Commentary

Diesel Exhaust and Lung Cancer—Aftermath of Becoming an IARC Group 1 Carcinogen

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The International Agency for Research on Cancer reclassified diesel exhaust from Group 2A (probably carcinogenic to humans) to Group 1 (carcinogenic to humans) in 2012. Since then, reevaluation and reanalysis of 2 major studies (Diesel Exhaust in Miners Study and Trucking Industry Particle Study) that were influential to the International Agency for Research on Cancer evaluation have replicated the original findings and demonstrated the suitability of these epidemiologic data for the quantitative risk assessment needed to set safe exposure limits in occupational and outdoor ambient environments. The challenge now is to protect the workers and general populations in urban areas from the carcinogenicity of diesel exhaust.

diesel exhaust; lung cancer; lung neoplasms

Abbreviations: CI, confidence interval; DEMS, Diesel Exhaust in Miners Study; EC, elemental carbon; EMA, Truck and Engine Manufacturers Association; HEI, Health Effects Institute; REC, respirable elemental carbon.

In 2012, the International Agency for Research on Cancer reclassified diesel exhaust from Group 2A (probably carcinogenic to humans) to Group 1 (carcinogenic to humans) in 2012. This action triggered a flurry of activity in 3 areas: reanalysis of data from 2 major epidemiologic studies critical to the International Agency for Research on Cancer evaluation, quantitative risk assessment to determine safe exposure limits for regulation in the workplace and in the outdoor ambient environment, and mechanistic research.

BACKGROUND

The first epidemiologic studies of diesel exhaust exposure and lung cancer risk were conducted in the 1980s, and by the 1990s, approximately 30 studies on the relationship between exposure to diesel exhaust and lung cancer had been published (2). First, in most studies, diesel exposure was inferred from job title in the absence of information on level of diesel exposure, which likely introduced nondifferential exposure misclassification and biased relative risks toward the null. Second, the magnitude of effect observed in most studies was low, with relative risks typically under 1.5, which could be explained by confounding, particularly from smoking. Only about half of the studies controlled for cigarette smoking or other potential confounders.

These weaknesses, coupled with the ubiquitous nature of diesel exposure both in the occupational setting and in the general environment, led to the launching of 2 epidemiologic studies on the carcinogenicity of diesel exhaust in the United States, one in nonmetal miners and one in truck drivers. In the early 1990s, the National Cancer Institute and the National Institute of Occupational Safety and Health initiated the Diesel Exhaust in Miners Study (DEMS), a large cohort study (n = 12,315) of heavily exposed workers, with historical information and measurements to develop quantitative estimates of respirable elemental carbon (REC) (a surrogate for diesel exposure) and with information on cigarette smoking and other potential confounders obtained from telephone interviews with...
next of kin in an accompanying nested case-control study of lung cancer (198 cases and 562 controls) (3, 4). Confounding from underground exposure to radon, silica, and asbestos was minimal in these nonmetal mines (4). Several years later, the Trucking Industry Particle Study (Truckers Study) was initiated; this was a large cohort study (n = 31,135) of workers employed in trucking facilities across the United States (5). The Truckers Study included an intensive effort to develop exposure estimates for individual-level submicron elemental carbon (EC), also a marker for diesel exposure, for all cohort members (5, 6). Individual-level data on smoking to control for confounding were not available, however.

Both studies yielded positive findings. In the Truckers Study, the association between lung cancer mortality and cumulative submicron EC lagged 5 and 10 years was weak; adjustment for the healthy-worker survivor bias by including duration of employment in the model strengthened the exposure-response (5). Trucking industry workers in the top quartile of cumulative submicron EC lagged 5 years (≥1,803 μg/m²-months) had a hazard ratio of 1.48 (95% confidence interval [CI]: 1.05, 2.10), with a nonsignificant exposure-response (P for trend = 0.16). In DEMS, significant trends in lung cancer mortality with increasing REC exposure lagged 15 years were seen in both the cohort and nested case-control study with adjustment for smoking, employment in other high-risk occupations, and a history of nonmalignant respiratory disease (3, 4). Underground workers had a significant positive risk gradient with cumulative REC lagged 15 years (P for trend = 0.004); workers in the top exposure quartile (≥878 μg/m²-years) had an odds ratio for lung cancer mortality of 5.10 (95% CI: 1.88, 13.87) (3).

