all risk assessments for diesel exhaust have been based on selected rat bioassay data, except for one analysis, which was based on human data (California Environmental Protection Agency 1994). The use of the rat bioassay data for dose-response extrapolation is consistent with standard risk assessment procedures; the rat is the animal species most sensitive to inhaled diesel exhaust. It is uncertain, however, if it is the most relevant model for extrapolation to humans.

CONCLUSIONS

- Because of the lack of exposure information, epidemiologic data from occupational studies do not provide a reliable basis for calculating cancer risk factors for diesel emissions.
- The rat is the animal species most sensitive to the carcinogenic effects of inhaled diesel engine emis-

sions; however, we do not know whether the mechanism by which diesel exhaust induces lung tumors in rats is relevant to humans.

ISSUE 9: *In what ways do the rat lung tumors induced by diesel emissions resemble human lung tumors?*

The lungs are the major target site for inhaled diesel exhaust in laboratory rats. With one exception (Iwai et al. 1986), no tumors have been reported at other sites. The rat data agree with the epidemiologic data that indicate the lung as the site most affected by exposure to diesel exhaust.

The bladder is another potential target site for diesel exhaust because nitro-PAHs are readily reduced by mammalian enzymes or bacterial flora to aromatic amines, which are known to be bladder carcinogens in humans. Interestingly, no bladder tumors were reported in any of the rodent bioassays. This suggests that the animal bioassays do not support the results of those epidemiologic studies that found an elevated risk of bladder cancer in some occupational cohorts (see Cohen and Higgins, this report). However, if PAHs are not bioavailable or, as Rosenkranz (this report) suggests, dinitropyrenes are not activated under the bioassay conditions, then the absence of tumors in sites distant from the lungs in the rat is not surprising.

TUMOR TYPE

The links between the rodent bioassay and the human situation are strengthened when the observed effects in animals and those in humans are comparable. Human lung cancers are generally classified into five types based on their histopathologic characteristics: squamous cell and small cell carcinomas (commonly found in the central region of the airways, and the most common types in men), adenocarcinomas (usually located in the lung periphery, and commonly found in women), and large cell carcinomas and bronchoalveolar cell carcinomas. Despite intensive efforts with cigarette smoke and other lung carcinogens, no animal model for lung cancer exhibits the same pattern of lung tumor types that occurs in humans.

Exposure to high concentrations of diesel exhaust or carbon black produces a spectrum of benign and malignant neoplasms in rat lungs, including adenomas, adenocarcinomas, squamous cell carcinomas, and adenosquamous carcinomas. The rat tumors induced by diesel exhaust are located in the peripheral regions of the lung, whereas the squamous cell and small cell lung tumors found in humans are more commonly located in the central bronchus. For this reason, the relevance of the animal lung tumor data has

sometimes been questioned, although one of the EPA's default assumptions for cancer risk assessment is that site and histopathologic concordance are not required for animal-to-human extrapolations. Interestingly, in recent years, humans have shown an increased frequency, relative to other types of lung tumors, of peripheral adenocarcinomas (el-Torky et al. 1990). Human peripheral adenocarcinomas, which resemble the lung tumors found in rats exposed to diesel exhaust, do not have as strong an association with cigarette smoking as other types of tumors. Some scientists have suggested that the recent increase in this tumor type may be linked to exposure to environmental tobacco smoke (which has a smaller particle size than mainstream smoke), to deeper inhalation by smokers to compensate for the low nicotine dose from modern cigarettes (Fiore 1992), or to other environmental factors.

SQUAMOUS CYSTS VERSUS BENIGN SQUAMOUS TUMORS

Pathologists disagree about how to classify one type of lung lesion that has been observed in rats following prolonged inhalation exposure to high concentrations of diesel exhaust and other poorly soluble, nonfibrous particles. The lesion, which appears to be unique to the rat, has been classified as a "squamous cyst" (Mauderly et al. 1994), a "benign keratinizing cystic squamous cell tumor" (Heinrich et al. 1986,1995; International Agency for Research on Cancer 1992), and as a "proliferative keratin cyst" (Carlton 1994) by different pathologists. This controversy, which is unlikely to be resolved soon, has implications for dose-response assessments of diesel exhaust because lesions classified as neoplastic (such as "benign squamous tumors") are included in the tumor counts, and nonneoplastic lesions (such as "squamous cysts") are not.

For some particulate substances, whether a lung lesion is classified as a squamous cyst or a benign squamous tumor determines whether there is a statistically significant increase in tumor incidence. For diesel exhaust, the classification affects the magnitude of the response (Figure 9); however, exposure to diesel emissions still causes a statistically significant increase in lung tumors when these lesions are excluded. The original bioassay by Mauderly and colleagues (1987), which forms the basis of most current diesel exhaust risk assessments, classified these lesions as lung neoplasms and they accounted for a significant fraction of the observed tumors. However, in a recent study from the same laboratory, the participating pathologists (with one exception) agreed that the lesion in question was a squamous cyst and not a tumor (Mauderly et al. 1994; Nikula et al. 1995). The appropriateness of this diagnosis

was substantiated by transplantation studies: lung masses diagnosed as adenocarcinomas and squamous cell carcinomas grew after transplantation into nude (athymic) mice, whereas none of the transplanted squamous cysts grew.

CONCLUSIONS

- Although the adenomas, adenocarcinomas, and carcinomas produced in the peripheral regions of the lungs of rats exposed to diesel emissions differ from the most common smoking-related lung cancers in humans (which are found in the central airways), they do resemble peripheral adenocarcinomas in humans, which, in recent years, have increased in frequency compared with other types of lung tumors.
- Given the current disagreement about whether a lesion that occurs frequently in rat lungs exposed to high concentrations of diesel emissions should be classified as a squamous cyst (nonneoplastic) or a benign squamous tumor (neoplastic), the contribution this lesion makes to the reported tumor incidence should be clearly noted in risk assessments of diesel emissions and unit risk factors should be calculated both with and without these lesions.

ISSUE 10: *What factors need to be considered when extrapolating the rat lung tumor data to humans?*

Risk assessments for carcinogens are based on dose-response data from exposure to either individual agents or, if the carcinogen is a mixture of substances, to a fraction or constituent of the mixture. Diesel exhaust is a highly complex mixture that contains particles and hundreds of chemical constituents.

COMPARATIVE DOSE TERM

Data from the rat, the most sensitive species studied to date, provide information about the carcinogenicity of different fractions of diesel exhaust. As discussed in Issue 6, recent comparisons of diesel exhaust and carbon black (Mauderly et al. 1994; Heinrich et al. 1995; Nikula et al. 1995) support the idea that the organic constituents in diesel exhaust are not responsible for the lung tumors observed in rats exposed to high concentrations of diesel exhaust. No qualitative or quantitative differences were found in the rat's responses to carbon black and diesel exhaust; this suggests that, other than their contribution to the lung burden, the organic chemicals in diesel exhaust do not appear to have a role in inducing lung tumors in this species under the bioassay conditions. Thus, the available

scientific evidence supports using the particulate fraction (including the organic material) rather than the organic fraction alone as the comparative dose term in conducting dose-response assessments of diesel emissions.

What is uncertain is how much confidence we can have in using dose-response data that was obtained at high diesel exhaust exposure rates in rats to predict effects that might occur in humans at much lower exposure rates.

SPECIES DIFFERENCES IN PARTICLE DEPOSITION AND CLEARANCE

One key factor concerning the relevance of the rat particle dose-response data for humans is whether inhaled particles behave similarly in rats and humans. In Part II of this report, Green and Watson discuss inter- and intraspecies differences in particle deposition and clearance. Fine particles such as diesel exhaust particulate matter generally deposit in the lung alveoli at similar rates in different species. These rates do not seem to be affected by previous exposure to particles. Conversely, particle clearance differs across species and takes much longer in humans than rodents. Clearance depends on the rate of particle accumulation, the extent of prior exposure to particles, and whether clearance processes have been overwhelmed and thus significantly impaired by continuous exposure to high particle concentrations.

The difference in particle clearance rates between rats and humans is one principal variable that affects the extrapolation of the rat data to humans. Various models (reviewed by Green and Watson, this report) have been used to characterize the kinetics of particle deposition, clearance, and retention in different animal species. Comparisons of rates predicted by models using experimental observations suggest that these models do a good job of characterizing particle kinetics for individual animal species. However, using these models to extrapolate from animals to humans is fraught with uncertainties because of significant interspecies and interindividual variations in clearance rates and particle lung burdens, and because the influence of the biologic environment on the bioavailability of adsorbed organic chemicals is uncertain.

THRESHOLDS FOR PARTICLE-INDUCED RESPONSES

Current data suggest that (1) diesel exhaust induces lung cancer in rats only under exposure conditions that produce particle overload and subsequent biological responses such as impaired alveolar clearance, inflammation, and cell proliferation, and (2) for each of these events, there may be an exposure threshold.

In laboratory animals, there appears to be a threshold for impaired clearance; however, the level of this threshold depends not only on the exposure concentration, but also on the dose rate (i.e., intermittent or continuous exposure) and the length of exposure (reviewed by Green and Watson, and Watson and Green, this report). In prolonged exposures at high concentrations of particulate matter (mg/m^3), clearance is retarded by a high dose rate (Bellmann et al. 1983); however, in prolonged exposures at low concentrations ($\mu\text{g}/\text{m}^3$), clearance is more efficient with a high dose rate (Strom et al. 1990). In addition, a previously deposited lung burden can slow lung clearance, and in the rat there is a threshold for this effect (600 to 800 μg of particulate matter/g of lung). In the studies reviewed by Watson and Green, the only exposure concentration for which alveolar clearance was not impaired in rats after prolonged exposure (24 months) to diesel exhaust particulate matter was a weekly exposure rate of $12.3 \text{ mg}/\text{m}^3 \cdot \text{hr}$ (Wolff et al. 1987).

In this report, Watson and Green note that, in the rat, markers of chronic inflammation, especially the number of neutrophils in bronchoalveolar lavage fluid, and epithelial cell proliferation are the most sensitive indicators of the lung's response to inhaled particulate matter. These two responses also are precursors of particle-induced lung tumors in the rat (Table 4). In this species, the lowest rate of exposure to diesel particulate matter that produced signs of inflammation or alveolar epithelial cell proliferation was a weekly dose rate of approximately 70 to $80 \text{ mg}/\text{m}^3 \cdot \text{hr}$. Generally, diesel particulate matter exposure rates below 200 to $500 \mu\text{g}/\text{m}^3 \cdot \text{hr}$ produce minimal or no inflammation or cell proliferation.

