Executive Summary

Diesel engines are an important part of the world's transportation and industrial infrastructure, especially in heavy-duty applications such as trucks, buses, construction and farm equipment, locomotives, and ships. Energy efficiency and durability account for the dominant use of diesel engines worldwide, and their use may expand in the future. In Europe, 20% to 50% of the new light-duty passenger fleet is powered by diesel engines. Although the percentage of diesel-powered light-duty vehicles is much lower in the United States, advanced technology diesel engines are being proposed as part of the nation's energy conservation and climate change strategies.

The economic advantages of diesel engines are clear; nevertheless, environmental concerns and related health issues must be addressed. Emissions from all types of engines are highly variable and complex mixtures. Diesel engines are more efficient than gasoline engines, and they emit less carbon dioxide (a greenhouse gas), carbon monoxide, and hydrocarbons. Therefore, diesel engines have some advantages over conventional gasoline engines in terms of global warming. However, they emit higher levels of oxides of nitrogen, which are ozone precursors, and particulate matter per vehicle mile traveled than do gasoline engines. The particulates are of special concern in possible health outcomes; they are small enough to be readily respirable, and they have many chemicals adsorbed to their surfaces, including known or suspected mutagens and carcinogens.

Cellular, animal, and human studies have investigated the association between exposure to diesel exhaust and adverse health effects, including cancer. Lung tumors have occurred in rats exposed to diesel exhaust, but the relevance of these lesions to human risk assessment has been questioned. Epidemiologic studies fairly consistently show an elevation in lung cancer rates among occupationally exposed individuals. In most studies, rates are 20% to 50% greater than those in unexposed individuals; however, these studies did not obtain quantitative measurements of exposure during the time period of the study.

Although epidemiologic data have been used generally to identify the hazards associated with exposure to diesel exhaust, questions remain as to whether the human data can be used to develop reliable estimates of the magnitude of any risk for lung cancer (that is, through quantitative risk assessment [QRA]), and whether new research efforts could provide any additional data needed. In response to such issues, the Health Effects Institute initiated the Diesel Epidemiology Project in 1998. The Project includes the evaluation by HEI's Diesel Epidemiology Expert Panel of occupational epidemiologic studies that have been used for QRA, and the development of new research initiatives to improve understanding about the health effects of diesel exhaust.

The Diesel Epidemiology Expert Panel was chaired by John C. Bailar, III, M.D., Ph.D., of The University of Chicago and the HEI Review Committee, and included six other scientists who have expertise in epidemiology, biostatistics, exposure characterization, and exposure assessment. It was charged to (1) review the epidemiologic data that form the basis of current QRAs for diesel exhaust, (2) identify data gaps and sources of uncertainty, (3) make recommendations about the usefulness of extending or conducting further analyses of existing data sets, and (4) make recommendations for the design of new studies that would provide a stronger basis for risk assessment.

Although lung cancer was the health outcome of interest to the Panel's charge, it was not charged to evaluate either the broad toxicologic or epidemiologic literature concerning exposure to diesel exhaust and lung cancer for hazard identification purposes, which has been done by others. State, national, and international agencies have all reviewed the broader animal and human evidence for carcinogenicity and, in either their draft or final reports, have all identified diesel exhaust as a probable human carcinogen or placed it in a comparable category (National Institute for Occupational Safety and Health 1988; International Agency for Research on Cancer 1989; World Health Organization 1996; National Toxicology Program 1998; Office of Environmental Health Hazard Assessment [California Environmental Protection Agency] 1998; U.S. Environmental Protection Agency 1998).

In response to the first charge, the Panel examined published epidemiologic studies of diesel exhaust emissions and lung cancer for possible use in support of QRA. Only two such studies reported any quantitative exposure data associated in some manner with the occupational epidemiologic studies, and they were considered in the Panel's review.