REANALYSIS OF DATA

In 2013, an independent panel assembled by the Health Effects Institute (HEI), a research organization that receives balanced funding from the worldwide motor vehicle industry and the US Environmental Protection Agency, reevaluated both the Truckers Study and DEMS to determine the suitability of data from each study for quantitative risk assessment. The panel carefully evaluated both studies, but reanalysis and sensitivity analyses were possible only in DEMS because only DEMS data were publicly available at that time. The HEI panel’s reanalyses replicated the DEMS findings, indicating that the REC–lung cancer results were “robust to numerous investigations. . . of alternative modeling approaches [based on different assumptions for modeling exposure], control for confounding factors [e.g., different approaches to control for smoking and radon], and estimates of exposure” (7, p. 5).

A second group of investigators funded by an international coalition of trade organizations coordinated by the Truck and Engine Manufacturers Association (EMA) reanalyzed the DEMS cohort and case-control data (8–10) using exposure estimates from the original DEMS exposure assessment (11–15), and they also conducted reanalyses using alternative exposure estimates based on horsepower, ventilation rates, and temporal trends in particulate matter emission per horsepower. One such reanalysis of the cohort data by Chang et al. (8) appears in this issue of the Journal. Based on alternative exposure estimates, EMA reanalyses yielded positive associations between diesel exposure and lung cancer that were attenuated and often nonsignificant. For example, the hazard ratios for underground workers in the top quartile of cumulative REC lagged 15 years (≥946 μg/m²-years) ranged from 1.04 (95% CI: 0.46, 2.32) based on alternative exposure estimates with radon adjustment to 1.63 (95% CI: 0.86, 3.11) without radon adjustment (8, in supplemental material), compared with the significant 5-fold risk based on the original DEMS REC estimates with adjustment for smoking, employment in other high-risk occupations, and a history of nonmalignant respiratory disease (3).

Several factors appear to be contributing to the disparity between the findings from the EMA reanalyses and the originally published DEMS results. First, the EMA reanalyses are based mainly on alternative exposure estimates that were generated as part of the EMA reanalyses after the original study results were published. Validity of these alternative exposure estimates has not been formally tested, as was done for the original DEMS REC estimation models (15), hampering direct comparisons.

Second, and perhaps most important, EMA’s cohort analysis was not adjusted for cigarette smoking, a powerful risk factor for lung cancer. Results of the nested case-control study indicated that smoking was a negative confounder in DEMS because diesel exposure was inversely related to current smoking in underground workers (3, 16). Failure to adjust for smoking and to take worker location (surface vs. underground) into account in estimating the exposure-response relationship can lead to underestimation of the risk associated with diesel exposure (3, 16). Chang et al. were unable to directly adjust for smoking because smoking data were collected only for subjects in the DEMS nested case-control study. However, in a separate reanalysis of the nested case-control study by some of the same investigators, Crump et al. (9, 10) did adjust for smoking but failed to include worker location in some of their models (9), biasing results of parts of the EMA reanalyses of the nested case-control study toward the null.

Third, some EMA reanalyses suggest that radon is a confounder (8, 10), even though radon levels at these mines were very low (i.e., arithmetic mean ≤ 0.02 working levels) and never exceeded the residential limit of 4 pCi/L (4, 7). Additionally, the effect of radon in this study is weak, with an odds ratio of 1.32 (95% CI: 0.76, 2.29) in the top quartile of exposure (3), making it highly unlikely that confounding by radon explains the 5-fold risk observed among heavily exposed underground workers in the nested case-control study. In fact, in the reanalysis of the nested case-control study by Crump et al. (10), adjustment for radon among “ever” underground workers had virtually no impact on the odds ratio for cumulative REC lagged 15 years from the original analysis (3). The HEI panel also examined the possible confounding effect of radon and estimated a relative risk of 1.06 for the top quartile of radon exposure in DEMS using Biological Effects of Ionizing Radiation (BEIR) VI models to estimate lifetime lung cancer risk due to radon exposure in miners (7). They concluded that “radon is not a major confounder in this study, that adjustment is not necessary in this study, and in fact could lead to unintended biases in the results” (7, p. 5).
Two additional issues regarding the reanalyses and findings by Chang et al. (8) merit discussion. Their findings indicated that the observed exposure-response relationship is present only in the limestone mine and absent in the other 7 study mines (8). This observation is at odds with results of both the DEMS cohort (4) and nested case-control studies (3), which indicated increased risk with cumulative REC lagged 15 years among workers in both the potash and trona mines (odds ratios for top quartile [≥536 μg/m^3]-years) were 5.53 (95% CI: 1.68, 18.21) and 2.38 (95% CI: 0.44, 13.00), respectively (3). Moreover, the HEI panel (7) replicated these results, as did Crump et al. (10) in the EMA reanalysis of the nested case-control data. Chang et al. (8) also raise concerns about a healthy-worker survival bias operating in the DEMS cohort. Indeed, Neophytou et al. (17) evaluated the potential for healthy-worker survivor bias using an accelerated failure time model and found an effect of REC exposure on time to termination of employment among DEMS underground workers. This bias, however, may have resulted in relative risks for cumulative REC that would be biased toward the null because workers more susceptible to lung cancer may leave work and accumulate less exposure. Because many of the DEMS cohort findings were restricted to workers with at least 5 years of tenure, however, the bias is less likely to be an issue for DEMS (17).

