Urban air pollution at the crossroads of the allergic pandemic

Lidia Proietti, Lucia Spicuzza*, Riccardo Polosa*

In these past decades an important increase in the prevalence of allergic respiratory diseases has been documented in most countries of the world with large differences being reported within different areas, particularly in industrialized countries. Persistent environmental exposure to particulate air pollution from motor vehicles has been suggested to be an important factor contributing to the observed increased prevalence of allergic diseases. Data from various investigators in different parts of the world have shown an important association between environmental levels of motor vehicle exhaust emissions and increased symptoms of asthma and rhinitis. In addition, recent human and animal laboratory-based studies have shown that particulate toxic pollutants, and especially diesel exhaust particles, can enhance allergic inflammation and induce the development of allergic immune responses.

This article reviews the current state of knowledge on the role of diesel exhaust particles in the susceptibility to allergy. It scrutinizes the epidemiological evidence that supports the causative link between particulate air pollution from motor vehicles and the increasing prevalence in allergic conditions and the immunologic mechanisms by which diesel exhaust particles enhance the susceptibility to allergy.

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Key words: Allergy; Diesel exhaust particles; Immunoglobulin E; Road traffic pollution.

Introduction

It is common knowledge that the prevalence of allergic respiratory symptoms among subjects dwelling in industrial and inner city areas is higher than that observed among individuals living in rural ones. In relation to this it is likely that exposure to elevated levels of particulate air pollution from motor vehicles is frequently associated with an increased morbidity and mortality due to cardiovascular disorders, lung cancer and non-malignant respiratory illnesses such as asthma, bronchitis and respiratory tract infections1. Health effects due to air pollution arising from motor vehicles are a major public and political concern worldwide. These initial studies dealt simply with the respiratory effects of airborne toxic pollutants and only recently more attention has been given to the relationship between allergy and elevated outdoor concentrations of suspended particulate matter. In the majority of the epidemiological studies it has been difficult to identify the specific agent(s) responsible for the contingent excess of allergic conditions observed in polluted areas. For example, a number of studies have shown that urban air pollution contains not only exhaust fumes but also large quantities of respirable abraded tire fragments. These fragments are known to contain highly allergic latex particles that may be responsible for the increase in allergic prevalence2,3.

Already in 1873 Charles Blackley, having lived through the Industrial Revolution in England, recognized a link between urbanization and atopy4. Since that time, in spite of the difficulties due to exposure assessment, hundreds of assorted epidemiological studies conducted in different parts of the world have shown a significant and consistent association between elevated ambient levels of particulate pollutants and an increase in allergic conditions5,6. The growing use of diesel-powered vehicles has led to the recognition that emissions from diesel engines are a substantial threat to public health. Although the diesel engine was originally promoted as a more environmentally friendly alternative to the petrol engine, it is now clear that exhausts from diesel engines are major contributors to the particulate matter that pollutes the air of most urban cities worldwide. Unfortunately, clear data about particle emission rates, size distribution, and chemical composition from light-duty and heavy-duty vehicles is scarce, especially in the real-world operating conditions.

The purpose of the present article is to review the available data with regard to the controversial topic on the role of diesel exhaust particles (DEPs) in the initiation of allergy and the related increased prevalence of atopic diseases.
Rising prevalence in allergic diseases and road traffic fumes

The pathological hallmark of airway allergic diseases such as asthma, hay fever and atopic eczema consists of epithelial damage, thickening of the basement membrane and inflammatory infiltration including mainly activated eosinophils, Th2 lymphocytes and degranulated mast cells. These cellular events are known to result from the activation of specific biological pathways at the environment-body interface and may also represent a form of abnormal response to tissue injury. The prevalence of allergic diseases has steeply increased over the past decades both in the developed as well as in the developing countries of the world. Between 100 and 150 million people around the globe suffer from asthma; it is estimated that approximately 20% of the global population is now atopic. In particular, it appears that in recent years the prevalence of allergic disorders has substantially increased among children and young adults worldwide. The incidence of allergic rhinitis in Japan due to cedar pollen was 3.8% in

What is diesel exhaust?