Exposure concentrations below certain weekly dose rates of diesel exhaust particulate matter (approximately $200 \text{ mg}/\text{m}^3 \cdot \text{hr}$) have not produced lung tumors (Figure 9). Although this suggests a threshold, it is also possible that the rodent studies did not have adequate statistical power to detect a response at a low exposure concentration. The Diesel Working Group examined the data from the eight rat carcinogenesis bioassays illustrated in Figure 9 to evaluate whether there is an exposure concentration of diesel particulate matter below which no statistically significant increase in lung tumors occurs. The results of this analysis are presented in Figures 13 and 14. The lung tumor data for each group of animals exposed to a given concentration of diesel exhaust was tested against the corresponding control group by a two-tailed comparison of tumor incidence (Fleiss 1981). Figure 13 shows that weekly exposure rate of diesel particulate matter above $200 \text{ mg}/\text{m}^3 \cdot \text{hr}$ generally produced a statistically significant increase in tumor incidence, whereas weekly exposure rates below that level did

not. In this analysis, the lowest weekly exposure rate that produced a significant result was $176 \text{ mg/m}^3 \cdot \text{hr}$ (Brightwell et al. 1989). The highest weekly exposure rate that failed to produce a significant result was $225 \text{ mg/m}^3 \cdot \text{hr}$. Further examination of the data for the effect of sample size shows that experiments containing between 100 and 200 animals produced both significant and nonsignificant results (Figure 14). The smallest sample sizes (coupled with relatively high exposures), in fact, produced the most statistically significant results (Iwai 1986; Heinrich et al. 1995).

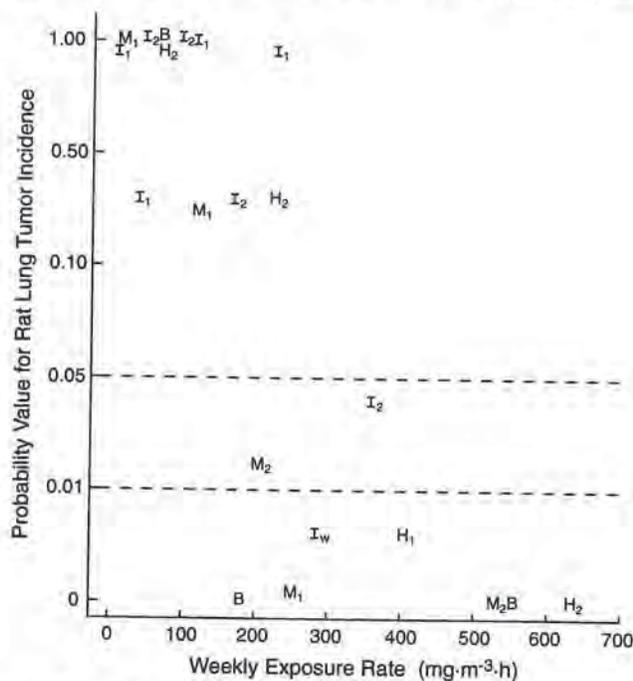
These findings support the idea that a particle burden sufficient to impair lung clearance mechanisms is a significant risk factor in the rat, and that there may be an exposure threshold below which diesel exhaust particulate matter does not cause inflammation and alveolar epithelial cell proliferation and, thus, will not induce lung tumors.

EXTRAPOLATING FROM RATS TO HUMANS

One reason that we cannot confidently extrapolate the results of this rat bioassay to humans is because we do not know if the particle-induced mechanisms of lung tumor formation postulated to occur in the rat under conditions of high levels of exposure to diesel exhaust also operate at low exposure concentrations. Such an assumption requires

that the particle-induced effects on cell initiation and proliferation continue to exist at low doses. As illustrated in Figure 9, the studies that have included exposure concentrations of diesel exhaust below those that impair lung clearance mechanisms have not shown a tumor response. Moreover, the histologic analyses of tissues from rats exposed to different concentrations of diesel exhaust have not indicated any alterations indicative of inflammation and alveolar epithelial cell proliferation below weekly particulate matter dose rates of 70 to $80 \text{ mg/m}^3 \cdot \text{hr}$ (see Watson and Green, this report).

A second reason why we cannot confidently extrapolate the rat results to humans is because we do not know whether the particle-induced mechanisms of rat lung carcinogenesis also operate in humans. The animal bioassay data indicate that different species are not equally sensitive to the effects of inhaled diesel exhaust or other poorly soluble particles (see Figure 10). Moreover, the epidemiologic data for coal miners (Merchant et al. 1986) and workers exposed to high concentrations of carbon black (International Agency for Research on Cancer 1984, 1987; Rivin 1986) indicate that high lung particle burdens do not necessarily lead to the development of lung cancer in humans. Equally plausible explanations for the small elevations in lung cancer risk in some occupational groups exposed to diesel exhaust would be exposure to nondiesel



particulate material or direct genotoxic action by the organic constituents of diesel exhaust, possibly in combination with a promoting effect of particle-induced cell proliferation.

Impaired lung clearance of particles at high levels of exposure has been observed in rats, mice, hamsters, and dogs. At present, only limited information is available about clearance impairment in humans. Simple extrapolation modeling suggests that prolonged exposure to high concentrations of respirable particles could, over a lifespan, result in particle burdens in human lungs similar to those found in rats (Morrow 1992; 1994). Studies of coal miners (Stöber et al. 1965) and smokers (Bohning et al. 1982) also suggest that pulmonary clearance is compromised in humans chronically exposed to high concentrations of particles.

There is no evidence, however, that impaired particle clearance in humans triggers the development of lung cancers. The most frequently cited example is coal miners (Mauderly et al. 1994). Although coal dust particles are larger than diesel exhaust particulate matter and have a different chemical composition, the extensive data base on coal miners provides insight into human responses to particle overloading of the lungs. Because miners are exposed to high concentrations of coal and other dusts for prolonged periods, they accumulate heavy lung burdens of particles and develop coal workers' pneumoconiosis (a nonneoplastic disease). Despite the presence of inflammation and fibrosis, several epidemiologic studies suggest that coal dust exposure does not increase the risk of lung cancer in this occupational cohort (Merchant et al. 1986).

Yu and Yoon (1991) developed a mathematical model that can be used to estimate what the threshold for lung overload (assuming there is one) might be in humans exposed to diesel exhaust particulate matter in one of two scenarios: a continuous exposure pattern (24 hours/day, 7 days/week), or an intermittent exposure pattern typical of occupational exposures (8 hours/day, 5 days/week) (Figure 15). With continuous exposure, lung clearance rates in humans were predicted to be gradually impaired as the exposure concentrations of diesel particulate matter rose from 100 to 1,000 $\mu\text{g}/\text{m}^3$. The model suggests a threshold for particle overload and impairment of lung clearance in humans of approximately 100 to 200 $\mu\text{g}/\text{m}^3$. For intermittent exposures, the model predicted that humans would be able to tolerate exposure to a 5- to 10-fold higher concentration of diesel particulate matter without experiencing overload than they could if exposed continuously. These values apply only to healthy adults; the models predict that the thresholds would be lower in adults with lung disease or in children.

Understanding the factors that govern the thresholds for clearance impairment and how they vary among species is critical to assessing permissible human exposure to diesel emissions and other types of poorly soluble particles.

CONCLUSIONS

- Diesel exhaust appears to induce lung cancer in rats only under conditions that impair particle clearance mechanisms and produce particle overload (i.e., a lung burden of 600 to 800 μg of particles, created by prolonged exposure to concentrations of diesel exhaust particulate matter greater than 2,000 $\mu\text{g}/\text{m}^3$). The presence of a particle burden sufficient to produce overload appears to be a significant risk factor for the carcinogenic response in the rat.
- Rats chronically exposed to diesel exhaust or other poorly soluble nonfibrous particles at exposure concentrations below 200 to 500 $\mu\text{g}/\text{m}^3$ show no signs of the biologic responses (such as inflammation and alveolar epithelial cell proliferation) that are associated with subsequent neoplasia. Moreover, weekly exposure rates above 200 $\text{mg}/\text{m}^3 \cdot \text{hr}$ are required to produce a statistically significant increase in lung tumor

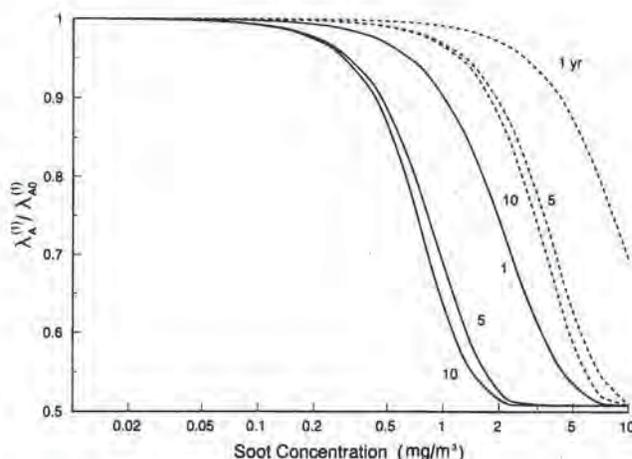


Figure 15. Model predictions for normalized clearance rates ($\lambda_c^0 / \lambda_c^0_0$) for diesel exhaust particulate matter in human adults at the end of a continuous exposure for 1, 5, or 10 years. Solid lines represent an exposure pattern of 24 hours/day and 7 days/week and dashed lines represent 8 hours/day and 5 days/week. (Reprinted from Yu and Yoon 1991.)

incidence in rats. This suggests that there may be an exposure threshold below which diesel exhaust will not induce lung tumors in rats.

- Extrapolating this no-effect level to humans is problematic because humans have substantially different particle clearance rates than rats. Moreover, current data are insufficient to quantify accurately or to model the differences between animals and humans in particle clearance; this injects uncertainty into the use of the rat bioassay data to estimate the human risk of exposure to diesel exhaust. The two species may also differ in their secondary responses (such as inflammation and cell proliferation) to particle overload and in their susceptibility to cancer.
- One mathematical model predicts that impaired particle clearance would not occur in the lungs of healthy adults unless they were continuously exposed for more than one year to levels of diesel exhaust particulate matter greater than 100 to 200 $\mu\text{g}/\text{m}^3$. The model also predicts that humans could tolerate 5- to 10-fold higher concentrations without experiencing particle overload if the exposures were intermittent (8 hours/day, 5 days/week).
- Mathematical models for extrapolating particle-induced effects from animals to humans have several limitations due to our lack of understanding of the following factors: the biological basis for the effects of high particle lung burdens, how particles in the alveoli are transferred to the interstitium, how organic compounds are transferred to macromolecules, and how particle-laden macrophages are transported through the alveoli to the points of storage or excretion.

