HEALTH EFFECTS OF DIESEL EXHAUST: AN HEI PERSPECTIVE

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Introduction

Diesel engines have many advantages, including good fuel economy, power, durability, lower emissions of some pollutants (such as carbon monoxide) and of carbon dioxide (a greenhouse gas). However, there are a number of concerns that need to be addressed: (1) emissions of nitrogen oxides (which contribute to ozone formation) and of particulate matter (PM); (2) questions about cancer and other health effects from exposure to diesel PM; and (3) as efforts to decrease emissions progress, a need to understand whether the nature and toxicity of the PM emitted has changed. This paper focuses on (1) carcinogenicity data, (2) noncancer effects, and (3) diesel as part of the complex ambient mixture of PM.

Carcinogenicity of Diesel Particulate Matter

Diesel PM is a complex mixture consisting of solid carbon spheres with adsorbed compounds that include organics, metals, and sulfate. In the early 1980s, the finding that extracts of diesel particles were mutagenic in a variety of test systems and carcinogenic in skin painting tests in mice raised concern about the potential carcinogenicity of diesel PM inhaled by people and stimulated a great deal of research. Since then, effects of diesel exhaust on lung cancer have been studied in rats, mice, and hamsters, with significant findings only in rats, and at high levels (several mg/m^3) (Busby and Newberne 1995, Mauderly 2000). The rats also accumulated large particle burdens in their lungs that caused an epithelial cell proliferation that may be unique. Rats exposed to carbon black (which essentially lacks the adsorbed organic compounds found on diesel particles) developed the same kinds of tumors as diesel-exposed rats (Mauderly et al. 1994, Heinrich et al. 1995). These results suggested that mechanisms of carcinogenicity in rats are related to the particles themselves rather than the adsorbed organic compounds, but do not rule out a mutagenic mechanism at lower levels of exposure or in other species. There is also evidence of a threshold level for development of tumors in rats (Valberg and Crouch 1999; Mauderly 2000).

More than thirty studies of railroad workers and truckers exposed to diesel exhaust have shown a relatively consistent association between diesel exhaust exposure and lung cancer (Cohen and Higgins 1995). The association is considered weak because relative risks are small (generally an increase of about 20 to 50%) (Figure 1), many studies have insufficient control for confounders such as cigarette smoking, and none have concurrent exposure measurements. Two studies have subsequent detailed exposure measurements, however. In recent years there has been much debate about using data from diesel epidemiology studies for quantitative risk assessment (QRA) for lung cancer. In 1998, HEI organized a Diesel Epidemiology Expert Panel to examine the published diesel epidemiologic studies for use in QRA. The Panel focused on two sets of studies that had retrospective exposure assessment, the Garshick studies of railroad workers (Garshick et al. 1987, 1988; Woskie et al. 1988a,b) and the Steenland studies of truckers (Steenland et al. 1990, 1992; Zaebst et al. 1991). The Garshick data have been evaluated by additional analysts who found different dose-response results using different assumptions. Because of the importance of understanding the exposure-response association in the railroad worker data, the HEI Panel did a limited analysis of the data, and found that the lung cancer risk decreased with increasing duration of employment, although the risk was still greater in worker groups with higher exposures (Figure 2) (HEI 1999). Based on these findings the Panel recommended against using the current railroad worker data as the basis for QRA in ambient settings. The Panel also recommended further scrutiny of the truckers data, including estimation

of uncertainty in both the exposure estimates and selection of controls, in order to improve the use of these data for QRA. Because the truckers' exposure assessment is relatively new, the Panel recommended further review and analysis be carried out, including developing alternative retrospective exposure models.

Recently, the U.S. Environmental Protection Agency (EPA) released its draft Diesel Health Assessment for public comment (US EPA 2000). In this revised draft, EPA concluded that diesel exhaust is likely to be carcinogenic, based on human, animal, and other data (such as the mutagenicity of substances adsorbed to diesel particles), and presumed that the hazard extends to ambient levels. EPA concluded that the human evidence that diesel exhaust is a carcinogen is strong but that the data are not sufficient for concluding causality. They also concluded that the rat dose-response data are not suitable for human risk at low exposure levels, and that there is uncertainty about the exposure-response relation in the Garshick study and about the exposure data in the truckers study. Because of these uncertainties, they did not calculate a unit risk estimate, but did provide a possible range of lung cancer risk from environmental exposure to diesel exhaust (10^{-3} to 10^{-5} deaths per lifetime exposure) as an indication of the significance of the potential hazard. Many other agencies have reviewed this evidence in the last few years, and most (World Health Organization, International Agency for Research on Cancer, National Institute of Occupational Health Sciences) concluded that diesel exhaust is a potential or probable human carcinogen, a similar conclusion to the EPA's. The California Office of Environmental Health Hazard Assessment concluded that diesel exhaust is a known carcinogen and used the Garshick data to calculate a unit risk of 3 excess deaths in 10,000 people per Fg/m^3 diesel PM lifetime exposure (OEHHA 1998)