Diesel exhaust is a complex mixture of gases and fine particles emitted by a diesel-fuelled internal combustion engine. The particles are mainly aggregates of spherical carbon particles coated with inorganic and organic substances. The inorganic fraction primarily consists of small solid carbon particles ranging from 0.01 to 0.08 µm in diameter (Fig. 1). As a result of incomplete combustion, the gaseous fraction also contains air pollutants such as carbon monoxide, sulfur oxides, nitrogen oxides, volatile organic compounds, alkenes, aromatic hydrocarbons, and aldehydes (including formaldehyde and 1,3-butadiene) and low-molecular weight polycyclic aromatic hydrocarbons (PAHs) and PAH-derivatives. The most widely studied PAHs contained in DEPs are fluoranthene, phenanthrene, pyrene, naphthalene and fluorene (Fig. 2).

Because diesel engines burn fuel more efficiently than conventional spark ignition gasoline engines, they offer better fuel economy. Nonetheless, diesel engines emit 10 times more particles per mile than conventional gasoline engines and approximately up to 100 times more than engines equipped with catalytic converters. The widespread use of diesel engines in transportation leads to a significant risk of environmental exposure to these emissions. In addition to environmental exposure, more and more employees such as mine workers, bridge and tunnel workers, and truck drivers are exposed to diesel exhaust due to the expanding use of diesel equipment, and face the risk of adverse health effects ranging from headaches and nausea to reactive airway disease and cancer.
1974, but increased to 5.8% in 1977, while now the figure is well over 10%12. Around 24% of the population in the United Kingdom13, 20.6% of that in Norway14 and 19.6% of that in Germany now suffer from allergic rhinitis15. These increases have occurred despite a decrease in the severity of grass pollen seasons16. While genetic factors in addition to allergen exposure are important in the induction and elicitation of type 1 allergic responses, the observed rise in the prevalence of allergic diseases can only be explained by changes occurring in the environment17-19. It has been proposed that modifications in the rate of bacterial, viral and parasitic infections in childhood (a reduction in the incidence of severe infections may have led to a loss of the protective factor related to the Th1 pathways), changes in diet and lifestyle, lack of exercise due to prolonged television watching and exposure to cattle/endo-toxins (which are known to induce a strong protective effect against the development of allergy) may play a pathogenetic role. However, it has now been suggested that the rapid increase in motor vehicle traffic and its associated emissions in recent years may be an important contributory factor for the rise in the prevalence of allergic diseases20,21. This is supported by the findings from various experimental and epidemiological studies. Rats kept in a polluted ambient atmosphere of the highly polluted city of Sao Paolo (Brazil) demonstrated an increased airway hyperresponsiveness which was attenuated when the rats were moved to a non-polluted city22 whereas guinea pigs exposed to diesel exhaust have been shown to develop nasal mucosal hyperresponsiveness, and an increased numbers of sneezes induced by histamine23. A number of epidemiological studies have shown an increase in the prevalence of allergic diseases which paralleled the increase in the number of circulating vehicles. Over the last 50 years the global vehicular fleet has expanded dramatically; for example in the United States from 1950 to 1997 an approximately 600% increase in the number of circulating trucks, the vast majority of which are powered by diesel, has been reported24. Among the various pollutants emitted from motor vehicles, the largest single source of airborne particulate matter is that derived from diesel exhaust. This is not only because of a sharp increase in the number of diesel vehicles, but also because of the large amount of particles generated from diesel engines; diesel vehicles emit approximately up to 100 times more particles than those released from catalyst-equipped petrol cars of corresponding performance (Table I). Therefore, DEPs have been implicated to play an important role in the rising prevalence of allergic diseases25-26.

### Table I. Absolute and relative order of emissions between cars powered by petrol and diesel engines.

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Petrol engine (mg/km)</th>
<th>Diesel engine (mg/km)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon monoxide</td>
<td>2720 ‡</td>
<td>950 *</td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>160 ‡</td>
<td>110 *</td>
</tr>
<tr>
<td>Nitrogen oxides</td>
<td>250 *</td>
<td>550 *</td>
</tr>
<tr>
<td>PAHs</td>
<td>210 *</td>
<td>410 *</td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td>225 *</td>
<td>1150 *</td>
</tr>
<tr>
<td>PM</td>
<td>10 *</td>
<td>855 *</td>
</tr>
</tbody>
</table>

PAHs = polycyclic aromatic hydrocarbons; PM = particulate matter. * lowest; ‡/‡ intermediate; ‡ highest emission.