ISSUE 11: *How can information about mechanisms of action guide the selection of scaling factors, dosimetry models, and extrapolation models for dose-response assessments of diesel emissions?*

For diesel exhaust, as for most carcinogens, we lack experimental data to tell us what the biologic response is at the low doses typical of human exposure, and we lack specific dose-response data on the human response to diesel emissions at any exposure level. Using the rat data for human risk assessment involves two extrapolations: extrapolation from high doses to low doses, and extrapolation from animals to humans. High- to low-dose extrapolations are performed using mathematical models to extrapolate the experimental high-dose animal data down to predict the type of response that might be expected at the lower doses experienced by humans (see Box 5). Interspecies extrapola-

tions are usually performed using scaling factors or dosimetry models, unless experimental data support a different approach. A number of models and scaling factors are available. Ideally in a risk assessment, the available data will be sufficient to help indicate which extrapolation model and scaling factor are most appropriate.

HIGH- TO LOW-DOSE EXTRAPOLATION MODELS

Scientists conducting risk assessments generally use the linearized multistage model, which is based on genotoxic mechanisms of carcinogenesis, for dose-response extrapolations. However, some scientists now argue that more recent models that incorporate mechanistic data on how the particular carcinogen causes cancer provide more accurate risk assessments, especially for carcinogens that operate through nongenotoxic mechanisms.

This debate is relevant to diesel emissions because the rat data imply that the particulate matter in diesel exhaust induces lung tumors in the rat by an indirect or nongenotoxic mechanism involving particle overload and associated inflammatory and proliferative processes. If so, a two-stage model, such as the one proposed by Moolgavkar and Knudson (1981), may be a better model for extrapolating the dose-response data for diesel exhaust-induced lung tumors than the linearized multistage model because it incorporates proliferative and mutagenic events. However, we currently lack mechanistic information to determine which dose-response model most accurately reflects the underlying biological processes for diesel exhaust-induced carcinogenesis.

SCALING FACTORS AND DOSIMETRY MODELS

The early risk assessments for diesel exhaust based their extrapolations on either the exposure dose of diesel particulate matter or adsorbed organic material, and used conventional scaling factors to convert estimates of the dose of diesel particulate matter per unit of rat body weight to humans. More recently, Pepelko and Chen (1993) based their extrapolations on the inorganic carbon core of the diesel exhaust particulate matter. To extrapolate these data to humans, they used a dosimetry model (Yu and Yoon 1991) that accounted for species differences in respiration and particle clearance rates, instead of more simplistic scaling factors. Using this model, they first converted the exposure dose to the burden of inorganic carbon per unit of lung surface area in the rat. They then extrapolated the rat lung burden data to estimate the human lung burden of diesel exhaust particulate matter. This extrapolation as-

sumes that a given concentration of particulate matter induces the same tumor incidence rate in rats and humans. Other adjustments were made to accommodate the effect of impaired clearance mechanisms on the lung burden of particulate matter. The model also assumed that lung burden of particulate matter is a better predictor of biologic effects than exposure concentration, an assumption that was not substantiated by the recent animal bioassays that compared the carcinogenic effects of different particulate materials (Mauderly et al. 1994; Heinrich et al. 1995; Nikula et al. 1995). These latter results indicate that the incidence of rat lung tumors is more closely related to exposure concentration of particulate matter than to lung particle burden.

CONCLUSION

- The use of extrapolation models for particle-induced lung cancer that do not account for particle overload and associated inflammatory and proliferative processes will, in all likelihood, overestimate the carcinogenic risk of diesel exhaust.

CRITICAL ISSUES IN ASSESSING HUMAN EXPOSURE TO DIESEL EMISSIONS

Exposure assessment, the third step in risk assessment, seeks to measure or estimate the intensity, frequency, and

Box 5

EXTRAPOLATION MODELS

There are many types of high-dose to low-dose extrapolation models. The EPA and many other regulatory agencies have traditionally used the linearized multistage model, which is based on dose-response data for radiation-induced cancer in humans. This model makes two conservative assumptions:

- It always predicts a linear dose-response relationship in the low-dose region (even if a nonlinear relationship is experimentally observed in this region).
- It assumes there is no threshold for carcinogenicity.

Thus, the linearized multistage model produces relatively conservative dose-response assessments and may overestimate risk, particularly for carcinogens that have threshold levels.

Many scientists have questioned whether the linearized multistage model, which is based on genotoxic mechanisms of carcinogenesis, should be used for nongenotoxic carcinogens. These scientists have proposed using alternative models that are based more on biologic processes, such as Moolgavkar and Knudson's (1981) two-stage model. Their model incorporates many parameters considered important for carcinogenesis, such as cell division, mutations, cell differentiation, and cell death. They argue that these models would likely provide more accurate estimates of cancer potencies, particularly for nongenotoxic carcinogens.

Two National Research Council committees recently reviewed risk assessment procedures and considered whether these newer models should be used for dose-response assessments. The Committee on Risk Assessment Methodology (National Research Council 1993) noted that the use of the two-stage model required many assumptions and extensive data. Therefore, the Committee did not recommend its use for routine dose-response extrapolations, but did encourage its use to increase understanding of mechanisms. The National Research Council's Committee on Risk Assessment of Hazardous Air Pollutants (1994) also concluded that the EPA should continue to use the linearized multistage model as the default for extrapolating from high doses to low doses. It also recommended that alternative extrapolations be made if sufficient "information on the mechanism of cancer induction suggests that the slope of the linearized multistage model is not appropriate for extrapolation," and that "evidence for both estimates should be made available to the risk manager." In its recent "Draft Revisions to the Guidelines for Carcinogen Risk Assessment," the EPA (1994a) noted that extensive data would be required to support the use of the two-stage model, and therefore recommended that the multistage model be the default option in the absence of such data.

duration of human exposures to pollutants and to identify the size and demographic characteristics of the populations exposed.

ISSUE 12: What do we know about human exposure to diesel exhaust in occupational and ambient settings?

The most accurate exposure measurements use an exposure index that is relevant to early biological effects or markers of disease and assesses the dose of pollutant, or a surrogate for the pollutant, that reaches the target tissue (the lungs, in the case of diesel exhaust). For risk assessment purposes, the more links that can be established between the animal and human experience, the more confidence one has in the extrapolation. Scientists can measure the tissue dose of particulate matter in laboratory animals, but not in humans because the procedure is too invasive. Therefore, they have developed both direct and indirect approaches to estimating human exposure to diesel exhaust.

BIOMARKERS

The most direct and biologically relevant approach to estimating exposure to diesel exhaust would be to find a unique biomarker, that is, a compound that consistently appears in tissues or fluids only after exposure to diesel exhaust and that can be measured noninvasively. Although there has been intense interest in developing a biomarker for constituents of diesel exhaust, none has yet been developed that is sufficiently sensitive or selective to be applied in epidemiologic studies.

Both PAHs and nitro-PAHs have been considered as potential biomarkers of exposure to diesel emissions because of their mutagenic and carcinogenic potencies, their elevated concentration in diesel exhaust, and their ability to form adducts with DNA and proteins. Existing assays can detect PAH- and nitro-PAH-DNA adducts if the exposure concentration is high, but more work is needed to develop sensitive and specific assays that can detect these adducts in humans when the exposure concentration is low. The use of 1-nitropyrene as a biomarker has not been established because its complex metabolism is species- and tissue-specific. The 1,6- and 1,8-dinitropyrenes, by contrast, may be better suited as biomarkers because they are metabolized similarly by different species. However, they occur at such low levels in diesel emissions that we currently lack techniques to detect protein and DNA adducts from these compounds in human subjects under environmental exposure conditions. Other potential biomarkers of diesel exhaust exposure are being investigated. These include mutational spectra, oncogenes, and other molecular markers.

TRACERS FOR MONITORING PERSONAL EXPOSURES AND AMBIENT CONCENTRATIONS

Other approaches to exposure assessment include using personal monitors or measuring pollutant concentrations in representative air samples. The complexity of diesel exhaust prohibits the measurement of all exhaust constituents. Therefore, scientists usually select one or more constituents that can be used as surrogate measures of the other constituents. The particulate matter and the PAHs in diesel exhaust are the most likely candidates for unique tracers. Although PAHs occur in all combustion emissions, some substituted PAHs are enriched in diesel emissions; however, none appear to occur in sufficiently high concentrations to serve as a selective tracer for diesel emissions (Daisey et al. 1986; Zielinska 1991).

Several techniques have been developed to distinguish the particulate matter in diesel exhaust from the many other fine particles emitted into the atmosphere by natural sources (dust, fires, volcanoes) and other anthropogenic sources (mobile and stationary sources, fireplaces, and food cooking operations). These techniques identify diesel particulate matter based on the small particle size (the mass median aerodynamic diameter is approximately 0.2 μm , and 90% of particles have diameters less than 1 μm in size) and high elemental carbon content. Techniques that employ elemental carbon analysis must be carefully standardized because the proportion of elemental to organic carbon in diesel particulate matter varies depending on fuel, engine type, duty cycle, engine maintenance, the operator's habits, use of emission control devices, lubrication oil consumption, and other factors. Despite these limitations, fine elemental carbon particles presently provide the best surrogate measure for diesel exhaust.

Two papers in this report discuss how the above techniques have been applied to measure diesel exhaust particulate matter in occupational settings (Watts, this report) and to estimate regional emissions and atmospheric concentrations of diesel exhaust particulate matter in the Los Angeles basin (Cass and Gray, this report).

OCCUPATIONAL EXPOSURES

Occupational exposures to diesel exhaust are generally higher than ambient exposures. Recent industrial hygiene surveys of miners, forklift truck operators, truck drivers, and railroad workers indicate a wide range (4 to 1,700 $\mu\text{g}/\text{m}^3$) of daily occupational exposures to the particulate matter in diesel exhaust. Not surprisingly, the highest oc-

cupational exposures to diesel exhaust particulate matter (100 to 1,700 $\mu\text{g}/\text{m}^3$) were in enclosed spaces such as mines that use heavy-duty diesel engines and supply fresh air by forced ventilation. The mean concentrations of diesel exhaust particulate matter for several occupations ranged from 20 to 100 $\mu\text{g}/\text{m}^3$; truck driver exposures were in the ambient range (4 to 6 $\mu\text{g}/\text{m}^3$). It is important to note that these are recent measurements and cannot be related to past exposures to diesel particulate matter with any degree of certainty.

Watts (this report) notes that the levels of diesel exhaust particulate matter in underground mines have declined over the last 20 years. In general, stricter occupational health standards, better ventilation, altered work practices, improved engine maintenance, engine design modifications, improved fuel quality, and the use of exhaust control technology have reduced workers' exposure to diesel exhaust over the last two decades.