Noncancer Effects

Although most attention regarding diesel exhaust has focused on cancer, emerging data on acute effects are of potential concern. These include enhanced allergic responses, exacerbation of asthma, and childhood illness. Additional studies are needed to understand mechanism, dose-response relationships, and sensitivity. This topic is addressed in depth by Dr. Diaz-Sanchez in his talk at this meeting. In its draft Diesel Health Assessment (US EPA 2000), EPA also evaluated noncancer effects. With respect to acute noncancer effects, EPA concluded that the lack of dose-response information precluded development of recommendations about levels of exposure that would be protective. EPA noted, however, that available animal and human evidence supports a number of effects of diesel exhaust, including acute irritation, neurophysiological symptoms, and respiratory symptoms. EPA also noted evidence of possible immunologic effects and exacerbation of allergic responses. Because of the need for more information on these effects, HEI is issuing a Request for Applications for Research on the effects of diesel and other PM on asthma and other allergic diseases in the fall of 2000.

For chronic, noncancer effects, the EPA draft Diesel Health Assessment (US EPA 2000) noted that animal studies demonstrate dose-dependent chronic inflammation and histopathological changes in several species, and that occupational studies provide additional supportive information. EPA concluded that there are sufficient dose-response data to calculate an inhalation reference concentration (RfC), which is an air level of diesel PM for human lifetime exposure that will not cause adverse noncancer effects. Using data from several chronic rat inhalation studies with effects on inflammation and histopathology, they calculated a reference concentration of 14 Fg/m^3, a level similar to the annual National Ambient Air Quality Standard for $PM_{2.5}$ (particulate matter less than 2.5 Fm in aerodynamic diameter).

Diesel as Part of the Complex Ambient PM Mixture

To put particulate matter from diesel exhaust in perspective, it is important to consider that it is part of the complex ambient PM mixture. Particles in the air come from diverse sources, including many combustion sources as well as natural sources and secondary particles from chemical transformation in the air. These particles vary in size and chemical composition; they contain hundreds of inorganic compounds and thousand of organic compounds. The levels of PM in the air are regulated by mass standards for

$PM_{2.5}$ and PM_{10} (particles less than 10 Fm in aerodynamic diameter) . Although $PM_{2.5}$ is a subset of PM_{10}, it is regulated separately to ensure that the smaller particles, which have less mass but may be more toxic, are adequately controlled. Effects of both short-term and long-term exposure formed the basis for the standards. Many epidemiology studies in different locations with different levels of PM and other pollutants have shown an association between daily increases in PM and increases in daily numbers of deaths, particularly in people over 65 and those with cardiovascular disease. Two studies of the effects of long-term exposure were important in setting the $PM_{2.5}$ standard, the Harvard Six-Cities Study (Dockery et al. 1993) and the American Cancer Society Study (Pope et al. 1995). Because of questions about these studies and their importance in regulatory decisions about PM, HEI funded a reanalysis of these studies, which validated and replicated the original results (Health Effects Institute 2000). In alternative analyses, the reanalysis investigators identified relatively robust associations of mortality with sulfur dioxide as well as with fine particles and sulfate.

There are many hypotheses about attributes of PM that may be related to toxicity; these include size and surface area, chemical composition (e.g., metals, organic compounds, acidity), and biological constituents. A popular hypothesis has been that very small or ultrafine particles (less than 0.1 Fm in diameter) may be particularly toxic because they are more likely to reach the deep lung, penetrate more readily into cells, have greater surface area per unit mass for chemical reactions, and dissolve more rapidly in the lungs. Because diesel particles tend to be very small, this issue is particularly relevant to them. Many toxicology and epidemiology studies have investigated the effects of ultrafine particles (e.g, Oberdörster et al. 2000, Wichmann et al. 2000), and at this time there is evidence that ultrafine particles are associated with toxic effects and mortality, but not that they stand out as being particularly hazardous compared to fine particles.