**Allergic sensitization and exposure to diesel exhaust**

### Epidemiological evidence

Exposure to high levels of diesel fumes is frequently associated with increased morbidity and mortality from acute respiratory illnesses such as asthma, bronchitis and respiratory tract infections1. However, the greatest danger of pollutants generated from diesel exhaust may be related to its long-term health effects. In particular, the development of new asthma cases in individuals exposed to diesel fumes and the substantial differences in the prevalence of atopy between populations living in urban and rural areas appears to support a pathogenetic role for pollutants contained in diesel exhaust.

That pollutants contained in diesel exhaust may have an important role in this allergic pandemic has been suggested by Wade and Newman27 who were the first to report the development of asthma in 3 railroad workers exposed to excessive amounts of diesel fumes. More recently, the association between lung function measures and the estimated 20-year ambient concentrations of suspended particles was investigated in a sample of 1391 non-smokers followed since 197728. A significant rise in the incidence of new asthma cases in association with long-term increases in the levels of total particulate matter was observed.

The pioneering studies of Ishizaki et al.29 reported a higher incidence of cedar pollinosis in those individuals living along intercity main roads with heavy vehicular traffic when compared with those living in rural areas with less intense traffic. A large US health survey has shown a higher prevalence of positive skin tests in those individuals living in urban compared to rural areas30. In Germany, high levels of specific immunoglobulin (Ig) E were found in 43.7% of the urban and in 32.6% of the rural population31. In Sweden, Braback and Kalvesten32 demonstrated that 31% of the schoolchildren dwelling in large cities were atopic as opposed to only 19% of those living in rural areas. A Swiss study has demonstrated that living along
busy roads is associated with a higher risk for sensitization to pollen\textsuperscript{33}, thereby suggesting an interaction between pollen and air pollutants.

When comparing the prevalence of hay fever and positive skin tests to common allergens between former West and East Germany\textsuperscript{34,35} and between Hong Kong and China\textsuperscript{36} important differences were observed. A possible explanation is that different levels of air pollution due to automobile exhaust in these countries might have accounted for the higher prevalence of atopy in West Germany and Hong Kong. Car ownership in the former East Germany is currently rising\textsuperscript{37}, and a predictable increase in the levels of particulate air pollutants from motor vehicles is to be expected. The rising levels of these pollutants in cities such as Leipzig (formerly in East Germany) since the German reunification has paralleled the marked increase in the prevalence of hay fever and childhood atopy\textsuperscript{38}. These findings may suggest a causative link between the rising levels of particulate air pollution from motor vehicles and the increase in the prevalence of atopy.

Although it has been difficult to provide evidence that road traffic pollution from automobile exhausts may be a risk factor for atopic sensitization, a number of epidemiological studies have reported a clear association between the prevalence of allergy and road traffic-related air pollution\textsuperscript{29,39-42}. Furthermore, due to expanding use of diesel equipment, more and more workers are exposed to diesel exhaust and face the risk of adverse health effects including allergic conditions. We have reported an increase in the proportion of positive skin prick tests in traffic wardens with a well-defined occupational history of road traffic fume exposure\textsuperscript{43} (Fig. 3). Likewise, loading dock workers exposed to diesel fumes were found to have a significant increase in the proportion of serum IgE\textsuperscript{44}.

When studying the effects of air pollution on the prevalence of allergy it is crucial to consider the role of additional allergic risk factors such as indoor air quality and parental allergy. A recent cross-sectional health survey of 1129 schoolchildren has investigated the effect of four increasing levels of urban air pollution (based on measurements obtained from the local air pollution monitoring stations and on questionnaire data regarding the sources of local emission) on the prevalence of allergy\textsuperscript{45}. These authors computed in a multivariate logistic regression analysis a number of potential confounding factors including parental allergy, environmental tobacco smoke and moulds on the apartment’s walls and found that a higher prevalence in allergy was independently associated with exposure to increasing urban air pollution levels.