The Panel recognized that no epidemiologic study can be perfect. Therefore, the Panel viewed its task as addressing the question: To what extent can limitations in the design and performance of a particular study affect its contribution to the body of epidemiologic knowledge under examination for QRA? The Panel also recognized that frequently it is very difficult to obtain retrospective data for estimating job-related work exposures, and that this process may require assumptions that cannot be validated. In the studies considered here, which form the core of the Panel's review, reasonable attempts were made to reconstruct past exposures to diesel engine emissions using approaches that were feasible when the studies were conducted. These data subsequently have been used, in some cases, for purposes that were not envisioned by the original investigators. The studies reviewed for this report include:

Railroad Worker Studies

- Case-control: Garshick et al. 1987
- Cohort: Garshick et al. 1988
- Industrial hygiene: Hammond 1988, and Woskie et al. 1988a,b
- Exposure-response analyses: Crump et al. 1991, Office of Environmental Health Hazard Assessment 1998, and Crump 1999

Teamster Studies

- Case-control: Steenland et al. 1990, 1992
- Industrial hygiene: Zaebst et al. 1991
- Exposure-response analysis: Steenland et al. 1998

The reports of these studies were supplemented by published articles and by presentations to the Panel by the principal investigators and others, including secondary analysts of the railroad worker data. The Panel did not consider other completed lung cancer and diesel epidemiologic studies because they included no directly associated quantitative exposure data.

Certain strengths are evident in the studies reviewed by the Panel. The epidemiologic studies include large numbers of study subjects (55,407 subjects, and 1,694 lung cancers, for the railroad worker cohort study; 1,256 deaths from lung cancer for the railroad worker case-control study; and 996 deaths from lung cancer for the teamster case-control study), all of whom were employed in industries where many workers are exposed to diesel exhaust. Job categories with known exposure to asbestos were either excluded or controlled for in the analyses. Both of the case-control studies adjusted data analyses to control for cigarette smoking as a confounding variable. Overall, the results are generally consistent with findings of a weak association between lung cancer and exposure to diesel exhaust. However, published secondary analyses of exposure-response relations in the railroad worker cohort data produced conflicting results (Crump et al. 1991; Office of Environmental Health Hazard Assessment 1998).

Measurements from the industrial hygiene studies in general supported the job exposure categories used in the epidemiologic studies. The industrial hygiene studies measured different markers for diesel exhaust exposure—respirable-sized particles (RSP) for railroad workers and submicron-sized elemental carbon (EC_1) for teamsters. Although the RSP measures were adjusted for the environmental tobacco smoke component, EC_1 is more sensitive and specific to diesel exhaust than adjusted RSP.

In response to the second charge, the Panel developed a framework of general epidemiologic questions about study design, exposure assessment, outcome determination, and analysis. These are meant to help in systematically understanding and revealing the strengths and uncertainties of these studies. This framework was then used to evaluate the studies of railroad workers and teamsters. This process helped to address the third and fourth charges to the Panel, and to assist HEI in focusing its future research directions to inform apparent gaps for QRA.

The original findings of the cohort railroad worker study reported by Garshick and coworkers (1988) indicated a steadily increasing risk of lung cancer for exposed workers with increasing years of employment. This increase with duration of employment, however, was not supported in later, unpublished analyses (Garshick 1991). This increasing risk, plus the availability of some quantitative exposure data in railroad workers (Woskie et al. 1988a,b), prompted additional analyses to explore the exposure-response relation in these data (Crump et al. 1991; Office of Environmental Health Hazard Assessment 1994, 1998; Crump 1999). Crump and colleagues found a negative association between lung cancer risk and several measures of cumulative exposure; that is, risk decreased with increasing cumulative exposure. In contrast, the statistical models used by the Office of Environmental Health Hazard Assessment analysts, using the same data but different assumptions, showed a positive association in which risk increased with increasing cumulative exposure.

The Panel explored these apparent inconsistencies in the exposure-response relation to verify and obtain a better understanding of the previous analyses, and to help clarify differences. These issues are central to whether the railroad worker data can be useful in a QRA for lung cancer.