### QUANTITATIVE RISK ASSESSMENT AND REGULATION

The conclusion of the HEI panel’s evaluation of DEMS and the Truckers Study was that both studies were “well designed and well conducted” and “lay the ground work for a systematic characterization of the exposure-response relationship,” and that data from both studies “can be usefully applied in quantitative risk assessments” (7, pp. 6–7). To that end, Vermeulen et al. (18) conducted a meta-regression of data from DEMS (3), the Truckers Study (5), and an older study of truck drivers (19) to derive the exposure-response relationship between cumulative EC and lung cancer mortality. Based on the derived exposure-response relationship, they estimated the excess lifetime risk of lung cancer mortality in the United States in the workplace and in the ambient environment under various exposure scenarios. The number of excess lung cancer deaths through age 80 years for lifetime occupational exposures of 1, 10, and 25 μg/m^3 EC were estimated to be 17, 200, and 689 per 10,000 individuals, respectively, which exceed the typically acceptable levels of occupational risk of 1/1,000 in the United States and Europe (18). For environmental exposures, they estimated 21 excess lung cancer deaths per 10,000 for lifetime environmental exposure to 0.8 μg/m^3 EC, a rate that exceeds the typically acceptable level of 1/100,000 in the United States and Europe.

Based on DEMS data, Neophytou et al. (17) applied the parametric g-formula to evaluate the effect of various interventions in the workplace on lifetime lung cancer mortality, while adjusting for time-varying employment status. They observed a 20% reduction in mortality with an EC limit of ≤25 μg/m^3 compared with no intervention, providing hypothetical evidence of the beneficial effect of lowering EC exposure limits in underground nonmetal mining. The authors concluded that to achieve a risk of 1/1,000 would require reducing EC exposure to below 1 μg/m^3, a difficult target for old-technology diesel engines.

Governmental regulatory agencies have responsibility for determining safe exposure levels in the occupational and outdoor ambient environments. Much of the recent regulatory activity has focused on the workplace (20). Workplace regulations are nonexistent in many countries, and many others have regulations that bear reevaluation in light of the new research findings. With this goal, advisory groups in Norway and the Netherlands have considered relevant exposure indicators and perspectives for setting occupational exposure limit values for diesel exhaust (21). Comparable efforts are needed in other countries to protect workers’ health.

In the environmental arena, several major cities are planning to ban diesel-powered vehicles in the next decade (20), and Britain, France, and India want to ban new sales of diesel vehicles by 2040 or sooner (22). Others are relying on the transition from old- to new-technology diesel engines to reduce emissions from EC and many other compounds. The safety of emissions from new-technology engines, however, has not been thoroughly evaluated, particularly for cancer risk.

### MECHANISTIC RESEARCH

Much research has been conducted to understand the biologic effects of diesel exhaust (1). Yet, the relevance and relative importance of these effects on diesel exhaust-induced lung cancer are not clear. Recent cross-sectional studies of diesel-exposed workers have reported exposure-response relationships with levels of lymphocyte subsets (23) and certain immune/inflammatory markers (24) that have been prospectively associated with lung cancer risk (25). These findings add to the evidence that diesel exposure may alter key immunologic and inflammatory processes that are recognized as playing critical roles in lung cancer etiology (1). Additional molecular epidemiology studies using both hypothesis-driven biomarkers and -omic technologies such as transcriptomics and epigenetics are needed to provide mechanistic insight into the relationship between diesel exhaust and lung cancer.

In the aggregate, experimental, epidemiologic, and mechanistic findings provide clear evidence that diesel exhaust causes lung cancer in humans (1). Findings from DEMS and the Truckers Study provide the epidemiologic data needed to conduct quantitative risk assessment underpinning safe exposure limits in the occupational and outdoor ambient environments. The challenge now is to determine how to protect the millions of workers and the general populations of urban areas worldwide from the carcinogenicity of diesel exhaust.

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