ATMOSPHERIC CONCENTRATIONS

One of the most in-depth characterizations of the atmospheric concentrations of diesel exhaust particulate matter was conducted in the Los Angeles area in the early 1980s, and is summarized in the paper by Cass and Gray, this report. These investigators based their analysis on the size and elemental carbon content of airborne particles. Using emissions inventory data for more than 70 different types of air pollution sources, they calculated that diesel exhaust accounted for approximately 3% of total particulate matter emissions and 7% of respirable fine particle (mean aerodynamic diameter less than 2 μm) emissions.

To estimate the contribution of diesel engine exhaust to the ambient levels of fine particles, they focused on the elemental carbon content of ambient particles, a parameter they determined was closely related to diesel exhaust. As illustrated in Figure 16, they estimated that diesel engines contributed approximately two-thirds of the fine aerosol

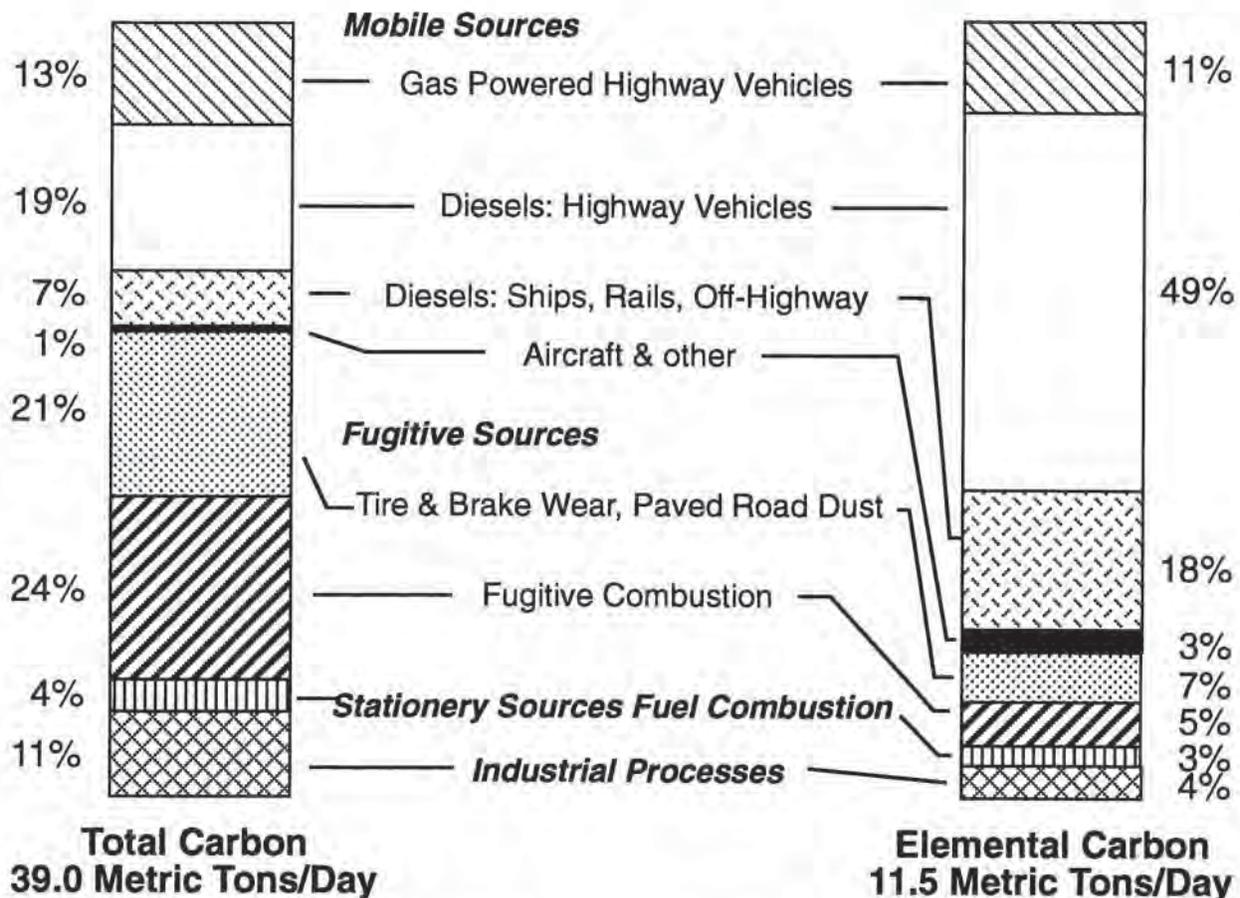


Figure 16. Source apportionment of fine aerosol carbon emissions in the Los Angeles basin in 1982. (Cass and Gray, this report.)

elemental carbon emissions in the Los Angeles area in 1982. Using an air quality model for computing the contributions from various sources to the atmospheric elemental carbon particle concentrations (which were tested against ambient measurements), Cass and Gray calculated that the monthly average ambient concentrations of diesel exhaust particulate matter ranged from 10 $\mu\text{g}/\text{m}^3$ at the most polluted locations to 1.7 to 3.3 $\mu\text{g}/\text{m}^3$ in less polluted areas.

Cass and Gray's analysis of historical trends in elemental carbon particle concentrations in the Los Angeles atmosphere suggests that ambient concentrations from 1958 to the mid-1980s were similar to those determined for 1982. During that period, elemental carbon particle concentrations declined slightly at the most urbanized sites and increased at sites that were progressively urbanized. This analysis does not include 1990s data for ambient concentrations of carbonaceous particles in the Los Angeles basin. However, because emissions controls have substantially reduced particle emissions from diesel engines when compared with 1982 (Figure 6), aerosol carbon likely has declined since that time.

The Cass and Gray estimates for average concentrations of diesel exhaust particulate matter in the ambient atmosphere are similar to those obtained by the EPA using an emissions inventory model. In its "Motor Vehicle-Related Air Toxics Study," the EPA (1993) estimated annual average exposures to diesel exhaust particulate matter for 1990 through 2010. This study used a series of steps to calculate diesel engine particulate emissions for each vehicle class by model year for the last 20 years. The factors entered into this analysis were emission rates (based on either federal certification test results or design targets) and vehicle miles traveled (based on past market shares for diesel-powered vehicles and future projections of vehicle sales and fuel use). Conversion factors were used to account for efficiency factors and the use of low-sulfur fuel, and to transform the emission rates for particulate matter from grams/brake-horsepower • hours to grams/mile, and ultimately to micrograms/cubic meter. The resulting estimates for annual average exposures to diesel exhaust particulate matter in 1990 were about 2 $\mu\text{g}/\text{m}^3$ in urban locations and 1 $\mu\text{g}/\text{m}^3$ in rural areas. These estimates agree well with Cass and Gray's estimates of the average concentrations of diesel exhaust particulate matter in less-polluted areas in the Los Angeles basin in 1982. The EPA's analysis reflects the projected effect of increasingly stringent diesel engine particulate matter standards on atmospheric concentrations. Its estimates of the ambient levels of diesel exhaust particulate matter for the year 2000 are one-third of those calculated for 1990.

CONCLUSIONS

- Experimental data for assessing general population exposure to diesel engine emissions are limited because diesel exhaust particulate matter represents only a small fraction of total particulate air pollution, and no totally satisfactory markers have yet been developed to distinguish between the organic components of diesel emissions and the products of other combustion processes.
- At present, elemental carbon particles of less than 2 μm in mass median aerodynamic diameter are the best available surrogate for the particulate matter in diesel exhaust.
- Exposure to diesel exhaust particulate matter has been measured in some occupational settings, but information on ambient exposures is very limited. Consequently, inferences about the relation between the exposure concentrations of diesel exhaust that produce lung cancer in rats and those to which humans are exposed are tenuous.
- Occupational and ambient concentrations of the particulate matter in diesel emissions have been estimated using sampling procedures that measure fine respirable particles and analyze elemental carbon. These studies indicate a wide range of human exposures to diesel exhaust particulate matter: from 4 to 1,740 $\mu\text{g}/\text{m}^3$ in occupational settings, and 1 to 10 $\mu\text{g}/\text{m}^3$ (over long averaging times) in the ambient atmosphere.

ISSUE 13: *What do we know about the size and characteristics of the populations exposed to diesel emissions?*

The second aspect of exposure assessment is evaluating the number of people who are likely to be exposed to diesel emissions and the characteristics of the exposed populations. This is an area of considerable uncertainty because (1) only a limited number of measurements have been made of the levels of diesel exhaust particulate matter in different environmental settings, and (2) air quality models have only been applied in a few instances to estimate the distribution of diesel emissions exposures in different microenvironments.

It is easier to characterize pollutant exposures in settings where populations have substantial and continuous exposures to diesel emissions than it is in settings where the exposures are low or intermittent. Therefore, it is not surprising that we know more about exposures of workers to diesel emissions than we do about the general population.

Workers who are exposed to diesel emissions (as well as to other types of particulate air pollution) include: miners, railroad workers, loading dock workers, truck drivers, bridge and tunnel workers, fork-lift operators, and fire-fighters. Measurements of airborne concentrations of diesel exhaust particulate matter exist for these occupations. The International Agency for Research on Cancer (1989) reviewed the older literature on occupational exposures to diesel exhaust and Watts provides recent information in this report. However, it is important to note that the time scale of occupational measurements (usually an eight-hour averaging time) differs from the long-term averaging times (weeks or months) that are typically used to express environmental levels of diesel exhaust particulate matter (see Cass, this report). Moreover, because investigators use different techniques to measure diesel exhaust particulate matter, the values obtained in different studies are not always directly comparable.

The National Institute for Occupational Safety and Health (1988) estimates that approximately 1.35 million people are exposed to diesel emissions in the work place. Underground miners (approximately 30,000 miners are potentially exposed to diesel exhaust in the United States; Watts, personal communication) are probably the most heavily exposed population. Recent measurements of eight-hour average concentrations of diesel exhaust particulate matter generally range from 100 to 1,000 $\mu\text{g}/\text{m}^3$ for most mines, although levels in excess of 2,000 $\mu\text{g}/\text{m}^3$ have been reported. Workers in most other occupations are generally exposed to 10 to 100 $\mu\text{g}/\text{m}^3$. Investigators have not identified subgroups within these occupational cohorts according to gender, health status, or other characteristics. Given the nature of these occupations, it is likely that male workers predominate and their health status is probably better than that of the general population.

