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# Diesel Exhaust Causes Lung Cancer – Now What?

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After three decades of epidemiologic research, diesel exhaust was classified as a carcinogen in humans by the International Agency for Research on Cancer (IARC) in 2012 based on evidence of its carcinogenicity to the lung (1). This determination was largely based on results from two recent epidemiologic studies of occupational diesel exhaust exposures among nonmetal miners (Diesel Exhaust in Miners Study (DEMS)) (2, 3) and truck drivers (4). The next challenge is to determine how to regulate exposure to diesel exhaust. Governmental regulatory agencies are charged with setting safe levels of exposure in the workplace and in the outdoor ambient environment in various countries. Much of the current regulatory activity has been focused on the workplace. Many countries lack workplace regulations, and many others have regulations that need re-evaluation by quantitative risk assessors in light of the new research findings. The new findings and the potential need for regulation has stimulated exposure assessments such as that led by Peters and colleagues in Western Australian mining (5).

In 2013, the Health Effects Institute (HEI) convened an independent panel of scientists to evaluate whether the findings from the two new studies of nonmetal miners and truck drivers were suitable for conducting quantitative risk assessment. In 2015, the HEI panel issued a report indicating that they found the studies to be "well designed and well conducted"; through re-analysis of the primary data, the panel replicated the published results of these studies and concluded that these data were useful for quantitative risk assessment (6). In the past two years, several investigators have attempted to determine what level of exposure would be "safe" in the workplace and in the environment. Based on the exposure-response relationship between cumulative elemental carbon (a key surrogate of diesel exhaust) and lung cancer mortality derived from a meta-regression of data from the studies of nonmetal miners (2), truck drivers (4), and an older study of truck drivers (7), Vermeulen and colleagues (8) estimated the excess lifetime risk of lung cancer mortality in the U.S. under various exposure scenarios. The estimated numbers of excess lung cancer deaths through age 80 for lifetime workplace exposures of 1, 10, and 25 $\mu g/m^3$ elemental carbon (EC) were 17, 200, and 689 per 10,000, respectively, which exceed the typically acceptable levels of occupational risk of 1/1,000 in the U.S. and Europe (8). With regard to environmental exposures, they estimated 21 excess lung cancer deaths per 10,000 for lifetime

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environmental exposure to 0.8 μg/$m^3$ EC, which exceeds the typically acceptable level of 1/100,000 in the U.S. and Europe.

In Western Australia, Peters et al (5) conducted an extensive diesel exhaust exposure assessment in 124 mine sites (mainly metal and nonmetal). Based on an approach similar to that taken by Vermeulen et al (8), they estimated that a lifetime underground mining career (45 years), with an estimated average exposure of 44 μg/$m^3$ EC in 2011, was associated with 38 excess lung cancer deaths per 1,000 miners. However, EC exposure levels have been decreasing over time in these Australian mines, so use of recent measurements likely results in an underestimation of lifetime exposure, and thus, an underestimation of excess lung cancer deaths. Australia has a recommended level of occupational exposure to EC of 100 μg/$m^3$, but no workplace regulations exist (5). This lung cancer risk exceeds levels that are acceptable in Europe and the U.S., leading the investigators to call for "the implementation of stringent occupational exposure limits for diesel exhaust" (5).

In 2016, Vermeulen and Portengen (9) conducted a quantitative risk assessment based on the exposure-response relationship derived from the 2014 meta-regression (8) and additional sensitivity analyses based on alternative exposure-response relationships. They estimated workplace EC exposure levels for both acceptable risk (AR) and maximum tolerable risk (MTR) of $4 \times 10^{-5}$and $4 \times 10^{-3}$, respectively, for lifetime cumulative excess risk of dying from lung cancer. To achieve these AR and MTR limits, they found that EC exposures would need to be 0.01 and 1.0 μg/$m^3$, respectively, which are at or far below current workplace exposure levels, leading the authors to suggest that "diesel engines using older technologies should be removed from the workplace when possible or emissions strictly controlled" (9). Lastly, to correct for healthy worker survivor bias that may have led to an underestimation of lung cancer mortality in underground diesel-exposed nonmetal miners in DEMS, Neophytou and colleagues (10) applied an accelerated failure time model to assess the effect of exposures to EC on time to termination of employment and found time to termination decreased with increased EC exposure. Adjusting for time-varying employment status, they applied the parametric g-formula to evaluate the effect of various interventions on lifetime lung cancer mortality. They observed a 20% reduction in mortality with an EC limit of ≤25 μg/$m^3$ compared to 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/$m^3$, making continued use of diesel equipment based on older technology difficult.

With an eye to future research, several pressing scientific questions merit our attention. First, is the carcinogenicity of diesel exhaust in humans limited to the lung? As we observed for cigarette smoke, a product of combustion and a powerful lung carcinogen that causes cancer of 20 other sites, diesel exhaust may cause cancer of sites such as the urinary bladder, larynx, and colon (1). Additionally, diesel exhaust is a major contributor to air pollution in most urban areas, specifically the fine particulate component ($PM_{2.5}$). IARC classifies outdoor air pollution, specifically particulate matter, as a cause of lung cancer (11). How much of the carcinogenicity of air pollution is attributable to diesel exhaust? Air pollution also causes cardiovascular disease (12). Does diesel exhaust cause cardiovascular disease and other diseases such as nonmalignant respiratory disease?

Finally, the gravity of the adverse health effects of air pollution in some metropolitan areas is perhaps best reflected by the recent proposals by mayors of Mexico City, Paris, Madrid and Athens to ban diesel vehicles by 2025; possibly, more cities will follow suit. Alternatively, would the replacement of “old” with “new” technology diesel engines, which drastically reduce emissions of many compounds and elemental carbon, prove to be sufficient for safety from disease for the millions of diesel-exposed workers and the populations in urban areas worldwide? If so, improving air quality to protect health may depend to a large extent on the turnover rate from old- to new-technology engines in both developed and developing countries.

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