

FORUM

Diesel Emissions: Is More Health Research Still Needed?

Joe L. Mauderly¹

National Environmental Respiratory Center, Lovelace Respiratory Research Institute, P.O. Box 5890, Albuquerque, New Mexico 98785

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It can legitimately be asked whether we need any more research on the health effects of diesel emissions. However, despite a research effort spanning at least 5 decades and the generation of a huge literature, there are still key uncertainties about the health impacts of present and future diesel emissions. This article briefly characterizes current knowledge and information gaps, and then proposes some key issues requiring further research. These issues include the adjuvant effect, the bioactivity of inhaled emissions at realistic doses, the toxicity of aged diesel exhaust particles, the importance of ultrafine particulate emissions, the need to improve our ability to predict the impacts of changes in emissions, and the placement of diesel health risks in context regarding other exposures.

Key Words: diesel emissions; engine exhaust; health hazards; risk assessment; dose-response; immune sensitization; adjuvant; ultrafine particles; copollutants; mixtures.

Introduction

Do we need more research on the health effects of diesel emissions (DE)? The question is certainly arguable. There has probably been more health research on DE than on emissions from any other single source, possibly excepting cigarette smoke. One could argue that further research would be superfluous because we already have sufficient knowledge to warrant regulatory action and to guide emissions reduction strategies. Moreover, DE as they have existed in the past will largely be eliminated by progressive regulations already in place.

Our large body of knowledge of DE has been reviewed in detail (California EPA, 1998; EPA, 2001; HEI, 1995, 1999; Mauderly, 1999). Emissions from diesels are a mixture of gases, vapors, semivolatile organic compounds, and particles. The particles are all respirable and fall into 2 general chemical classes: (1) "soot," or elemental carbon particles coated with condensed organic and inorganic compounds, and (2) ultrafine particles of condensed organic material and sulfur compounds

having little or no elemental carbon content. Acute exposures to high concentrations of fresh DE can cause respiratory inflammation and symptoms. Nasal deposition of large doses of DE soot amplifies immunological responses to antigens. Lifetime exposures of rodents to high concentrations cause chronic inflammation and fibrosis. The semivolatile and soot-borne organic material is mutagenic; soot extract is carcinogenic to mouse skin, and inhalation exposures of rats (but not mice or Syrian hamsters) to high concentrations cause lung tumors. Most retrospective studies show associations between occupations having presumed high diesel exposures and modest ($\approx 40\%$) increases in lung cancer risk.

Despite our large and lengthy effort, we are faced with information gaps bearing on current concerns about DE. Some gaps are long-standing and others have arisen as our information and the nature of DE have evolved. A few of these issues are summarized below, without prioritization.

Selected Research Needs

The Adjuvant Effect

Early studies of the potential immunological effects of DE concerned reduced function, but found that subacute or chronic inhalation of DE did not reduce immune function in the pulmonary lymph nodes, spleen, and blood of rodents (Bice *et al.*, 1985; Dziedzic, 1981; Mentnech *et al.*, 1984). Takafuji *et al.* (1987) then found that IgE responses of mice to intranasally instilled ovalbumin antigen were increased by adding diesel exhaust particles (DEP) to the instillate. Attention has since focused on the potential for DE or DEP to enhance allergic immune responses in the respiratory tract. Interest in this adjuvant-like effect was spurred in part by the potential association between DE and asthma and other allergic diseases (Edwards *et al.*, 1994; Keil *et al.*, 1996; Peters *et al.*, 1997).

Studies of rodents have demonstrated that instilled or inhaled DE can enhance responses to instilled antigens, but have not addressed inhaled antigens. Using human subjects, Diaz-Sanchez *et al.* demonstrated that nasal instillation of DEP increases local IgE (1994) and cytokine (1996) responses to

¹ For correspondence via fax: (505) 845-1193. E-mail: jmauderl@lrri.org.

antigen, instillation of DEP increases responses to both a recognized antigen (ragweed) (1997) and a new antigen (KLH) (1999), and that the activity is largely attributable to the organic fraction of DEP (1997; Tsien *et al.*, 1997).

We need additional information to understand the implications of the above findings. We need to determine whether the adjuvant effect is significant at current occupational or environmental exposure levels. We need to know if human thoracic airways, as well as noses, are affected by realistic inhalation exposures. We need to know the causative compounds in order to understand how changes in DE composition might reduce the effect, and the extent to which the effect is unique to DE.

Bioactivity of Emissions at Realistic Doses

One of the more troublesome barriers to placing health risks from DE in their proper perspective is our lack of understanding of the bioavailability and bioactivity of DE components at realistic doses. Occupational studies have provided little information on exposures or doses. Only a few laboratory studies of either cancer or noncancer effects have extended the dose range down to the “no observed adverse effects level” (NOAEL). Without such information, NOAELs have required estimations or interpolations attended by considerable uncertainty (EPA, 2001), and cancer hazard is assumed to have no threshold.

The need for dose-response information down to realistic doses is especially obvious in studies of cellular mechanisms. For any health outcome or “critical path” mechanism proposed to link exposure to DE or its components to a health response, we need to know whether or not there is an exposure or an organ, tissue, or cellular dose at which the effect no longer occurs.