Only a few studies shed light on the number or characteristics of people who are exposed to diesel exhaust in the environment or the duration and degree of their exposures. Although average ambient exposures to diesel exhaust particulate matter are generally low (1 to 10 $\mu\text{g}/\text{m}^3$), in some settings higher short-term or peak exposures occur. These include busy streets, bus and truck terminals, parking areas, and highways. Modeling studies suggest that the potential for environmental exposure to diesel exhaust is higher on busy urban streets where there is less opportunity for particle dispersion than near freeways (Volkswagen 1989). In urban streets, large numbers of people may receive short-term exposures to diesel emissions because the pollutants are emitted at street-level, in close proximity to the breathing zone. In these environments, localized peak levels of diesel exhaust particulate matter can reach 30 $\mu\text{g}/\text{m}^3$ (A.W.

Gertler, Desert Research Institute, personal communication). Also, diesel exhaust from urban vehicle emissions probably contributes to indoor exposures because the particulate and gaseous emissions can enter building ventilation systems.

CONCLUSIONS

- Information is available about the levels of diesel exhaust particulate matter in a variety of occupational settings; however, the size and characteristics of the exposed populations have not been well documented.
- Localized areas in urban settings represent the most likely sources of exposure of the general population to diesel emissions. More information is needed about (1) the levels of diesel particulate matter in different microenvironments, (2) the temporal pattern of exposure, and (3) the number and characteristics of the exposed population.

CRITICAL ISSUES IN CHARACTERIZING THE HUMAN RISK OF CANCER FROM EXPOSURE TO DIESEL EMISSIONS

ISSUE 14: Considering the currently available data for diesel emissions, how can we best characterize the human cancer risk associated with exposure to diesel exhaust?

Risk characterization, the final step in risk assessment, integrates information from hazard identification, dose-response evaluation, and exposure assessment to characterize the public health risk associated with exposure to a specific pollutant. A risk characterization should not only estimate risk but also describe the uncertainties inherent in the estimate, thereby providing risk managers and the public with a balanced understanding of the type and magnitude of the adverse effect or effects a particular substance may cause under various circumstances.

Risk can be characterized either qualitatively or quantitatively. Quantitative characterizations of risk are stated as estimates of an individual's added lifetime risk, or as the number of extra cancer cases expected in an exposed population of particular size. Cancer risk estimates are based on a potency factor (produced in the dose-response evaluation step) and an estimate of lifetime average daily exposure (derived from the exposure assessment step). Quantitative risk characterizations inevitably involve making certain assumptions in order to compensate for data gaps. These risk estimates, therefore, are often conservative, but do give a general indication of the relative magnitude of potential cancer risk associated with a particular pollutant.

At present, several uncertainties are associated with characterizing the human cancer risk from diesel emissions:

- The animal response observed at concentrations of diesel emissions high enough to impair particle clearance may not apply to humans who usually are exposed to concentrations too low to impair clearance (see Issue 10).
- The fact that rats apparently exhibit a threshold for neoplastic and nonneoplastic responses to inhaled diesel exhaust and other particulate matter injects uncertainty in using rat data obtained at high doses to predict human responses at low doses.
- For these reasons, the potency factors calculated for diesel emissions (Figure 3) may not provide a sound basis for risk estimates because of uncertainties in the dose-response extrapolations (see Issue 10).

Because of these questions, HEI's Diesel Working Group found that a risk characterization of diesel exhaust cannot currently be based on a single set of studies. Rather, we integrated and evaluated information from diverse data sets to make judgments about the carcinogenicity of diesel exhaust. The group considered two integrative approaches to diesel risk characterization, as described below.

COMPARATIVE APPROACH

One approach is to compare the elevation in human lung cancer attributed to diesel emissions in epidemiologic studies to the elevation in cancer risk from environmental tobacco smoke and radon, both of which are known human lung carcinogens. The reported relative risks of prolonged exposure to diesel emissions in occupational settings generally range from 1.2 to 1.5. This can be interpreted as indicating that exposure to diesel exhaust increases the risk of lung cancer in the exposed population by between 20% and 50%. For comparison, the EPA's overall risk estimates for environmental tobacco smoke range from 1.19 to 1.59 (Environmental Protection Agency 1992). Risk estimates for radon are uncertain, but estimated to be less than 1.2 for a 25-year exposure at 4 pCi/L (Lubin 1994).

The reported lung cancer risk estimates for diesel exhaust are in the range of those reported for environmental tobacco smoke and radon. However, the lack of information on exposure in the epidemiologic studies of diesel exhaust limits using the reported risk factors to estimate population incidence or the number of extra cancer cases expected in exposed groups.

MECHANISTIC APPROACH

Qualitative approaches to characterizing the human cancer risk associated with diesel emissions involve integrating animal, epidemiologic, and exposure studies, taking

into consideration what we know about carcinogenic mechanisms. In the rat, lung tumors develop only after nearly lifetime exposures to concentrations of diesel exhaust particulate matter ranging from 2,000 to 10,000 $\mu\text{g}/\text{m}^3$ (the lower concentrations usually require longer exposures; for example, 16 or more hours/day). These concentrations are approximately three orders of magnitude higher than current estimates for long-term average atmospheric concentrations of diesel particulate matter (1 to 10 $\mu\text{g}/\text{m}^3$). However, the upper bound for diesel exhaust particulate matter in some occupational settings (1,700 $\mu\text{g}/\text{m}^3$) is within the exposure range that produced tumors in rats (Figure 17). Therefore, it is plausible that the particle exposure rates for occupationally exposed workers could sometimes be high enough to overwhelm lung clearance mechanisms (especially in individuals whose particle clearance mechanisms are impaired due to smoking or lung disease) and possibly could lead to the development of lung cancer. However, the limited data for coal miners suggest that even when particle clearance mechanisms are overwhelmed and the lungs contain heavy particle burdens, cancer does not necessarily develop.

Although the data for miners inject some uncertainty into using the rat data to estimate human risk at high diesel exposures, much greater uncertainty is associated with using the animal bioassay data to estimate human risk at lower exposures, such as those experienced by the most heavily exposed railroad workers or forklift operators (100 to 200 μg of diesel exhaust particulate matter/ m^3). In rats, the appearance of inflammatory cells in the lungs has been observed only under conditions of continuous exposure to concentrations of diesel exhaust particulate matter that exceed approximately 200 $\mu\text{g}/\text{m}^3$ (Watson and Green, this report), and tumors are produced when particulate matter concentrations are in excess of 2,000 $\mu\text{g}/\text{m}^3$ (Busby and Newberne, this report). This suggests that workers exposed to concentrations of diesel exhaust particulate matter less than 200 $\mu\text{g}/\text{m}^3$ would not be at risk for lung cancers that develop through particle-related mechanisms. However, because of the wide interspecies variability in lung clearance rates and the added burden from inhaling other particulate matter, it is possible that the elevated risk associated with occupational exposure to diesel exhaust reported in some epidemiologic studies could be due to a particle-induced effect. Also, at this time, we cannot exclude the possibility that a genotoxic mechanism involving direct action between DNA and the mutagens in diesel emissions might operate in humans.

Most of the U.S. population is exposed to relatively low long-term average atmospheric concentrations of diesel particulate matter (1 to 10 $\mu\text{g}/\text{m}^3$), and for this population the relevance of the rat bioassay data to estimate human lung cancer risk is questionable. At these exposure concentra-

tions, no evidence of chronic inflammation or epithelial hyperplasia in laboratory animals has been identified (Watson and Green, this report). Moreover, one modeling study (Yu and Yoon 1991) predicts that under conditions of continuous exposure to diesel exhaust particulate matter for up to 10 years, the alveolar clearance rate in adult humans would not be affected at exposure concentrations of respirable particles below 50 to 100 $\mu\text{g}/\text{m}^3$. The model also predicts that healthy adults could tolerate exposures five to ten times higher without a decline in clearance rates if the exposures were intermittent rather than continuous. These results provide some support for the idea that current ambient exposures to diesel emissions alone do not pose a significant risk of particle-induced cancer. This analysis applies to healthy adults; there are subpopulations, such as infants (Yu and Yoon 1991), smokers, and individuals with chronic obstructive pulmonary disease (Bohning et al. 1982), who have slower long-term particle clearance rates.

The above discussion is based on the premise that the mechanisms of diesel exhaust-induced carcinogenesis are comparable in rats and humans. Until this can be established, it would be premature to exclude consideration of the cancer-causing potential of the organic constituents. As discussed in Issue 3, epidemiologic studies of occupationally exposed workers suggest a small incremental risk of lung cancer associated with exposure to diesel exhaust. This increased risk in workers is, however, not expected to be accompanied by impaired lung clearance that is characteristic of rats after a lifetime exposure to high concentrations (in excess of 2,000 $\mu\text{g}/\text{m}^3$) of diesel emissions. Thus,

it is possible that human exposure to diesel engine emissions in occupational settings may involve a risk that is not accounted for by the rat model. Moreover, the rat model evaluates the biologic effects of emissions and does not account for the activity of atmospheric transformation products.

CONCLUSION

- There is a biologic rationale for extrapolating the rat bioassay results to people exposed to high concentrations (greater than 1,000 $\mu\text{g}/\text{m}^3$) of diesel exhaust and other particulate matter in certain occupational settings, and perhaps to exposure concentrations as much as one order of magnitude lower. However, the toxicologic data do not support the assumption that particle-induced mechanisms of lung carcinogenesis operate in the ambient exposure range (1 to 10 $\mu\text{g}/\text{m}^3$). This raises questions about the validity of using the rat bioassay data to characterize the potential human risk associated with ambient exposures to diesel emissions.

