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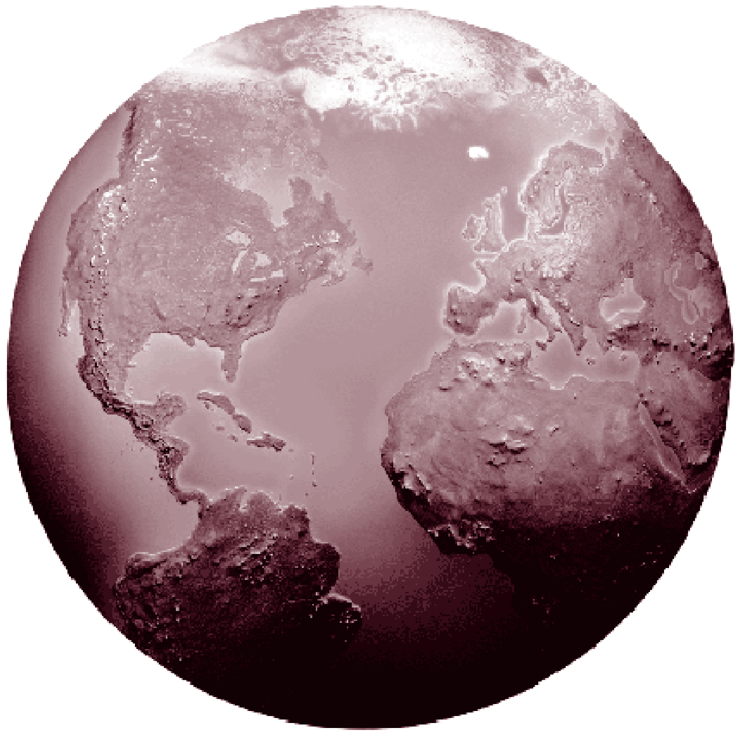

Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment

HEI Diesel Epidemiology Panel

EXECUTIVE SUMMARY

Health Effects Institute

ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI typically receives balanced funding from the U.S. Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 330 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 1000 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research. For this report, the HEI Board of Directors appointed a special Diesel Epidemiology Panel to fulfill this role.

All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

EXECUTIVE SUMMARY

Diesel Emissions and Lung Cancer: An Evaluation of Recent Epidemiological Evidence for Quantitative Risk Assessment

INTRODUCTION AND SCIENTIFIC BACKGROUND

Since their introduction in the early 20th century, diesel engines have become the workhorses in a wide range of industrial settings and forms of transportation. Their power and durability, better fuel efficiency, and lower emissions of some air pollutants (in particular, carbon monoxide) made them attractive in heavy-duty applications such as trucks, buses, construction, farming and mining equipment, locomotives, and shipping in marine and inland waterways. Given these attributes, dependence on diesel engines for all forms of transport, including light-duty passenger vehicles, is strong and appears likely to grow in the foreseeable future.

At the same time, exposures to emissions from diesel engines and their potential impact on human health in both environmental and occupational settings have long been a subject of concern. Over the past several decades, epidemiological and toxicological studies have reported associations between short-term and long-term exposures to diesel exhaust and its components and a range of acute and chronic adverse health effects, including lung cancer. HEI conducted the first of its comprehensive reviews of the scientific literature on diesel exhaust emissions, exposures, and health effects in 1995 (HEI Diesel Working Group 1995). In that review, HEI identified weak increases in lung cancer risk in exposed relative to unexposed workers. Diesel exhaust has also been the subject of numerous scientific reviews by national and international organizations. Most recently, in 2012, the International Agency for Research on Cancer (IARC*) reviewed the body of scientific evidence on the carcinogenicity of diesel exhaust, and concluded that there was now sufficient evidence in humans and experimental animals to reclassify diesel exhaust from Group 2A (probably carcinogenic to humans) to Group 1 (carcinogenic to humans). As a result, the potential use of these studies for characterization of the exposure–response relationship and for quantitative estimation of lung cancer risk in occupational and general populations has become an issue of considerable interest in the scientific and regulatory communities.