The Panel's data exploration demonstrated that within the three broad railroad job categories of train workers (e.g., engineers, conductors), shop workers (e.g., electricians, machinists), and clerks and signalmen, the relative risk of lung cancer decreased with increasing duration of employment, and this decrease was statistically significant for the clerks/signalmen and train workers. Although the relative risk decreased with increasing duration of employment, overall risks for train workers, within each duration of employment group, were higher than those for clerks and signalmen, and shop workers had intermediate risks (Figure 1).

These findings are not consistent with a steadily increasing association between cumulative diesel exposure and lung cancer risk. Furthermore, if the difference in risk between train workers and clerks/signalmen was due primarily to differences in exposure to diesel emissions, one would expect the relative risk for train workers compared with that for clerks and signalmen to be reduced or even eliminated after adjusting for exposure. In fact, adjustment for exposure increased this relative risk. Such a systematic pattern of decreasing risk with increasing exposure suggests that some form of bias is present in the data, which makes it difficult to determine the true nature of an exposure-response relation. Bias can result from uncontrolled confounding by cigarette smoking or by other occupational exposure, differential misclassification of exposures by job category, longer survival of "healthier" workers, or differential ascertainment of lung cancer as a cause of death.

Initial findings from the teamster case-control study (Steenland et al. 1990) showed an increased risk of lung cancer with increasing years of employment. The investigators published an exposure-response analysis for the teamster study (Steenland et al. 1998) after the Panel's work started, thus the evaluation of this set of studies was necessarily less extensive.

Reconstructing past exposures for which actual data are limited or nonexistent requires several assumptions. The Panel had concerns about several of the assumptions used by Steenland and colleagues in the exposure-response analysis of the teamster data. These concerns include (1) the data on 1990 emissions used to estimate past exposures to diesel exhaust may underestimate average exposures over a range of work histories, given that more recent data show higher emissions for that time; (2) the date assumed for dieselization in the trucking industry, which, if too early, may overestimate exposures; (3) the degree to which vehicle miles traveled accurately reflects actual exposure to diesel exhaust for various job groups, which may affect exposure estimates in either direction; (4) the possible effects of using various scenarios of emission levels to account for long fleet turnover times in the trucking industry; and (5) the difficulty in distinguishing truck driver exposures from background levels, because measured estimates are close. Also, among the assumptions Steenland and colleagues used, nondiesel sources of elemental carbon in ambient air, especially from gasoline engine emissions, were not considered.

The Panel also was concerned about the controls used in the case-control study. Lung and bladder cancers and motor vehicle accidents were excluded as control causes of death, and controls were selected from other causes. If those causes of death were associated with exposure to diesel emissions, smoking, or both, the study findings could be biased.

Important work is currently under way to study the health effects of exposure to diesel exhaust in nonmetal miners in Germany (Säverin et al. 1998) and in the United States (National Cancer Institute–National Institute for Occupational Safety and Health 1997). The Panel did not review these studies because they are still in progress. However, the Panel heard presentations from these investigators at the HEI Diesel Workshop: Building a Research Strategy to Improve Risk Assessment (HEI 1999) at Stone Mountain, GA, March 7–9, 1999. In particular, the National Cancer Institute–National Institute for Occupational Safety and Health study is large and appears to be well designed and comprehensive. It includes a cohort and nested case-control component, as well as extensive current measurements of exposure to diesel exhaust, detailed reconstruction of historical exposure, and bio-

Figure 1. Panel's analysis depicting consistently elevated risk of lung cancer for train workers compared with clerks for each time period, but decreasing risk by job category over duration of employment. See Appendix C for details.

marker development. These studies in progress are likely to inform hazard identification, exposure estimation, and exposure-response analyses, all components of risk assessment.

The Panel recognizes that regulatory decisions need to be made in spite of the limitations and uncertainties of the few studies with quantitative data currently available. The findings described here and the systematic evaluation of these and other studies are designed to inform the ongoing process and provide a means to weigh a study's strengths and limitations.