SUMMARY

Diesel exhaust is a complex mixture of gases and carbonaceous particles. The vapor phase contains typical combustion gases (e.g., sulfur dioxide, nitrogen dioxide [an ozone precursor], and carbon monoxide) and low-molecular-weight organic compounds, including aldehydes. The particles in diesel exhaust are of particular concern because

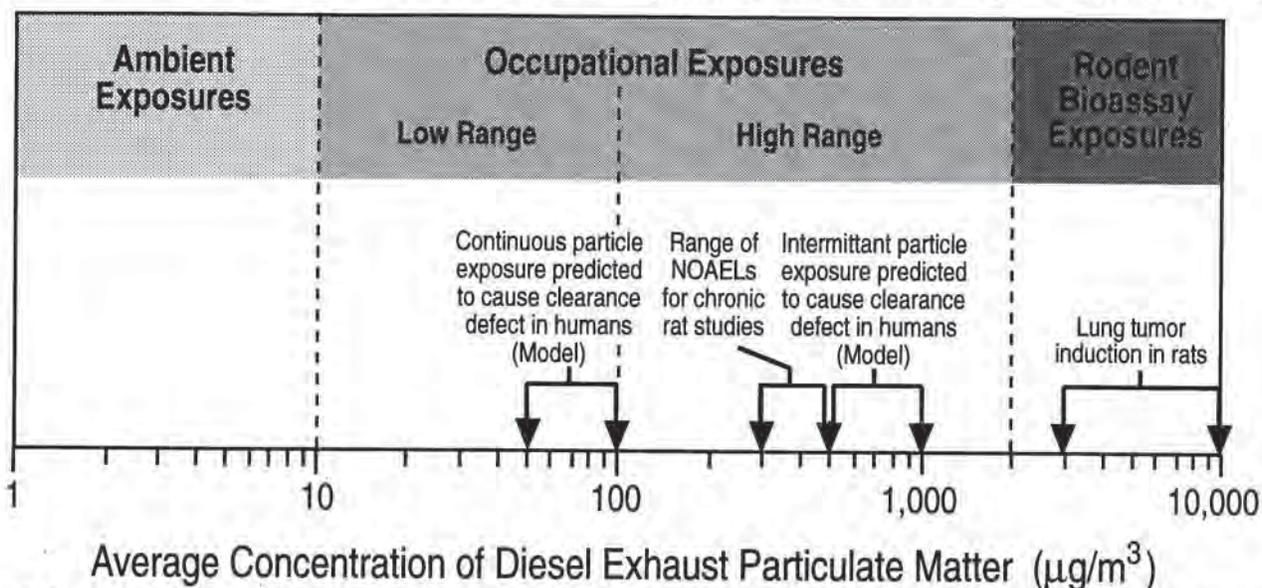


Figure 17. Levels of diesel exhaust particulate matter in the environment compared with those causing biologic effects in animals. The values for no observable adverse effects levels (NOAEL) are for increased neutrophils bronchoalveolar lavage fluid, and alveolar epithelial cell proliferation in rats exposed for 3 months or longer to diesel engine emissions. Occupational exposure levels taken from Watts, this report; ambient exposure levels taken from Cass and Gray, this report. (See Watson and Green, this report.)

they are of respirable size and have many chemicals adsorbed onto their surfaces. These chemicals include potent mutagens and carcinogens (e.g., PAHs and nitro-PAHs) that can be transformed into species that react with DNA. The particulate matter in diesel exhaust also contains sulfate compounds. Studies of the carcinogenicity of diesel exhaust originally focused on these chemical carcinogens; however, recent attention has been directed to the particles themselves.

The composition of diesel emissions is highly variable and depends on engine type, fuel, operating conditions, and emissions controls. As a result of improvements in engine technology, emissions of oxides of nitrogen, particulate matter, carbon monoxide, and hydrocarbons from new heavy-duty diesel engines are substantially lower now than they were 20 years ago. The particles emitted from today's diesel engines have a lower mass fraction of adsorbed organic chemicals than particles emitted from older engines. On-highway diesel engines also emit less particle-containing sulfate since the implementation of low-sulfur fuel in 1993. Further reductions in diesel engine emissions are expected with the implementation of emissions control systems and fuel reformulation. However, these reductions will be gradual because of the long life of heavy-duty diesel engines. Anticipated changes in future diesel emissions should be considered in risk characterizations of diesel exhaust.

Evaluating human exposures to diesel exhaust is complex because diesel emissions are only one of many contributors to ambient particulate and chemical air pollution. In the workplace, diesel emissions can contribute a significant proportion of the exposure atmosphere. Moreover, emissions data for individual chemical constituents of diesel exhaust cannot completely account for all diesel-related exposures because atmospheric transformation of primary diesel emissions produces additional chemical species (e.g., PAH derivatives) that may have significant, but presently unknown, biological impact.

The data base on the potential carcinogenicity of diesel emissions is large and diverse. Epidemiologic studies, animal bioassays, molecular research, emissions data, exposure assessments, and modeling all contribute important information to the characterization of human health risks from diesel exhaust. These data are generally consistent in indicating the potential for diesel emissions to cause lung cancer; however, gaps in the animal and human data limit our ability to evaluate the magnitude of that risk for human populations.

Based on data from more than 30 epidemiologic studies, prolonged exposure to diesel exhaust appears to pose a small (1.2- to 1.5-fold) additional relative risk of lung cancer

to workers in certain occupational settings. Although these studies vary in quality and the strength of the statistical association, the findings of elevated lung cancer risk in occupational cohorts are consistent. Only a few studies addressed potential confounding by factors such as cigarette smoke, environmental tobacco smoke, other particles, asbestos exposure, diet, and socioeconomic status. Most studies that controlled for smoking found that the association with lung cancer persisted after such controls were applied, although in some cases the excess risk was lower. There is insufficient evidence to evaluate whether confounding by other factors influenced the results. Some occupational cohorts exhibited an elevated incidence of bladder cancer, but the strength and weight of evidence for bladder cancer is not as great as for lung cancer.

The main methodologic problem limiting interpretation of the epidemiologic data is that none of the occupational studies measured concurrent exposure to diesel exhaust or other particles, or provided information about the emissions characteristics of the exposure source. Thus, the epidemiologic studies do not provide information about the causative agent or agents, nor can their results be used for dose-response extrapolations.

The carcinogenicity of diesel exhaust has been confirmed in one animal species. Prolonged exposure to high concentrations of diesel exhaust causes lung tumors in rats. No tumorigenic response was seen in hamsters at the same exposure levels, and the results in mice are equivocal. Recent studies indicate that the particulate matter in diesel exhaust is the constituent responsible for inducing lung tumors in rats, and that under exposure conditions involving high particle concentrations, the organic chemicals do not have a major role.

The relevance of the rat data to humans is questionable because the lung tumors were produced under exposure conditions involving high concentrations of diesel particulate matter that overwhelmed normal lung clearance mechanisms, leading to progressive inflammation, alveolar epithelial cell hyperplasia, fibrosis, and metaplasia. We only partially understand the mechanisms in the rat lung that respond to diesel exhaust particulate matter or to other poorly soluble nonfibrous particles. The data are consistent with nongenotoxic mechanisms of carcinogenesis driven by particle-induced inflammatory and proliferative processes. We currently lack sufficient data, however, to know whether the apparent carcinogenic mechanism that operates in rats exposed continuously to these high concentrations of diesel exhaust particulate matter (greater than 2,000 μm^3) also operates in humans exposed intermittently to either the levels of diesel exhaust particulate matter found in some occupational settings (100 to 1,000 $\mu\text{g}/\text{m}^3$) or the

long-term average levels found in the ambient environment (1 to 10 $\mu\text{g}/\text{m}^3$). The data suggest that there may be a threshold level for the rat neoplastic response. This suggestion injects additional uncertainty into extrapolating data from high-dose to low-dose exposures using the nonthreshold models typically employed in risk assessments. Finally, we cannot presently exclude the possibility that, at low-level exposures, the organic compounds in diesel exhaust may either initiate or promote tumor development in the lungs or at other sites. A better understanding of the mechanisms of carcinogenesis would help to establish scientifically valid links between lung cancer in laboratory animals and the human disease, thus improving the accuracy of cancer risk assessments.

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APPENDIX A. RISK ASSESSMENT: AN EVOLVING PROCESS

In regulatory terms, risk is the possibility or probability that adverse health effects will result in an individual or population exposed to a hazardous substance. Risk assessment is a systematic approach for evaluating information on the hazardous properties of a substance, determining the extent of human exposure to that substance, and characterizing the resulting risk. Although risk assessment has its historical roots in occupational health and radiation biology, the process we use today is based on the framework developed by the National Research Council (1983). The key features, which are illustrated in Figure 2 of the main text, include four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. As noted in Figure 2, the National Research Council made a clear conceptual distinction between risk assessment (the process of evaluating risk) and risk management (integrating risk assessment results with other information to make policy decisions).

Hazard identification, the first step in risk assessment, draws on the results of epidemiologic and animal studies to determine whether a compound or mixture poses a health threat, and, if so, what type of hazard it presents; cellular studies play a supporting role. In categorizing a suspected carcinogen, both the EPA and IARC have developed procedures to classify the available scientific evi-

dence as "sufficient," "inadequate," or "limited," and then, based on these designations, to further rank the material into categories. For example, the EPA's categories are: human carcinogen, probable human carcinogen (with two subgroups), possible human carcinogen, not classifiable, and noncarcinogen.

A National Research Council Committee that recently reviewed the EPA's risk assessment procedures for hazardous air pollutants strongly recommended that hazard identification include additional narrative information to inform readers about the nature of the evidence on which the conclusions are based (National Research Council 1994). Such a narrative would include an evaluation of the strength of the data and a weight-of-evidence evaluation of (1) the relevance of the animal model to humans, (2) the exposure conditions under which the carcinogenic response was observed in animals, and (3) the relevance of these conditions to the types of exposures likely to be experienced by human populations.

Establishing the hazardous properties of a suspected carcinogen is not the same as estimating its risk. To estimate cancer risk, two other pieces of information are needed: a potency factor, which is derived from the dose-response assessment, and an estimate of exposure made during the exposure assessment step.

Dose-response assessment is the process of estimating the relation between the dose of a substance and the incidence of an adverse health effect. It is probably the most contentious step in cancer risk assessment because analysts move beyond the observational data to develop a quantitative estimate of risk using various models. Although unit risk estimates are sometimes used to compare the carcinogenic potential of different environmental carcinogens, they can be misinterpreted because they do not fully reflect all of the underlying assumptions made when calculating the risk estimates.

Biologic responses to low exposure doses usually cannot be measured directly in either epidemiologic studies or animal bioassays; therefore, they are estimated by applying mathematical models to extrapolate responses observed at high doses to predict responses at low doses. Because the doses required to produce a statistically significant effect in an animal bioassay are usually quite high compared with ambient concentrations, the models typically are used to extrapolate over three or four orders of magnitude. If animal data are used, then additional models or scaling factors must be applied to extrapolate from animals to humans. Thus, when calculating the dose-response relation for diesel exhaust, analysts are making two interrelated extrapo-

lations: from high to low doses and from animals to humans. Understanding the biologic mechanisms that are operative in animals and humans exposed to diesel exhaust can either increase or decrease confidence in the validity of the assumptions that underlie these extrapolations.

Many types of models can be used to extrapolate from epidemiologic observations or experimental observations at high doses in laboratory animals down to the low doses usually experienced by humans in the general population. The high-dose data are fit into the parameters of a mathematical model, and the model is then used to fit a curve that predicts the dose-response relation at doses below the experimental range. The EPA usually applies a 95% upper confidence limit on the slope of the low-dose linear portion of the curve to represent an upper bound on an agent's carcinogenic potency. This upper-bound potency factor is then used to calculate the unit cancer risk, which is the upper bound of the probability of cancer developing in humans exposed continually to one unit of the carcinogen (typically $1 \mu\text{g}$ of agent/ m^3 of air for an airborne carcinogen for a lifetime [70 years]).

