

SENSITIZATION AND EXACERBATION OF ALLERGIC DISEASES BY DIESEL ENGINE PARTICLES

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Most studies of the health effects of diesel exhaust have focused on the controversial issue of its role in cancer. However, recently the role of combustion products such as diesel exhaust particles (DEP) in modulating the immune response has garnered much attention. In particular the effect of DEP on allergic and asthmatic diseases has been the focus of many studies. A link between industrialization and allergic disease has long been presumed. Indeed, only 50 years after the first recorded reported case of allergy in 1819, Charles Blackely wrote that the "hay-fever epidemic" was associated with the movement of people from the country into the cities. Ishizaki et al. (1987) found that people in Japan living on busy roads lined with cedar trees have more allergies to cedar than residents living on similar streets with much less traffic. Since that time other epidemiological studies have reported similar findings. Kramer, et al., showed that hay fever is greater in residential areas with heavy truck traffic, while Weiland, et al., reported that allergic symptoms correlate with the distance of residences to roads with heavy traffic.

The studies cited above have sparked renewed focus on the role of fossil fuel combustion products on allergic inflammation. Because of their universal nature, indoor concentrations of these products often equal or exceed those found in ambient outdoor air. Consisting of an inert carbon core containing unburned fuel petrochemicals, DEP have been used as model pollutants to understand the mechanisms involved. Much of the experimental work on pollution and allergy has centered on the ability to alter immuneoglobulin production. The formation of the allergic antibody IgE is central to the development of both allergy and asthma.

Muranaka et al. (1986) published the first demonstration that DEP could have an adjuvant activity. Instillation of a protein or a common

pollen (Japanese cedar pollen) mixed with DEP and injected intraperitoneally enhanced the production of allergic antibody in mice. Shortly after Takafuji, et al., demonstrated an identical effect if an intranasal route of administration was used. Since then, these studies have been repeated with variations many times by multiple groups, and DEP is consistently shown to have similar effects on allergic antibody production if administered intratracheally or by aerosol.

A major advantage of using DEP as a model pollutant has been the ease by which animal models have been transferred into human studies. These studies have categorically shown the potential of DEP to induce and exacerbate allergic antibody responses in the human upper respiratory tract (Diaz-Sanchez 2000, Diaz-Sanchez, et al., 1994, 1999). Human allergic volunteers were sprayed in the nose with DEP, ragweed pollen or both simultaneously. DEP was used at doses ranging up to 0.15 mg into each nostril. Although this dose may seem high, in certain occupational or everyday settings (such as waiting at a bus stop) exposure to DEP can be much higher. Nasal washes were performed at different days after challenge. At the peak of the response, the amount of allergic antibody to ragweed was 16-fold higher following ragweed plus DEP challenge compared to ragweed alone. In certain individuals it was up to 50-fold greater. In addition, DEP increased the severity of allergic symptoms to pollen and the levels of histamine, a key chemical mediator that causes many of the symptoms.

Unfortunately, it has been difficult to perform similar investigations on the lower airways in humans. In a series of studies headed by Dr. Sandström, volunteers have been exposed to diesel exhaust (Rudell et al. 1996). However, until now these studies have been limited to normal healthy subjects. Non-smoking subjects were exposed for 1 hour to diluted diesel exhaust and lung biopsies and lavages performed

before and after exposure. Increased number of inflammatory cells were found in the airways following exposure; similarly, there was an increase in histamine levels and increased levels of inflammatory mediators and molecules. Additionally, decreased macrophage function was observed. If similar findings were found in asthmatic subjects, one would expect a worsening of the disease.

Several agents have been shown to cause exacerbation of allergic disease, but few have been demonstrated to increase the frequency of allergy, that is induce allergic sensitization. Sensitization is defined as the ability to cause an allergy to a substance that was previously "harmless." We addressed the question of whether DEP can make subjects allergic to a "neo-allergen," that is a protein to which subjects have never encountered before. Keyhole limpet haemocyanin (KLH), found in the blood of an inedible water mollusk, is just such a protein. Allergic subjects given repeated doses of KLH produced no allergic antibodies and no allergic symptoms. In contrast, 60% of subjects who received DEP 24 hours prior to each KLH exposure produced allergic antibodies and showed allergic symptoms. It is unlikely that pollutants can convert a non-atopic into an atopic individual; however, these studies imply that DEP and similar combustion pollutants may cause those with the appropriate genetic predisposition to become sensitized to pollen and other proteins to which they may not otherwise have become sensitized.

Is the effect of DEP on the human allergic response due to its particulate nature or the chemicals it contains? To answer these questions, we have repeated the human exposure experiments above using either 1) carbon black, which is elemental carbon virtually devoid of chemicals, or 2) phenanthrene, an important hydrocarbon found in diesel. While carbon black caused inflammation, phenanthrene caused immunological changes (Table 1).

One of the most common treatments for severe hay-fever is the use of nasal steroids. It should be noted that while normal doses of steroids will block pollen-induced allergic responses, they have no effect on DEP-enhanced responses. In addition, since DEP increases histamine levels, it is probable that normal doses of anti-

histamines (the most common allergy medication used) will also be less effective.

Table 1
The effect of a model hydrocarbon and a model chemical-free carbon particle on human immune responses.

Phenanthrene	Carbon Black
Allergic antibody	Cellular inflammation
Symptoms	
Chemical mediators	

In conclusion, we need to ask whether diesel is unique. While DEP obviously has properties missing from other particles such as carbon black, it should be noted that allergic endpoints can be increased in cellular and mouse models by secondhand smoke, fly ash, phenanthrene, benzo(a)pyrene and TCDD. Therefore, while DEP is an excellent model to study the role of particulate pollution on allergic disease, it is likely that many of the results and underlying mechanisms are common to most combustion products.

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