In response to requests from its sponsors, HEI convened a panel in 2013, chaired by Dr. Daniel Krewski of the University of Ottawa (see list of contributors), to review new epidemiological studies of diesel exhaust and lung cancer that had been influential in IARC's determination. The Panel focused on two studies, the Trucking Industry Particle Study (the Truckers study) conducted by Dr. Eric Garshick of the VA Boston Healthcare System and Harvard University and his colleagues (Garshick et al. 2012a), and

What This Report Adds

- This report is a careful review by an independent scientific panel of two major epidemiological studies of historical exposures to diesel exhaust, the Diesel Exhaust in Miners Study (DEMS) and the Trucking Industry Particle Study (Truckers) to assess whether these studies could provide the basis for quantitative risk assessment.
- In the Panel's view, both the Truckers study and the DEMS were well-designed and well-conducted studies that each made considerable progress toward addressing a number of the major limitations that had been identified in previous epidemiological studies of diesel exhaust and lung cancer.
- The Panel found that the studies have many strengths, but any effort at quantitative risk assessment will need to acknowledge some key uncertainties and limitations.
- The Panel concluded that both the DEMS and the Truckers study provided results and data that provide a useful basis for quantitative risk assessments of exposures in particular to older diesel engine exhaust.

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Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83467701 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

* A list of abbreviations and other terms appears at the end of the Executive Summary.

the Diesel Exhaust in Miners Study (DEMS) conducted by investigators led by Drs. Debra Silverman and Michael Attfield and their colleagues at the National Cancer Institute (NCI) and the National Institute for Occupational Safety and Health (NIOSH), respectively (Attfield et al. 2012; Silverman et al. 2012). The overall charge to the Panel was to make a determination whether or not their data and results could now form the basis for a quantitative characterization of the lung cancer risks associated with diesel exhaust. This report provides the Panel's detailed evaluations of the studies and its conclusions.

THE HEI PANEL APPROACH TO ITS CHARGE

OVERALL PROJECT APPROACH

Beginning in April 2013, the Panel held a series of meetings in person and through webinars and conference calls to discuss the charge to the panel, the Truckers study and DEMS, and the criteria for evaluating them. Through formal applications to NCI and NIOSH, the Panel also obtained the cohort and case–control analytical data sets for DEMS, and after replicating the main results of the study, explored additional questions raised during its evaluation of the studies.

The Panel also took into consideration several published commentaries on both studies as well as the work of two analysts who conducted extensive additional investigations of the DEMS data on behalf of a consortium of firms organized by the Engine Manufacturers Association (Crump et al. 2015; Crump et al. in press; Moolgavkar et al. 2015). The Panel held a public workshop in March 2014 to hear presentations from the original investigators on their studies, from Drs. Crump and Moolgavkar, and from other scientists with expertise in quantitative risk assessment and risk management.

The Panel prepared a draft report that was sent to external peer reviewers, to the original authors of the Truckers and DEMS studies, and to Drs. Crump and Moolgavkar. The report's major findings were presented at the HEI Annual Conference in Philadelphia in May, 2015. The report was revised in response to the many useful comments received during the review process and at the conference.

EVALUATION OF EPIDEMIOLOGICAL STUDIES FOR USE IN QUANTITATIVE RISK ASSESSMENT

Quantitative risk assessments estimate the magnitude of the health burden caused by risk factors to which human populations are exposed. The paradigm for conducting a quantitative risk assessment has long been described in terms of four components: hazard identification; exposure–response assessment; exposure assessment, and risk characterization (National Research Council 1983). The IARC decision having identified a hazard, the Panel focused on the second component and assessed the utility of the Truckers study and the DEMS for quantitative characterization of the exposure–response relationship between diesel exhaust and lung cancer. However, no one set of criteria has been agreed upon to definitively identify studies that provide data of sufficient accuracy, precision, and relevance to be useful for quantitative risk assessment. Instead, this decision remains at the intersection of basic principles of sound epidemiological study design and analysis, of the scientific issues presented by individual studies, and of the needs of risk managers who must ultimately weigh the scientific evidence with uncertainties and other factors in coming to their decisions.

The HEI Diesel Epidemiology Panel therefore evaluated the Truckers and DEMS studies according to how they: 1) addressed major limitations of earlier epidemiological studies for use in quantitative risk assessment that had been identified by a previous HEI panel in 1999 (HEI Diesel Epidemiology Expert Panel 1999); and 2) embodied the attributes of high quality epidemiological studies that make them appropriate and useful for quantitative risk assessment, systematic review, and meta-analysis.