The observed association across different geographical locations of the world argues for a causal relationship between road traffic fumes and allergy but does not prove it. However, recent animal and human \textit{in vivo} exposure studies, as well as \textit{in vitro} cell-culture studies investigating the biological mechanisms underlying the fine interplay between DEPs and the development of allergy have helped to strengthen the argument that the association noted in the epidemiological studies is likely to be causal.

\textbf{Human studies}

Most \textit{in vivo} studies in man have looked into the effects of DEPs on the nasal mucosa and have shown that DEPs potentiate IgE production in the respiratory mucosal surface\textsuperscript{46,47} (Fig. 4). Nasal instillation of DEPs in atopic human subjects has been shown to be associated with a 25-fold increase in the IgE mRNA and with a 5-fold increase in the IgE levels in nasal lavage\textsuperscript{47}. DEPs induce proliferation of IgE secreting B cells as well as an \textit{in vivo} IgE iso-type switch, thereby eliciting both a quantitative and a qualitative increase in IgE production\textsuperscript{47,48}. Instillation of DEPs
Together with ragweed in ragweed-sensitized individuals induces a more than 50-fold increase in allergen specific IgE levels compared to instillation of either ragweed or DEP alone. Although this quantitative rise in IgE occurs by expansion of the local population of IgE secreting cells, DEP exposure is also associated with an increased expression of mRNA for a number of TH2 cytokines including interleukin (IL)-4 and IL-13 which are known to enhance IgE production. Moreover, it has been suggested that DEPs provide the required cognate and non-cognate signals that are necessary to drive local B cells to undergo an IgE isotype switch in vivo. These initial studies demonstrated that DEPs can strongly enhance mucosal allergic inflammation and specific Ig responses in already sensitized subjects, but whether exposure to DEPs could have led to the induction of primary sensitization to a neoantigen is uncertain. Recently, an elegant study by Diaz-Sanchez et al. has shown that coexposure of DEPs together with the neoantigen keyhole limpet hemocyanin, a glycoprotein isolated from the blood of a marine mollusk (Megathura crenulata), elicited an IgE anti-keyhole limpet hemocyanin response in humans, thereby demonstrating that DEPs are able to drive sensitization to the neoantigen. Overall, these studies indicate that diesel exhaust may drive the immunologic response towards allergic sensitization.

**Animal studies**

The pioneering studies of Takafuji et al. in mice immunized with ovalbumin were the first to show that the intranasal inoculation of DEPs had an enhancing effect on IgE production. Since then DEPs have also been reported to have an adjuvant activity in the production of IgE and IgG1 antibodies against *Dermatophagoides farinae* in mice immunized intranasally with mite allergen. This adjuvant activity is not merely restricted to the total IgE since exposure to diesel exhaust has been shown to increase allergen-specific IgE as well. It is well established that synthesis of IgE requires the presence of a number of soluble factors with IL-4 playing a major role. Co-administration of DEPs with allergen has been shown to significantly increase the levels of the TH2 cytokines IL-4 and IL-5 and to decrease the levels of the TH1 cytokine interferon γ in the lymph nodes compared with instillation of antigen alone. Likewise, IL-4 and IL-6 production from mouse bone marrow-derived mast cells was greatly increased when challenged with allergen and DEPs compared to mast cells inoculated with allergen alone suggesting that mast cells have the potential to indirectly regulate IgE synthesis. That mast cells have a critical role in the induction of IgE synthesis has been also the subject of enthusiastic debate. It follows that these animal studies...
highlight the fact that murine models are highly efficient for investigating the allergic sensitization due to DEPs.

In vitro studies

Takenaka et al.\textsuperscript{59} demonstrated that culturing B cells with IL-4 and CD40 monoclonal antibodies in the presence of PAHs derived from DEPs increased Ig production by at least 300\%. The enhanced IgE production in the human airways resulting from exposure to PAH-DEP may be an important factor contributing to the increased prevalence of airways allergic disease as it is well known that atopy is an important risk factor for asthma, hay fever and eczema. Moreover, the synergy between DEPs and natural allergen exposure is likely to be a key feature for the observed increase in the prevalence of numerous allergic conditions.