FINDINGS

GENERAL

Enhanced exposure and epidemiologic data and analyses are needed for the purposes of QRA; these might come from further exploration of existing studies or from new studies.

RAILROAD WORKER STUDIES

At present, the railroad worker cohort study (Garshick et al. 1988), though part of a larger body of hazard identification studies, has very limited utility for QRA of lifetime lung cancer risk from exposure to ambient levels of diesel exhaust for the following reasons.

- The various exposure-response analyses are limited by the scope and quality of currently available exposure data. Quantitative exposure data were not obtained during the cohort study period. Also, there is a paucity of qualitative data on individual exposures before 1959, and on the variation in exposure by railroad site, by season, and over time. The potential impact of concurrent exposures (for example, to grease, dust, other fumes, asbestos, and active and passive cigarette smoke) were not examined in depth. The diesel exhaust exposure data are suitable for a crude categorical measure of exposure by job category; but other measures, including duration of employment in a job category exposed to diesel exhaust, intensity of exposure concentration ($\mu g/m^3$), and lifetime exposure ([$\mu g/m^3$]-years), are not adequate to support quantitative exposure-response analyses.
- The Panel's analysis of the exposure-response association in the railroad worker data showed that the evidence for a positive association of lung cancer with cumulative exposure to diesel exhaust depends entirely on differences in risks among job categories. Train workers (with higher exposures) have higher risks compared with clerks (with low or no exposure). However, within all job categories, the relation of lung cancer risk to duration of employment is negative.
- Factors that might explain a negative association between duration of employment and lung cancer in these data include bias introduced by systematic differences in exposure misclassification among and within job categories; differentially incomplete ascertainment of lung cancer deaths by job category; lack of information on other occupational exposures and air pollutants; the presence of a healthy worker survivor effect; confounding by cigarette smoking; and analysis of relative risks rather than absolute risks. Also, in a case-control study, if causes of death among controls were associated with exposure to diesel exhaust, smoking, or both, the results could be biased.

TEAMSTER STUDIES

The investigators' analysis of the teamster data reported an exposure-response relation (Steenland et al. 1998) that may be useful for QRA; this relation will be better understood with further exploration of uncertainties and assumptions, particularly those relating to the reconstruction of past exposures and the selection of controls. Exposures of teamsters are more similar to ambient exposures of the public than are exposures of railroad workers, and the diesel exhaust to which teamsters are exposed comes from a source that is likely to be relevant to regulatory issues.

The Panel reviewed the teamster study without the benefit of additional analyses and interpretations, and its comments are not as detailed as those about the railroad worker studies. Understanding the teamster study will evolve with time; however, some conclusions can be drawn now.

- The set of teamster studies may provide reasonable estimates of worker exposure to diesel exhaust, but significant further evaluation and development are needed. The marker for diesel exhaust that was selected for study by Steenland and associates, EC_1, is more sensitive and specific than RSP adjusted for environmental tobacco smoke, but has several limitations (e.g., the contribution of diesel emissions to ambient EC_1 concentrations has not been constant over time). The industrial hygiene study, which was conducted after the period when workers in the case-control study were exposed, identified a range of exposures for various job categories, but did not consider (1) site-to-site variations, (2) seasonal variations, (3) concurrent exposures to other agents, (4) historical ambient particle concentrations, or (5) intra- and interindividual variability. The estimation of historical exposures needs to incorporate recent data on diesel emissions from vehicles in use, reassessment of when dieselization occurred, alternatives to estimating exposure by vehicle miles traveled, and historical regional ambient pollution data.

- The exposure-response relation reported in the teamster study increases in a linear manner. However, more can be learned from other analysts examining these data using different approaches.
- Neither a roster of the study population nor an alternative method of selecting controls to represent it was available to the researchers. It cannot be established with certainty whether the causes of death used for controls adequately represent the joint distribution of exposure to diesel exhaust and smoking in the case-control study. If smoking, or diesel exhaust exposure as determined by job category, or both were associated with causes of death used for controls, results could be biased.