The HEI Expert Panel convened in 1999 had the same mandate as the current panel; to review the epidemiological literature available at that time. The 1999 Panel reviewed studies in working populations in the trucking and railroad industries and concluded that the studies had a number of limitations that precluded their use in quantitative risk assessment. These limitations related to the quality and specificity of the exposure assessments for diesel exhaust, the absence of quantitative estimates of exposure that would support the exposure–response characterization, and the lack of adequate data to account quantitatively for individual exposure to possible factors that might confound the diesel exhaust and lung cancer relationship, smoking in particular. HEI recommended that these limitations be addressed in future research.

Many publications over the past 25 years have tried to identify the attributes of well-designed, well-conducted epidemiological studies that make them most reliable and useful for quantitative risk assessments. While individual recommendations may differ in details, they share common goals, some overlapping with the research needs identified by the 1999 Panel, which helped to guide the current Panel's evaluation of the details of each of the studies. These included several factors to be considered in the strength and appropriateness of: the study design; the analytical approach to the data and reporting of results; the quality of outcome assessments and follow up; the exposure assessment including the appropriate marker for, and estimates of exposure; the exposure–response assessment; control for confounding factors in both design and analysis; and sensitivity and uncertainty analyses that test the robustness of findings to major assumptions.

EVALUATION OF THE TRUCKERS STUDY

SUMMARY OF THE STUDY

The Truckers study by Garshick and colleagues (2012a) examined the risk of lung cancer in relation to quantitative estimates of personal exposure to submicron elemental carbon (SEC) in a large cohort (31,135) of workers employed in trucking facilities geographically distributed across the United States. This study was the culmination of decades of work investigating a number of health outcomes in association with employment in the trucking industry. Several peer-reviewed publications led up to this study, laying the groundwork for the retrospective reconstruction of individual-level SEC exposure estimates (for the period 1971 to 2000) and the subsequent epidemiological analyses (Davis et al. 2006, 2007, 2009, 2011; Garshick et al. 2008; Jain et al. 2006; Laden et al. 2007, Sheesley et al. 2008, 2009; Smith et al. 2006). Individual-level data on smoking were not available and therefore were not adjusted for in this study. Garshick and colleagues (2012a) found weak associations and evidence of trends in hazard ratios for cumulative SEC, lagged 5 and 10 years, and lung cancer in the cohort excluding mechanics; those associations and trends were strengthened when adjusted for duration of employment, a proxy for a healthy worker survivor bias.

PANEL EVALUATION

The 2012 Truckers study, with its related publications, was designed to address limitations of previous epidemiological studies of diesel exhaust. Specifically, the investigators chose an appropriate metric for diesel exhaust, SEC, a form of elemental carbon (EC). EC generally has been accepted as a reasonable marker for diesel exhaust and is less subject to interference by tobacco smoke and other sources. While gasoline and propane-powered engines also emit EC, the investigators conducted source apportionment analyses in selected terminals that identified diesel engines as a primary source of the SEC measured. The Panel found the investigators' retrospective exposure assessment to be conceptually and statistically sound, relying as it did on a statistically-designed exposure monitoring survey in U.S. trucking terminals, detailed job history and work practice records, and a creative, state-of-the-art structural equation modeling approach. The Truckers study provided estimates of job-specific SEC exposures; using regional coefficient of haze measurements, a reasonable surrogate for particulate EC, they also estimated the historical trends in those exposures. The investigators were able to validate some components of their exposure model, and they tested the sensitivity of their model estimates to some key assumptions. Finally, the conduct of the exposure assessment was independent of knowledge about outcome status, which removed one potential source of differential bias.

The Truckers study embodied other attributes of well-designed and well-conducted epidemiological studies that also make them more useful for quantitative risk assessment. The study was the largest of its kind in this occupation and was geographically representative of the United States. The use of Cox proportional hazards regression to evaluate associations between exposures to SEC and lung cancer was appropriate. The investigators also fit penalized splines in regressions using the continuous SEC exposures and lung cancer to explore the potential for nonlinearities in the exposure–response relationship. They explored the sensitivity of their results to the exclusion of workers in the mechanics job category, a category where there was evidence of greater uncertainty in the exposure estimates. They made the decision to address the suggestions of healthy worker survivor bias that they had observed in their data and did so by adjusting for duration of employment.

The Panel's overall assessment is that the Truckers study can support the development of quantitative risk assessments of diesel exhaust. However, as in any epidemiological study it has some limitations, with resultant uncertainties, that warrant consideration in its interpretation and application in quantitative risk assessments for diesel exhaust.