The EPA and many other regulatory agencies use the linearized multistage model to estimate dose-response relations for carcinogens (see Box 5). The key features of this model are (1) the dose-response curve is linear at low doses, even if it is nonlinear in the region of observation, and (2) it assumes the substance may cause cancer at any dose (i.e., there is no threshold).

Exposure assessment, the third step in risk assessment, is the process in which the intensity, frequency, and duration of pollutant exposures are either measured, or in the absence of data, estimated. There are two aspects of exposure assessment. The first involves determining the source or sources of a particular pollutant, how that pollutant leaves its source, how it is transported or changed in the environment, and how it makes contact with humans (National Research Council 1991). The dose term in exposure assessments can take different forms. The exposure dose is the amount of pollutant that is absorbed or deposited in the body. It depends on the exposure concentration, the uptake rate, and the duration of exposure. For inhaled pollutants, activity levels, which affect breathing rates, are important determinants of exposure dose. Another measure of dose is the tissue dose, that is, the amount of a pollutant or one of its metabolites in the target tissue. If exposure rates are excessively high, such as occurs when particle clearance rates are overwhelmed, then the localized tissue dose may be much higher than predicted. Also, changes in the physical characteristics of inhaled pollutants alter the site of

deposition in the respiratory tract (see Green and Watson, this report). Although tissue dose can be reliably measured in animal bioassays, the concept is difficult to apply to humans in epidemiologic studies. The second aspect of exposure assessment is determining the number of people who are likely to be exposed to the pollutant of concern and the distribution of exposures within that population.

Risk characterization, the final step in risk assessment, combines information from hazard identification, dose-response evaluation, and exposure assessment to estimate the probability that cancer will develop in an exposed population or individual. This step involves taking the unit risk factor obtained from the dose-response evaluation and applying scientific judgment to aggregate population groups that may vary in sensitivity and exposure. The result may be expressed qualitatively or, if risk scientists have sufficient confidence in the result, quantitatively. When expressed quantitatively, a risk characterization for a carcinogen represents the upper bound on the probability that, under the specified exposure conditions, lifetime exposure to the carcinogen will lead to an excess cancer risk in the exposed individual. The problem with quantitative risk characterizations is that they are expressed as a single numerical estimate, which can give a false sense of precision and obscure the underlying uncertainties and assumptions.

DEFAULT OPTIONS

Because of limitations in available data, cancer risk assessments are always performed without some information. The EPA has developed general approaches, called default options, to use at various stages of cancer risk assessment when specific information is missing. These include the following assumptions:

- Laboratory animals are an acceptable surrogate for humans in assessing cancer risks. Positive cancer bioassay results in laboratory animals are evidence of a chemical's potential to cause cancer in humans.
- Humans are as sensitive as the most sensitive animal species, strain, or gender evaluated in a bioassay with appropriate study design characteristics.
- Benign tumors are acceptable surrogates for malignant tumors. Therefore, the numbers of benign and malignant tumors are added when evaluating whether a chemical is carcinogenic and when assessing its potency. (Some particulate materials, including diesel exhaust, produce lung lesions that are classified as benign tumors by some pathologists and as cysts by others. Because the classification significantly affects

the final health risk estimates, it is important that risk assessments of particulate materials clearly indicate the impact of these lesions on the outcome.)

- At low exposure doses, chemicals act like radiation in inducing cancer, that is, there is a linear relation between dose and response, and any dose, no matter how small, may cause cancer. Therefore, the linearized multistage model is considered to be the appropriate extrapolation model.

Some of these default options are controversial because they often produce conservative risk estimates (that is, estimates that overestimate rather than underestimate human risk).

EVOLUTION IN RISK ASSESSMENT

In the last decade, U. S. regulatory agencies have widely adopted the National Research Council's risk assessment framework. Within this framework, however, procedures for risk assessments have evolved and become increasingly sophisticated. Nevertheless, they have been criticized for being too rigid and unresponsive to new scientific knowledge, and for failing to convey the uncertainties that are inherent in the process, the underlying scientific data base, and the modeling assumptions.

Recently, two committees of the National Research Council reviewed risk assessment procedures. The Committee on Risk Assessment Methodology issued reports on specific methodologic issues, such as the use of the maximum tolerated dose and the two-stage model of carcinogenesis (National Research Council 1993). The Committee on Risk Assessment of Hazardous Air Pollutants addressed many specific criticisms of risk assessment as well as general cross-cutting issues (National Research Council 1994). Concerning default options, the latter committee concluded that, given the EPA's mandate to protect human health, the Agency "should continue to regard the use of default options as a reasonable way to deal with uncertainty about underlying mechanisms in selecting methods and models for use in risk assessment." The Committee did not reach a consensus on what the principles should be for choosing default options or for judging when and how to depart from them (Finkel 1994; McClellan and North 1994). To eliminate confusion, the Committee recommended that when default options are used, they should be clearly identified and their scientific and policy basis clearly stated. The International Agency for Research on Cancer also has examined how mechanistic information could contribute to evaluations of cancer risks (International Agency for Research on Cancer 1992).

There is now a national debate about the role of risk assessment in the regulatory process. The congressionally mandated President's Commission on Risk Assessment and Management is considering various issues related to how human health risk assessments are performed and how the results are used in regulatory decision-making. A new development is the risk reform legislation that is now being considered by the 104th Congress. Title III of the Jobs Creation and Wage Enhancement Act, H.R. 9, which is part of the Republican Contract with America, would establish certain risk assessment principles that would apply to "major rules" and in certain instances require an analysis of risk reduction costs and benefits. If enacted into law, this legislation will have a profound impact on environmental regulations, including those for diesel engines.

ABBREVIATIONS

EPA	U.S. Environmental Protection Agency
g/bhp-hr	grams per brake-horsepower times hours
• hr	times hours
µm	micrometer
µg/m ³	micrograms per cubic meter (of air)
nitro-PAHs	nitro-derivatives of polycyclic aromatic hydrocarbons
PAHs	polycyclic aromatic hydrocarbons
pCi/L	picoCuries per liter



Part II

Background Papers



Diesel Emissions and Control Technology

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Introduction	67
Emission Standards	68
Current Emission Levels, Technologies, and Fuels	69
Control Technology Developments	74
Traps	75
Catalysts	75
Engine Design	76
Exhaust Gas Recirculation	77
Fuel and Additive Effects	77
Future Research Directions	79
Summary and Conclusions	79
Acknowledgments	79
References	79
Abbreviations	81



INTRODUCTION

Rudolf Diesel developed the compression ignition engine, which bears his name, at the end of the last century with the objective of improving on the low thermal efficiency of the early spark-ignited engines. Diesel engines continue to have an efficiency advantage over spark-ignited engines. This advantage and their excellent durability record are the primary reasons for their dominant use in heavy-duty applications—trucks, buses, construction equipment, locomotives, and ships.

The use of diesel engines in passenger cars and light-duty trucks was not popular in the United States until the energy crisis in the 1970s led to fuel economy regulations. Contrary to estimates in the early 1980s that as many as 25% of passenger cars sold would be powered by diesel engines in the near term (National Research Council 1982), peak sales reached only about 6% in 1981 and in 1990 amounted to about 0.1%. Sales of diesel light-duty trucks are greater, but still amount to only about 2% of the market. The primary market for diesel engines is represented by medium-duty and heavy-duty (over 8,500 pounds gross vehicle weight) truck fleets, for which about 43% of engine sales are diesel (U.S. Department of Energy 1988). In countries where motor fuels are expensive or tax policies favor diesel over gasoline-powered engines, diesel engines are much more widely used. Thus, in Europe about 25% of new passenger cars sold in 1994 were diesel powered. Our analysis focuses on diesel engine use in the United States, which is overwhelmingly in heavy-duty applications, both historically and currently.

Compared with gasoline-powered engines, diesels are inherently low emitters of carbon monoxide (CO)* and hydrocarbons. Heavy-duty diesel engine emissions of oxides of nitrogen (NO_x) and particulate matter, however, are much greater, on both a per mile and a per fuel consumed basis, than from current emissions-controlled light-duty gasoline engines. Moreover, emission standards for heavy-duty diesel engines (Table 1) are less stringent than for light-duty gasoline engines. As the light-duty fleet is replaced with stringently controlled vehicles, heavy-duty diesels, which will represent about 1% of the vehicle fleet in the year 2000, will become the primary on-road vehicle source of NO_x and particulate matter emissions (Figure 1).

Diesel engines offer a 10% to 25% reduction in carbon dioxide emissions over gasoline engines when comparing the full fuel cycles, which include emissions associated with resource production, transport, refining, and vehicle manufacturing as well as the vehicle emissions (DeLuchi

1992). A renewed interest in motor vehicle fuel economy in the United States brought on by reduced fuel availability, the balance of trade, and global warming concerns will eventually increase the interest in and use of diesel engines. Although the number of diesel vehicles is small, these vehicles are significant users of motor fuel (Figure 2). Diesel fuel use is projected to increase, both in absolute terms and as a percentage of engine fuels, from the current 16.6% to 18.4% in 2010 (American Petroleum Institute 1994; U.S. Energy Information Agency 1994).

Diesel fuel, a middle distillate of petroleum, was originally a low-value byproduct of lamp oil (Omen and Coley 1990). Current diesel fuels are blended for ease of ignition (measured by the cetane number), low deposit production, and moderate viscosities over a wide range of temperatures. Diesel fuel is a mixture of paraffins, naphthenes, and aromatics. The paraffins have the best starting characteristics but poor cold-temperature properties. Diesel fuel additives can include substances to improve cold flow and ignition and to reduce rust, corrosion, injector fouling, noise, and smoke. Sulfur, present as an impurity, is now limited by regulation (Table 2). Fuels for locomotives and ships are heavier (i.e., have a higher molecular weight) than fuels for

Table 1. Emission Standards for Vehicles Powered by Heavy-Duty Diesel Engines

Year	California ^a		Federal	
	Truck	Bus	Truck	Bus
Oxides of Nitrogen (g/bhp-hr)				
1985–1986	10.7 ^b	10.7 ^b	10.7	10.7
1987–1989	6.0	6.0	10.7	10.7
1990	6.0	6.0	6.0	6.0
1991–1995	5.0	5.0	5.0	5.0
1996–1997	5.0	4.0	5.0	5.0
1998	4.0	4.0	4.0	4.0
Total Particulate Matter (g/bhp-hr)				
1987	0.6	0.6	NA ^c	NA
1988–1990	0.6	0.6	0.6	0.6
1991–1992	0.25	0.10	0.25	0.25
1993	0.25	0.10	0.25	0.10
1994–1995	0.10	0.07	0.10	0.07
1996	0.10	0.05 ^d	0.10	0.05 ^d

^a California Air Resources Board (1993).