Recently, the carbon core of the DEPs has been shown to have a significant adjuvant effect on the local immune mediated inflammatory response as well as on the systemic specific IgE response to allergen\textsuperscript{60}. PAHs containing 3 to 5 benzene rings are major chemical components of DEPs. It has been shown that the organic extract of PAHs from DEPs promote IgE production from purified human B cells and peripheral blood mononuclear cells\textsuperscript{59}. The mechanism by which this occurs is an increase in the production of IgE by cells that are already committed to IgE-synthesis. In the same study, the prototype non-metabolized aromatic hydrocarbon 2,3,7,8 tetrachlorodibenzo-p-dioxin, which functions solely through activation of the cytosolic aromatic hydrocarbon receptor complex, also increased IgE production.

Fluorene, naphthalene, fluoranthene, pyrene, and phenanthrene are the major constituents of PAHs from DEPs (Fig. 2). Phenanthrene has been shown to induce a 3-fold increase in IgE production associated with an increased expression of the total IgE mRNA in an Epstein-Barr virus-transformed human B-cell line\textsuperscript{61}. It also appears that phenanthrene upregulates IgE production without influencing cytokine expression. In contrast, the reported production of higher levels of specific IgE in mice treated with pyrene during sensitization toward the house dust mite antigen Der f 2 is related to the enhanced secretion of IL-4 from spleen lymphocytes derived from these mice on antigen stimulation in vitro\textsuperscript{51}. These mechanisms are likely to increase the predisposition for the development of allergic sensitization. In agreement with the increased IL-4 production observed in these experiments, Bommel et al.\textsuperscript{62} have recently demonstrated that pyrene induces IL-4 mRNA transcription and IL-4 production in human peripheral blood mononuclear cells. Pyrene was also found to boost basal transcription of the human and mouse IL-4 promoter in T cells and mast cells whereas anthracene, fluoranthene and phenanthrene were not found to have any enhancing effect on the IL-4 promoter activity\textsuperscript{62}.

Additional mechanisms by which diesel fumes enhance allergic sensitization

A number of studies have shown\textsuperscript{63,64} that DEPs adsorb several antigens such as grass pollen onto their surface and therefore act as potential carriers of allergens thus increasing their deposition in the respiratory tract. Moreover, DEPs appear to enhance allergic presentation\textsuperscript{65}; DEPs can interact with interferon\(\gamma\) to significantly enhance HLA-DR expression in alveolar macrophages in vitro\textsuperscript{66}. This is an important step in the modulation of the total serum IgE concentration and IgE responses to allergens and therefore allergic airway responses\textsuperscript{67}. Similarly, it has been demonstrated that chemicals extracted from DEPs can increase major histocompatibility complex-II gene expression in murine macrophages, thereby theoretically enhancing their ability to act as antigen-presenting cells\textsuperscript{68}. Recently, it has been recognized that antigen presentation and interaction with T cells via the co-stimulatory molecules CD80 and CD86 on alveolar macrophages, allergen-specific T cells or dendritic cells are important for the polarization of the immune response toward a Th2-like profile, which appears to be critical for the development of allergies and asthma\textsuperscript{69-71}. Macrophages cultured with DEPs or nasal lavage cells from subjects challenged with DEPs show an enhanced expression of CD80 protein and message\textsuperscript{72}. Importantly, inhibition of the B7:CD28 pathway using a CTLA-4-Ig fusion protein completely inhibited the diesel-dependent increase in the allergen-induced production of macrophage-derived chemokine\textsuperscript{73}. As effective antigen presentation (at least by dendritic cells) is nuclear factor (NF)-\(\kappa B\)-dependent, it is likely that blocking NF-\(\kappa B\) will down-regulate HLA class II and co-stimulatory molecules such as CD80 and CD86. DEPs can activate NF-\(\kappa B\) in a variety of cells\textsuperscript{72,74,75}. It is now thought that this activation is dependent on the generation of reactive oxygen species by quinones and on the oxidation products of the chemicals found in DEPs\textsuperscript{76,77}. It is, therefore, plausible that DEPs can enhance antigen presentation by reactive oxygen species activation of NF-\(\kappa B\) resulting in an increased CD80/CD86 expression and function.