A major challenge in the Truckers study was the reconstruction of historical exposures to SEC. Several important issues that could impact the validity or uncertainty associated with the retrospective exposure assessment include: the use of the time trends in the coefficient of haze from only one area of the country (New Jersey) was assumed to represent time trends for all the other U.S. trucking terminals in the study; there were no coefficient of haze data prior to 1971 so prior exposures were assumed to be equal to the 1971 levels; SEC was assumed to represent diesel for all workers even though for exposures on or near roads, the mixture of diesel- and gasoline-engine–related ambient EC varies according to the mixture of vehicles (diesel or gasoline) traveling. The Panel agreed that these are potentially important sources of uncertainty in the exposure estimates and therefore could impact the exposure–response relationships that might be derived from the study. To date, no alternative exposure or sensitivity analyses that examine these assumptions have been conducted on these data. Despite the quality of the retrospective exposure construction in the Truckers study, including the careful efforts to validate interim steps in the process, it is the nature of such enterprises that independent data do not exist with which to assess the accuracy and precision of the final estimates.

The investigators were unable to obtain and adjust for individual-level smoking behaviors, an important confounder for lung cancer; however the Panel did not think that smoking alone could explain the findings for the study and noted that the investigators have pointed the way toward post hoc methods for adjusting for this missing information using job-level smoking data. While the investigators have made a reasonable case for adjusting for healthy worker survivor bias in this cohort, the adjustment using duration of work creates some challenges for interpretation of the results and their comparison to the results of other studies lacking such an adjustment.

EVALUATION OF THE DEMS

SUMMARY OF THE STUDY

The DEMS is a cohort and nested case–control study designed to study associations between retrospective estimates of exposure to diesel exhaust, represented by respirable elemental carbon (REC), and health outcomes in a large (12,315) cohort of mostly white male miners engaged in work in eight underground nonmetal mines in the United States (Attfield et al 2012; Silverman et al. 2012). Five peer-reviewed publications laid out the methods and results of the retrospective exposure analysis that was designed to estimate personal-level REC exposures from 2001 back to the start of diesel equipment use in the mines (1947 to 1967, depending on the mine) (Coble et al. 2010; Stewart et al.

2010, 2012; Vermeulen et al. 2010a,b). The mines were chosen because they involved low exposure to potential lung carcinogens other than diesel exhaust (including radon, silica, asbestos, and nondiesel polycyclic aromatic hydrocarbons [PAHs]), used diesel engines over a long period of time, and had good records of both work history and surrogate measures of exposure to diesel exhaust. The nested case–control study (198 cases, 562 controls) included detailed questionnaires to collect data from subjects or next of kin on other potential risk factors for lung cancer, including smoking and employment in other occupations where exposure to lung carcinogens might have occurred. The results of the cohort and the case–control studies were each explored with multiple sensitivity analyses; their results were broadly consistent with each finding an increasing risk of lung cancer in relation to increasing cumulative exposure to REC, lagged 15 years.

PANEL EVALUATION

Like the Truckers study investigators, DEMS investigators also set out to address limitations of exposure assessments in earlier epidemiological studies. They chose nonmetal mines with records of diesel equipment use and an exposure metric, REC, that is generally accepted as a marker of diesel exhaust. The Panel thought that the DEMS retrospective exposure assessment was logically constructed, was thorough in its collection and assessment of available sources of data, and incorporated state-of-the-art methods to develop quantitative estimates of personal exposures to REC for the full period of the study. To the extent possible, the investigators confirmed or justified the decisions they made at several stages in the development of their models, using independent approaches or data where available.

The Panel thought that the process by which DEMS had been designed, conducted, independently overseen, and peer-reviewed met high standards of scientific research. The study was designed with sufficient statistical power and relevant data on covariates to test the hypothesis of an association between long-term exposure to diesel exhaust in the mines and lung cancer in the cohort of mine workers. The study design and analytical approach both included strategies for collecting data on and controlling for potential occupational exposures (i.e., low levels of occupational carcinogens such as radon, PAHs, silica, asbestos, and respirable dust) and other confounding factors for lung cancer, in particular smoking. Ascertainment of health outcomes was of high quality and conducted independently of the exposure assessment. The statistical analyses followed a logical and standard progression beginning with the estimation of standardized mortality ratios and followed by Cox proportional hazards modeling using both categorical and continuous exposures to REC in the cohort and in the nested case–control study. The DEMS investigators also conducted numerous informative analyses of the sensitivity of their findings to alternative assumptions about exposure metrics, to alternative approaches to modeling relationships between diesel exhaust exposure and lung cancer, and to adjusting for confounding factors. The investigators also made their data and analytical information available through a public process, allowing for further analyses by other groups.