Influence of Aging of Diesel Exhaust Particles on Their Toxicity

Humans are exposed to DEP that are freshly emitted, DEP that have aged in the atmosphere for times ranging from minutes to weeks, and DEP that have been deposited on surfaces and resuspended by traffic, wind, etc. after various lengths of time. DEP undergo numerous atmospheric reactions, including photolysis, nitration, and oxidation (EPA, 2001). The atmospheric chemistry of organic compounds associated with DEP and other combustion emissions is known in some detail (e.g., Seinfeld and Pandis, 1998).

There has been little research on the effects of age and atmospheric reactions on the toxicity of DEP. With few exceptions, such as the aging and irradiation chambers used in early EPA studies (Pepelko and Peirano, 1983), laboratory inhalation exposures have aged DE only by a residence time on the order of minutes in the exposure chambers, with contact only among copollutants in DE, and without irradiation aside from room light penetrating the chambers. Reports of studies using collected DEP typically fail to describe the age or storage

conditions of the material, and most provide little or no chemical analysis.

The scanty older literature suggests that postemission reactions can act to both increase and decrease the toxicity of DEP (Claxton, 1983; Kamens *et al.*, 1988; Pitts *et al.*, 1981). Madden *et al.* (2000) recently reported that treatment of DEP with ozone increased its inflammatory potential in rat lungs. Future research should give attention not only to the chemical composition of freshly emitted material, but also to the likely nature and time-course of chemical alterations as the DEP ages. More advantage could be taken of experimental atmospheric reaction chambers (“smog chambers”) and other aging and chemical reaction models to determine the importance of aging in the toxicity of DEP including, but certainly extending beyond, its mutagenicity.

Importance of Ultrafine and Nanoparticle Emissions

Concerns for DEP have focused largely on soot, elemental carbon particles formed in the combustion chamber, coated with organic and inorganic compounds adsorbed by condensation throughout the engine-exhaust system, and emitted as respirable agglomerates. The results of Bagley *et al.* (1996) attracted attention to ultrafine DEP (commonly considered to be 100 nm or less) and nanoparticles (commonly considered to be 50 nm or less) with data suggesting that emissions of these particles may increase as mass emissions of soot are reduced. Concurrently, attention was drawn to the ultrafine fraction of ambient particulate matter (PM) by studies showing inverse relationships between particle size and health responses and by studies showing similar relationships for laboratory-generated solid particles (reviewed in Oberdörster *et al.*, 2000). The health importance of ultrafines remains an uncertain, but important issue (NRC, 1998). Ultrafines contribute little mass, but the majority of particle numbers to ambient PM. Although generally short-lived, they are always present, and are mostly emitted from combustion sources.

Laboratory research on ultrafines has focused almost exclusively on solid, poorly-soluble particles. However, a substantial portion of ultrafine DEP is not “soot” as such, does not contain elemental carbon (Kittelson, 1998), and is likely to be soluble upon contact with respiratory surfaces. These particles include both nitrate- and sulfate-based particles that are solid when inhaled and particles comprised largely of organic compounds, perhaps condensed on sulfuric acid nuclei that are droplets when inhaled. The size-specific chemical composition of ultrafine DEP depends heavily on DE dilution and measurement techniques (Wei *et al.*, 2001). The knowledge of the physical-chemical characteristics of ultrafine DEP is now sufficient to design toxicological studies of these materials. This issue extends beyond DE; a large portion of the ultrafine fraction of ambient PM (Hughes *et al.*, 1998) and the majority of the particulate mass emitted from gasoline-powered vehicles (Kleeman *et al.*, 2000) consists of organic matter.

Translating Composition into Hazard: The Impact of Changing Emissions and Comparative Hazards of Alternate Technologies

Another important research need applies not only to DE, but also to other air contaminants. We need a better ability to place the health impacts of present and future DE in their proper context among the impacts of other air contaminants. We need a better ability to identify the physical and chemical species of air contaminants that are most closely associated with the different health effects observed in exposed subjects. We need a better ability to predict the health implications of changing the composition of DE and other emissions. These needs have in common our limited understanding of the contributions of individual air contaminants, or classes of contaminants to the combined effects of the variable, complex mixtures of synthetic and natural pollutants that people breathe (Lewtas, 1993; Mauderly, 1993, 2000). Currently, this issue is most often framed as a “copollutant” problem and viewed as determining the modifying influence of accompanying pollutants on the effect of the pollutant (e.g., PM) receiving current emphasis (NRC, 1998; EPA, 1999).

We need a more integrated, or holistic, view of the air quality-health relationship. Epidemiology is largely limited to testing associations between health outcomes and the few pollutants that are measured routinely. Laboratory studies typically focus on single pollutants (e.g., ozone), classes of pollutants (e.g., PM), or complex mixtures (e.g., DE) with little emphasis on disentangling the causal contributions of components of mixtures. We need more research that helps to place the roles of individual pollutants, classes, and sources into context within the total exposure to myriad synthetic and natural air contaminants.

Conclusions

There is a need for additional research on the health effects of DE, but not necessarily for the same types of research done to date. The above DE-related issues warrant research, but it could be argued legitimately that other issues are of equal or greater importance. There is clearly more work to do. As a final point, it should be noted that none of the issues described above pertains solely to DE; each has broader applications that support its importance.

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