Summary

There are a number of important issues about the health effects of diesel exhaust that remain to be fully addressed in order to evaluate the toxicity of diesel PM in relation to other PM: (1) what are the active components of diesel PM and other PM? (2) what is a good marker for measuring diesel PM in the air so that exposure to it can be more accurately quantified? (3) how do acute toxicity and carcinogenicity of diesel PM compare to other PM? Over time, we need to understand the mechanisms of toxicity (and toxic PM components) so that future control strategies can be better targeted.

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Figure 1: Epidemiologic Studies in Railroad Workers (Cohen and Higgins 1995)

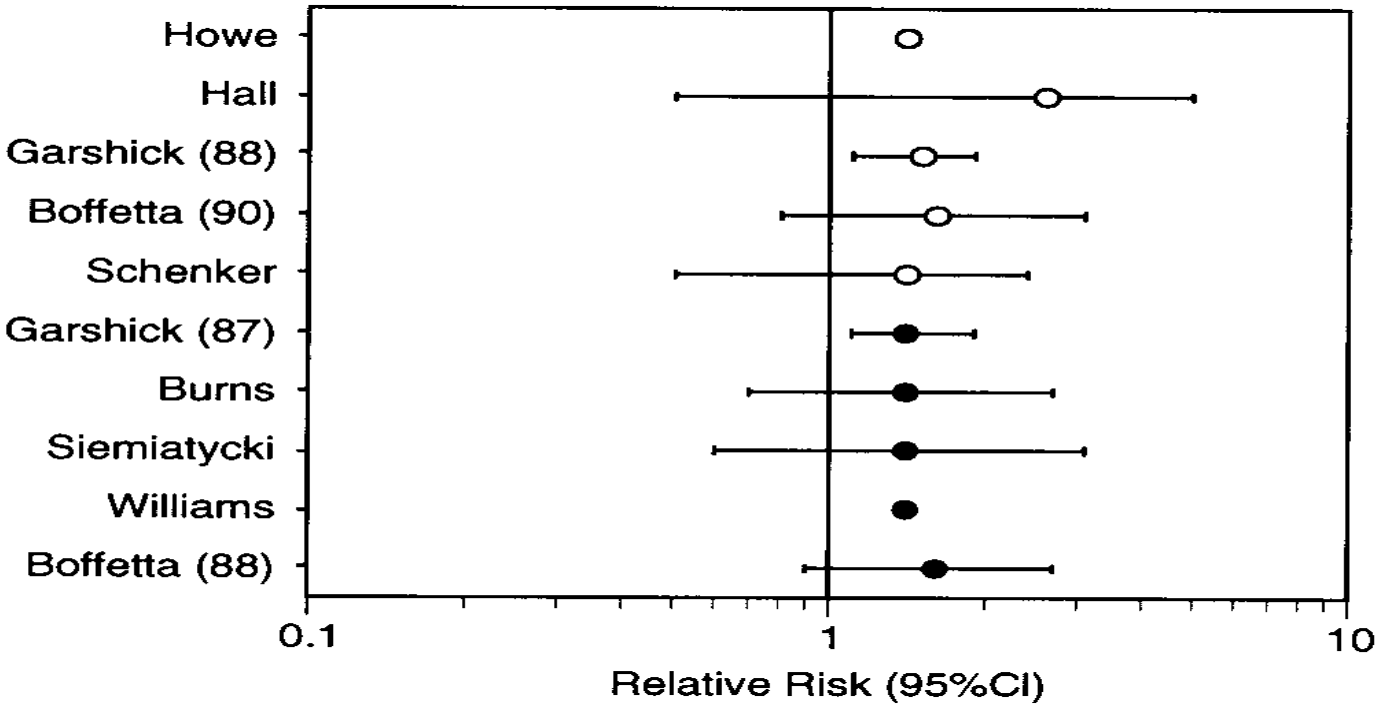

Figure 2: Diesel Quantitative Risk Assessment

- HEI Diesel Epidemiology Expert Panel Report (HEI 1999)
  - Reviewed two best epidemiology studies
  - Concluded:
    - Garshick has significant limitations in dose-response information
    - Steenland may be useful; additional work to reconstruct past exposures