The fundamental associations between estimated exposure to REC and lung cancer were replicable by and robust to numerous investigations — by both the HEI Panel and by other analysts — of alternative statistical modeling approaches, control for confounding factors, and estimates of exposure (Crump et al. 2015; Crump et al. in press; Moolgavkar et al. 2015). The HEI Panel focused on the robustness of the case–control results to alternative adjustments for the two most important potential confounders for lung cancer — smoking and radon. The Panel's analyses affirmed the finding of negative confounding of the REC association by smoking and also found that the REC–lung cancer results were robust to measures of smoking and modeling approaches. However, the Panel noted that the investigators' use of combined work location and smoking variables made the results more challenging to apply in quantitative risk assessments. The Panel's assessment of both the radon data from the mines and the effect of different approaches to adjusting for radon in the statistical models, left Panel members with a high level of confidence that radon is not a major confounder in this study, that adjustment for it is not necessary in this study, and in fact could lead to unintended biases in the results.

As in other retrospective epidemiological studies, a major challenge in DEMS was the reconstruction of historical exposures to REC. Several important questions have been raised about the validity of the retrospective exposure assessment including: the methods for imputing missing measurements; the choice of carbon monoxide (CO) with which to model trends in airborne contaminants in the mines over time; the relationships between horsepower (HP), CO, and REC relative to emissions; and the impacts of temporal changes in diesel engine technology and fuels on the characteristics and the concentrations of diesel exhaust in the mines. The Panel agreed that these are potentially important sources of uncertainty in the exposure estimates and therefore in the exposure–response relationships that might be derived from the study.

Many of these issues have been extensively explored, both by the original investigators in their own sensitivity analyses and by Crump and van Landingham (2012) and by Crump and colleagues (2015 and in press). Crump and colleagues demonstrated sensitivity of the odds ratios and the slope of the exposure–response relationships to alternative exposure estimates and statistical models. The variability in results was considerable in some cases. However, in the Panel's view of the most relevant analyses the variability was smaller, and the results still demonstrated a clear, significant association between REC and lung cancer risk. The associations remained even with the alternative exposure models that did not rely on the HP–CO–REC relationships used in the original investigators' main exposure models.

DISCUSSION

In the Panel's view, both the Truckers and DEMS were well-designed and well-conducted studies and each made considerable progress toward addressing a number of the major limitations that had been identified in previous epidemiological studies of diesel exhaust and lung cancer. These limitations related particularly to the need for metrics more specific to diesel, better models of historical exposures, and ultimately for quantitative estimates of historical exposures to diesel exhaust. They both also demonstrated many of the attributes of high quality epidemiological studies that scientists and regulators value in evidence used to support quantitative risk assessments.

As is true of most occupational epidemiological studies, the findings of these studies are most readily generalizable to workers in other populations exposed to similar concentrations of diesel exhaust, emitted from comparable older engines, over comparable periods of time. However, as part of its charge, the Panel was also asked to consider whether data or results from these studies might also be used to quantify lung cancer risk in populations exposed to diesel exhaust at lower concentrations and with different temporal patterns, such as those experienced by the general population in urban areas worldwide. Although characterization of the exposure–response relationship at low levels of exposure is challenging, the broad and overlapping ranges of exposures to SEC and REC in these studies mitigates to a considerable extent concern about their generalizability to ambient levels. In the Truckers study, the lowest job-specific SEC level was 1.8 μg/m^3 (representing background levels experienced by clerks, for example); in DEMS, the average facility-specific REC exposure for surface-only workers was 1.7 μg/m^3. The low end of the range of exposures in each of the studies is very close to the levels of EC that have been reported in ambient air in the United States (a range of 0.26 to 2.2 μg/m^3 of ambient EC reported from various studies).