Pacheco et al.\textsuperscript{78} have demonstrated that DEPs may enhance allergen presentation by altering cytokine expression; in vitro low doses of DEPs inhibit the production of IL-10, a cytokine critical for the maintenance of tolerance, by human peripheral blood mononuclear cells. Furthermore, DEPs also inhibit transforming growth factor-\(\beta\) production while increasing IL-1 and sCD23 synthesis.
They argue that such changes during the critical early phases of allergen presentation could result in the progression of an allergic response that would normally be suppressed. If DEPs can indeed break tolerance, then an intriguing possibility is that exposure to diesel fumes may also lead to an increased prevalence of food allergy. However, to our knowledge the experimental evidence available to date is too limited to suggest that diesel components may modulate oral tolerance. In addition, there is no epidemiological evidence in support of an association between traffic or diesel fumes and food allergy.

Concluding remarks
Epidemiological studies and laboratory and clinical research appear to indicate that emissions from diesel engines are associated with the increase in the prevalence of allergic diseases observed in most industrialized countries of the world. This association is probably causal in nature. It is largely acknowledged that diesel particles can increase the bronchial inflammatory response to inhaled allergens, and there is now accumulating evidence that these chemical compounds can enhance one’s susceptibility to environmental allergens both in vitro and in vivo. However, their relevance in the pathogenesis of allergic disorders is not so strong and requires further elucidation. It must be noted that much of the research on these effects of diesel exhaust has been conducted in animals and questions remain with regard to the relevance of exposure levels and whether findings in such models can be extrapolated to humans. It is very important to further assess the chronic effects of diesel exhaust in mechanistic studies with careful consideration of exposure levels. Long-term longitudinal studies in different human populations are needed to clarify this issue, but these studies are extremely complex and difficult to execute. As further mechanisms of diesel toxicity are elucidated, the potential role of diesel pollution in inducing human allergic conditions will become clearer. Understanding these mechanisms will allow a more accurate assessment of the true risks of diesel pollution, which in turn will have an impact on future public health policies. In the meantime monitoring and control of the particulate is necessary. Prudent policy dictates continued efforts to reduce emissions of soot from diesel engines and to decrease occupational exposure as a matter of good health and safety practice. Improvements in engine design, soot filters, and fuel modification will provide the best approach to exposure control.

Riassunto
Negli ultimi anni è stato messo in evidenza un aumento della prevalenza delle malattie allergiche in molte parti del mondo ed in particolare nelle zone industrializzate. È stato ipotizzato che la continua esposizione all’inquinamento ambientale dovuto al particolato dei motoveicoli contribuisca in maniera significativa all’aumento riscontrato della prevalenza delle malattie allergiche. Numerosi studi in differenti parti del mondo hanno evidenziato un’importante associazione tra i livelli di inquinamento ambientale legati alle emissioni dei veicoli a motore ed un aumento di asma e rinite. Inoltre recenti studi di laboratorio sull’uomo che sugli animali, hanno dimostrato che alcuni inquinanti, quali il particolato diesel, possono accen- tuare l’inflammazione allergica e lo sviluppo di risposte di tipo immunitario. Questo articolo passa in rassegna lo stato attuale delle conoscenze relative al ruolo del particolato diesel nell’indurre la suscettibilità allergica; analizza le evidenze epidemiologiche che dimostrano il rapporto causale tra l’inquinamento da motoveicoli e l’aumento della prevalenza delle patologie allergiche, descrive il meccanismo immunologico attraverso il quale il particolato diesel accentua la suscettibilità allergica.

Parole chiave: Allergia; Immunoglobulina E; Inquinamento legato al traffico stradale; Particolato diesel.

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E-mail: rpolosa@hotmail.com

Prof. Riccardo Polosa, Dipartimento di Medicina Interna e Specialistica, Università degli Studi, Via Passo Gravina 187, 95125 Catania.

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