RECOMMENDATIONS

The Panel's recommendations reflect its general understanding, as expressed in its framework for evaluating studies, of what constitute adequate data for QRA. They also reflect the preceding evaluation of the studies of railroad workers and teamsters. The Panel is aware that research currently in progress will respond to some of these research needs; however, results are not yet available, and it is not yet clear whether all of the proposed needs will be met.

COMPLETED STUDIES

1. The Panel recommends against using the current railroad worker data as the basis for QRA in ambient settings.
2. Further scrutiny of the teamster data, including estimation of uncertainty in both the exposure estimates and selection of controls, is recommended in order to improve the use of these data in QRA. Strengths of the teamster study include the relevance of exposure levels to the general population and the use of an exposure marker for diesel engine emissions that was an improvement over RSP. The teamster study exposure-response analysis is relatively new, and its further review and analysis by both the original investigators and others should be accelerated. Alternative retrospective exposure models need to be developed that use the alternative assumptions described above and in more detail in the body of the text.

NEEDS FOR NEW TECHNIQUES AND DATA

3. Better measures of exposure to constituents of diesel emissions, with careful attention to selection of the sample studied, are needed. Of particular importance are the selection and validation of a chemical marker of exposure to the complex mix of diesel exhaust emissions. Exposure models may include data from personal monitors, area monitors placed where diesel exposure is likely to occur, and current and historical data regarding emission sources. In any such modeling effort, the effects of environmental tobacco smoke should be removed as completely as possible.
4. Reliable estimates of past emissions and of factors affecting historical exposures in a range of settings are needed to improve the characterization of uncertainties, both quantitative and qualitative, in historical models of exposures.
5. Although biomarker technology was not available when the studies reviewed were conducted, appropriate, validated, and specific biomarkers of diesel exposures, health outcomes, and susceptibility are needed.

DESIGN NEEDS FOR NEW STUDIES OF EXPOSURE-RESPONSE ANALYSES

6. Exposures should be adequately and accurately characterized with respect to magnitude, frequency, and duration, rather than solely by duration of employment. Errors and uncertainties in exposure measurements should be quantified where possible; these should be fully reported to users, and taken into account in both power calculations and exposure-response analyses.
7. Cigarette smoking is a potent risk factor for lung cancer, and it must be controlled for in any study of risk factors for this disease. Smoking histories obtained for a cohort study subset that uses a case-control or case-cohort design will strengthen the interpretation of results.
8. The exposures considered should be close to levels of regulatory concern, including a range of exposures to provide a base for understanding the relation between exposure and health effects.

NEEDS FOR NEW STUDIES

A prospective epidemiologic study of the development of lung cancer in exposed and unexposed individuals could have many strengths. Information on confounders and exposures could be more complete than for a retrospective study, and many of the biases and uncertainties discussed in this report could be eliminated or reduced. These advantages, however, need to be weighed against the disadvantages, which include high costs and a long period of follow-up. Other study designs that include retrospective components are possible for a new epidemiologic study of lung cancer, but they are likely to include uncertainties and sources of bias that investigators will need to explore completely and acknowledge in their reporting.

9. The Panel recommends that a new, large, epidemiologic study of diesel exhaust emissions and lung cancer be considered after (1) currently ongoing or existing studies, including HEI's feasibility studies (to be completed in the spring of 2000), are evaluated, and (2) attempts to retrofit improved exposure assessments to existing epidemiologic studies are evaluated, including whether they can provide sufficiently accurate, complete, and relevant exposure data to support QRA.
10. Studies of lung cancer risk in general populations exposed to ambient diesel exhaust particulate matter will be difficult to conduct; however, such studies could usefully investigate other, noncancer health effects that occur in a shorter time after exposure.