RECOMMENDATIONS ON ADDITIONAL ANALYSES OR STUDIES

As part of its charge, the Panel was asked to consider the usefulness of extending or conducting further analyses of existing data sets and for the design of new studies that would provide a stronger basis for risk assessment. The Panel had no further recommendations for major analyses that would need to be done before it could come to its conclusions. Similarly, the Panel thought it would be difficult to identify alternative research designs that would substantially improve on these two studies in the foreseeable future. The major uncertainties in the studies arise from factors largely beyond the control of these investigators — and likely any future investigators — most notably the absence of or only partial historical exposure monitoring and other records necessary to develop more accurate and precise estimates of exposure. Even if a well-designed prospective occupational cohort study were to be initiated today, with detailed personal exposure monitoring for individual workers, it would take decades for results to become available. The Panel however, saw merit in the initiation of exposure-monitoring programs to track trends in exposure to diesel emissions in the future. Data from such programs could be useful for better estimation of future exposure reductions and for evaluating concomitant reductions in human lung cancer risk while avoiding the need for the kinds of historical reconstructions of exposure that have received so much criticism in these and other occupational epidemiological studies.

CONSIDERATIONS FOR FUTURE QUANTITATIVE RISK ASSESSMENTS

The Panel's evaluation of the Truckers study and the DEMS is only one step in a more comprehensive risk assessment process for both characterization of the exposure–response relationship and its application in different risk management settings. The National Research Council risk assessment–risk management paradigm makes it clear that these steps are informed not only by a broad set of evidence, including epidemiological studies, but by the particular decision that must be made and its regulatory context.

Additional considerations in translating the results from these studies to other target populations include generalizability of risk estimates from these predominantly healthy male, Caucasian workers to subpopulations thought to be more susceptible to the effects of exposure to diesel exhaust (e.g., children, elderly people, and those with preexisting comorbidities) and differences in patterns of exposure either at work or to the general population.

Future risk assessments also need to consider major changes in diesel fuels, engines, and aftertreatment technologies that have occurred since these studies were conducted, and the implications those changes have for ambient concentrations and composition of diesel emissions and the risk associated with them. Emissions of PM mass from new technology diesel engines — that is, those equipped with a diesel particulate filter and powered by ultra-low-sulfur diesel fuel — have been reduced by about 99% compared with older engines. The composition of diesel PM from the newer technology has also changed substantially with EC dropping from about 70% by mass in emissions from older engines to as low as 13%–16% in emissions from the newer technology diesel engines. Emissions of PAHs, nitroPAHs, metals and other compounds from newer engines have dropped by about 80% to 99% relative to their levels in 2004 (Khalek et al. 2011, 2015). A study of chronic exposure of rodents to these lower emissions from 2007 technology engines found no evidence of carcinogenicity and few other biological effects (McDonald et al. 2015).

While there remains debate, or uncertainty, about what the 'right' exposure or statistical models are, or the predictions that follow from them, that in and of itself does not mean that these studies and their data are not useful. It is unrealistic to expect that individual results would be universally applicable or that all of the issues could be anticipated for extrapolating the results of the studies to other populations, time periods, and exposure conditions, including different diesel exhaust technologies. Given the basic integrity of the studies, what is important for quantitative risk assessment is that they allow exploration and communication of the nature and magnitude of those uncertainties.

CONCLUSIONS

The HEI Panel found that the epidemiological information that has accrued since the previous HEI panel reported on this issue in 1999 is both relevant and informative. The occupational studies of nonmetal miners and workers in the trucking industry represent useful contributions by investigators who have worked carefully over extended periods of time to recreate historical exposure profiles and to describe exposure–response relationships between diesel exhaust and human lung cancer. Overall, these studies made considerable progress toward addressing the deficiencies that HEI had identified in the utility of earlier epidemiological research studies of diesel exhaust for quantitative risk assessment.

The detailed evaluations of these studies by IARC, the HEI Panel, and other analysts lay the groundwork for a systematic characterization of the exposure–response relationship and associated uncertainties in a quantitative risk assessment, should one be undertaken. In addition, the Panel has identified the challenges that should be confronted in extrapolating the results from these studies to different populations and time periods, particularly given the rapid changes in diesel technology and its deployment around the world. The Panel concluded that the DEMS and data from both the Truckers study and the DEMS can be usefully applied in quantitative risk assessments. The uncertainties within each study should be considered in any attempts to derive an exposure–response relationship.

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ABBREVIATIONS AND OTHER TERMS

CO	carbon monoxide
DEMS	Diesel Exhaust in Miners Study
EC	elemental carbon
HP	horsepower
IARC	International Agency for Research on Cancer
NCI	National Cancer Institute
NIOSH	National Institute for Occupational Safety and Health
PAHs	polycyclic aromatic hydrocarbons
REC	respirable elemental carbon
SEC	submicron elemental carbon

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