^b The California standard was 5.1 g/bhp-hr for the test procedure in use at that time; this value is equivalent to approximately 10.7 g/bhp-hr using current test procedures.

^c NA = no federal standard applying to this period.

^d The in-use standard is 0.07 g/bhp-hr.

* A list of abbreviations appears at the end of this paper.

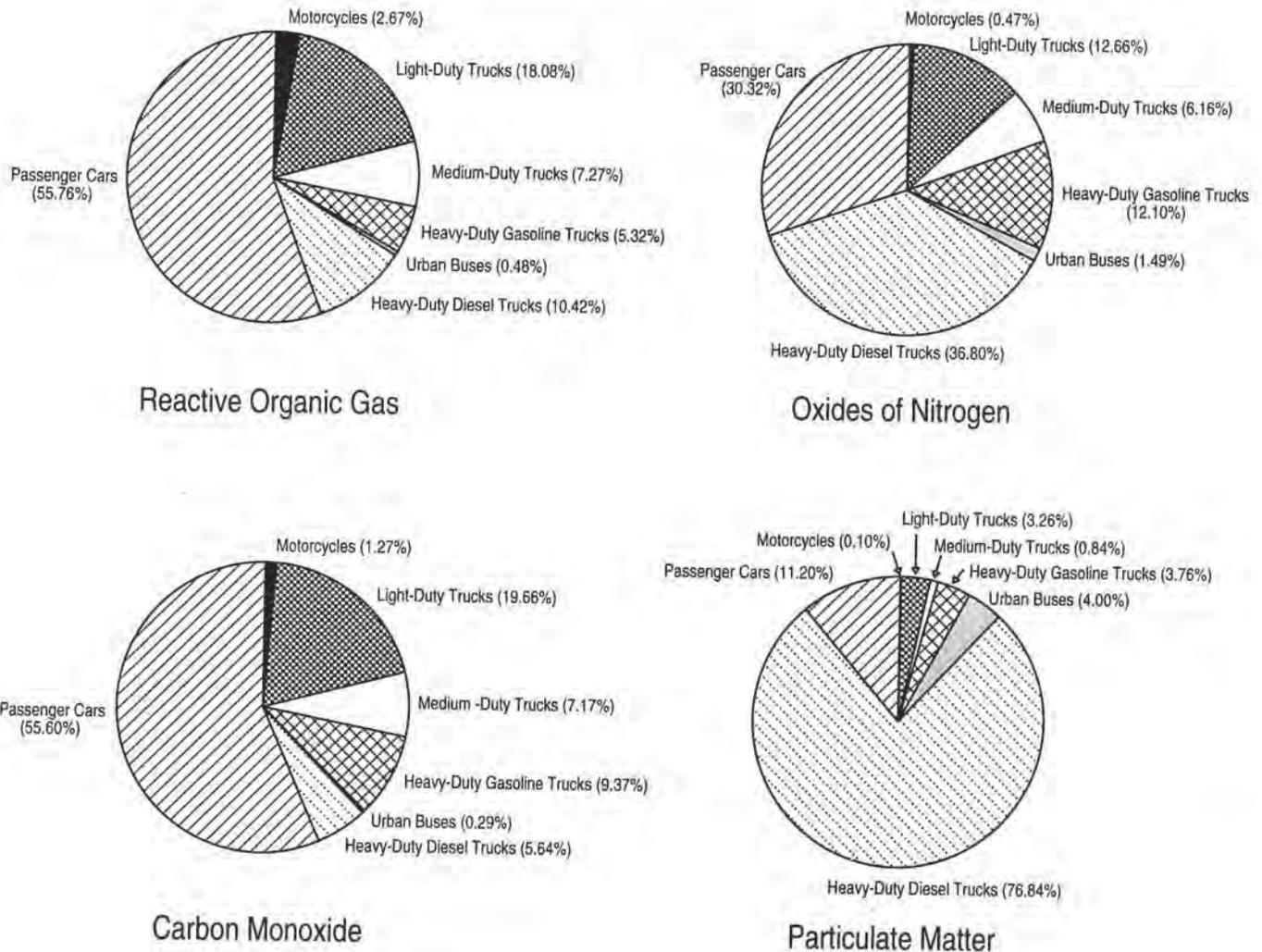


Figure 1. Estimated U.S. emissions distribution for on-road vehicle sources in the year 2000. (Reprinted with permission from Acurex Environmental Corporation, as published in Acurex Environmental Corporation 1993).

road vehicles (Figure 3). One consequence of these differences in diesel fuel is that emissions from locomotives, currently as well as in the past, can be quite different than emissions from road vehicles. Diesel engines, or their derivatives, that can burn alternative fuels, primarily natural gas and methanol, are being developed primarily for urban buses.

Pressures to increase fuel economy and to reduce carbon dioxide emissions are likely to play an important role in increasing diesel engine use in future years. Medium-duty trucks are the most obvious application for increased diesel engine use, followed by light-duty trucks and passenger cars.

The next section of this background paper discusses the emission standards promulgated by the U.S. Environmental Protection Agency (EPA) and the state of California since

1970. This is followed by a discussion of emission levels from engines in the 1970s, 1980s, and early 1990s and the type of technologies used in the engines of this period. The last major part of the paper focuses on control technologies being developed to meet the 1996 urban bus and the 1998 heavy-duty truck standards. Future research directions are also outlined.

EMISSION STANDARDS

In the United States, emission standards for light-duty diesel passenger cars and trucks generally are the same as for gasoline vehicles. Whereas light-duty vehicle emission standards for gaseous species, hydrocarbons, CO, and NO_x were first established in 1968 (1966 in California), particulate matter standards, which were aimed specifically at

diesels, were not established until 1986 (1984 in California). Heavy-duty vehicle emission standards have lagged behind those for light-duty vehicles, both in time of introduction and in stringency. Standards for heavy-duty diesel engines are similar, but not identical, to those for heavy-duty gasoline engines. The first heavy-duty particulate matter standards, which became applicable in 1988, required little reduction from the emission levels of uncontrolled engines for most vehicles.

Light-duty diesel emissions are measured using chassis dynamometers and the Federal Test Procedure (FTP) urban driving cycle. Heavy-duty diesel emissions are measured primarily using engine dynamometers, in the past with steady-state (13-mode) operating cycles and currently with transient operating cycles. To account for differing loads among vehicles, emissions are expressed in mass/work units (grams/brake-horsepower-hours [bhp-hr] or grams/joule) rather than in the mass distance (grams/mile) scale used for light-duty vehicles.

The 1990 Clean Air Act Amendments Tier 1 standards limit passenger car particulate matter emissions to 0.08 g/mile, which was to be phased in beginning in 1994. Light-duty

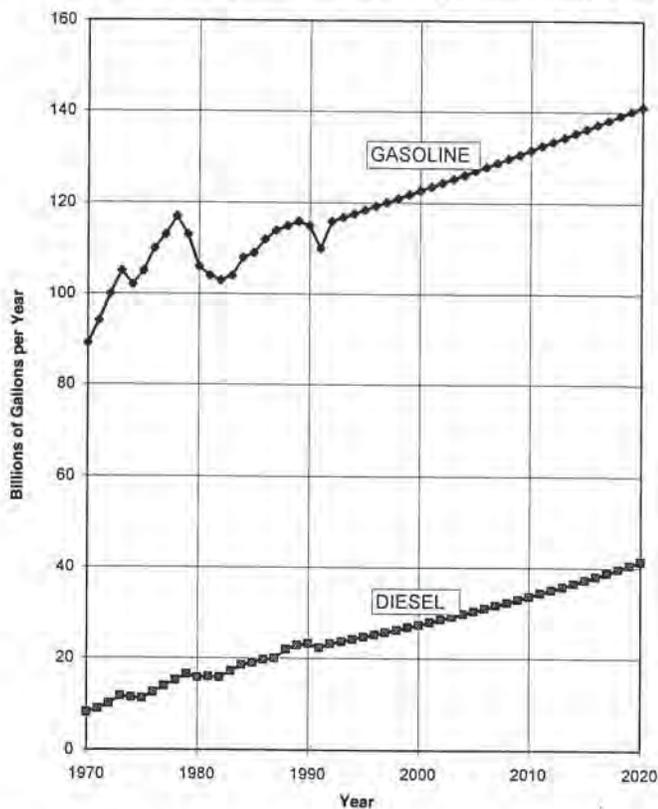


Figure 2. Historical and projected U.S. gasoline and diesel fuel consumption. Historical data to 1992 are from the American Petroleum Institute (1994); projections for 1993 to 2020 are from the U.S. Energy Information Agency (1994).

trucks must meet a standard of 0.10 to 0.12 g/mile, depending on the size of the truck. For diesel engines in heavy-duty applications, emission standards as of 1994 for hydrocarbons, NO_x , CO, and particulate matter were 1.3, 5.0, 15.5, and 0.10 g/bhp-hr. The particulate matter emissions standard would lead to approximately a 90% reduction from uncontrolled engine emissions. Recently the EPA promulgated emission standards for diesel nonroad vehicles (U.S. Environmental Protection Agency 1994a). These standards cover NO_x and smoke emissions from new nonroad compression ignition engines, especially construction and agricultural equipment. Diesel engines used in aircraft, ships, marine vessels, and mining operations are excluded.

CURRENT EMISSION LEVELS, TECHNOLOGIES, AND FUELS

Extensive work conducted in the 1970s and 1980s to characterize diesel emissions focused on light-duty vehicles, even though these did not and do not represent the major application of diesel engines in motor vehicles. Studies of emissions from heavy-duty diesel vehicles over the past 10 years, however, have greatly extended emissions characterization data. The studies indicate that emissions of CO and hydrocarbons from diesel engines are generally low, but NO_x levels from diesels are much greater than from gasoline engines with catalysts and control technology to meet 1994 federal and California Air Resources Board (CARB) standards. Sulfur dioxide emissions are directly related to the sulfur contained in the fuel.

The most troublesome diesel engine pollutant is carbonaceous particulate matter, which can produce a highly visible exhaust. This particulate matter is of complex physical and chemical character (Figure 4). Size distributions are

Table 2. Diesel Fuel Standards Effective October 1, 1993

	Environmental Protection Agency	California Air Resources Board
Sulfur (maximum % by mass)	0.05	0.05
Cetane number (minimum)	40 ^a	50
Aromatics (maximum % by volume)	35 ^a	10 ^b

^a Either cetane number or aromatics standard is acceptable.

^b Twenty percent for small refiners, or alternative formulation with higher content is acceptable if equivalent emissions are demonstrated.