

However, undoubtedly the use of echocardiography (including transoesophageal echocardiography), laboratory findings and venous ultrasonography should be encouraged in patients with suspected high-risk PE. Management decisions should be taken based on all collected data on a case by case basis. Each test comes to the rescue of the others. 'One for all and all for one'.

Competing interests None.

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How does diesel exhaust impact asthma?

John R Balmes

Both air pollution health effects researchers and air quality regulatory agencies have been paying increased attention to emissions from motor vehicles in recent years. A growing body of scientific literature supports the concept that exposure to roadways with high traffic density is associated with adverse health effects, including increased risk of negative asthma outcomes. Heavy-duty diesel-powered vehicles like trucks and buses are often driven more frequently on roadways with high traffic density and, as such, diesel exhaust has been suspected to be a major cause of traffic-associated asthma morbidity.

Diesel exhaust is somewhat akin to tobacco smoke in that it is a mixture of particles and gases with many chemical constituents. Diesel exhaust particulate (DEP) is mostly elemental carbon with about 20–40% adsorbed organic compounds, but sulfates, nitrates and metals are also present.¹ Polycyclic aromatic hydrocarbons (PAHs) and related compounds such as quinones have been touted as the most toxicologically relevant constituents of DEP, primarily because of their redox potential and ability to cause oxidative stress.² More than 90% of DEP mass is in particles >1 µm in diameter that can easily be inhaled into the deep lung.¹ The vapour phase of diesel exhaust includes carbon monoxide, oxides of nitrogen, sulfur oxides and volatile organic compounds, many of which are known to be respiratory tract irritants such as formaldehyde, acrolein and naphthalene (a volatile PAH).

Many in vitro and animal experimental studies support the toxicity of DEP.^{1–4} The concept of a tiered response to DEP that is dose-dependent has been advanced which posits that low doses induce oxidative stress and upregulation of antioxidant and phase II enzymes, intermediate doses lead to activation of inflammatory signalling cascades and higher doses to cytotoxicity and apoptosis.² Organic extracts of DEP have been studied with regard to their ability to induce oxidative stress and the polar fraction containing quinones showed the greatest effect.² Mechanisms by which DEP could potentially exacerbate asthma include enhancement of airway inflammation, non-specific airway hyper-responsiveness and specific allergic responses. Several groups have shown that DEP can act as an adjuvant when combined with an experimental allergen resulting in enhanced IgE antibody production and increased allergic inflammation and airway hyper-responsiveness in mice.^{5,6} One such study showed that treatment with the antioxidant N-acetyl cysteine blunted the adjuvant effects of DEP, providing further supportive evidence for the role of oxidative stress in DEP toxicity.⁶

A number of studies have found increased risks of asthma outcomes in

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children and adults who live near roadways with high traffic counts. The authors of two separate comprehensive reviews judged the evidence for traffic as a risk factor for both asthma exacerbation and onset to be strong.^{7,8} Several recently published reports have further highlighted the apparent causal link between exposure to traffic and asthma onset. In a study of over 2700 never-smoking adults enrolled in the Swiss SAPALDIA cohort study, Kunzli *et al* showed that new-onset asthma was associated with exposure to traffic-related particulate matter (PM).⁹ With a similar prospective design, McConnell *et al* found that development of asthma was associated with traffic-related pollution at home and at school in nearly 2500 young children participating in the southern California Children's Health Study.¹⁰ The results of a smaller study in 149 children aged 4–12 years with careful measurement of the composition and source apportionment of PM showed that asthma symptoms were associated with exposure to traffic-related PM.¹¹

Despite the increasing body of epidemiological evidence to support a causal link between traffic-related air pollution and asthma outcomes, it has been difficult to tease out the contribution of diesel emissions in large cohort studies due to the lack of either a good exposure metric or biomarker. Although diesel emissions are a major component of atmospheric elemental carbon, they are not the only source, especially as diesel engine technology improves and emissions of DEP decrease. Perhaps the most convincing evidence to date that diesel exhaust can induce exacerbations of asthma comes from a field study in London where subjects with asthma walked in Hyde Park and along a busy street with a lot of heavy-duty vehicle traffic.¹² Exposures to fine PM, ultrafine PM, elemental carbon and nitrogen dioxide were all considerably greater on the busy street than in the park. Significant reductions in forced expiratory volume in 1 s and increases in sputum myeloperoxidase were observed after the walk on the street compared with after the walk in the park.

Because it has been so difficult to isolate the effects of diesel exhaust from those of other traffic-related emissions in epidemiological studies, controlled human exposure studies have played a major role in our understanding of the potential effects of diesel exhaust in asthma. Evidence of airway inflammation has been observed in healthy volunteers in multiple studies,^{13–15} and increased airway hyperresponsiveness has been seen in asthmatic

subjects.¹⁶ Curiously, however, a previous controlled human exposure study of diesel exhaust in subjects with asthma found no increase in airway inflammation.¹⁷ The report in this issue of *Thorax* (see page 12) presents further convincing evidence from the same laboratory that exposure to a high concentration of diesel exhaust from a well-characterised engine has less inflammatory effect in subjects with asthma than in healthy individuals.¹⁸ This study has the usual limitations of controlled human exposure studies. The sample size was small compared with an epidemiological study, only subjects with relatively mild asthma were studied and the exposure was not necessarily representative of real-world conditions, such that the results may not be generalisable. In addition, the engine used in the study is no longer representative of current diesel technology.³

Given the consistency of the finding from the Sandstrom group that subjects with asthma have less diesel exhaust-induced inflammation than non-asthmatic subjects, the important question is why? This is of particular interest since individuals with asthma are typically considered by environmental regulatory agencies as having heightened susceptibility to inhaled oxidant pollutants precisely because they have underlying airway inflammation and hyperresponsiveness. The data on the lung function responses of subjects with asthma to diesel exhaust, both from the current report and a previous study,¹⁶ do indicate that they have increased airway responsiveness and greater bronchoconstriction than normal subjects, as one would expect. But what is the mechanism responsible for the down-regulation of the inflammatory response to diesel exhaust in asthma?

Asthma is known to be associated with increased oxidative stress in the airways.¹⁹ It is possible that antioxidant defences in individuals with asthma are sufficiently upregulated in the face of a chronic burden of increased reactive oxygen species such that insufficient airway injury from diesel exhaust occurs to trigger activation of inflammatory signalling cascades. Alternatively, the persistent airway inflammation of asthma may be associated with upregulation of anti-inflammatory pathways such that mild injury from inhaled diesel exhaust is an inadequate stimulus for the induction of an inflammatory response. Further research will be needed to clarify the mechanistic basis for the differential response of subjects with and without asthma to diesel exhaust.

If diesel exhaust is not inducing much of a direct airway inflammatory response in individuals with asthma, then how does one explain the strong links with traffic-related pollution and asthma outcomes observed in epidemiological studies? One possibility is that the primary impact of diesel emissions is as an adjuvant to the effects of aeroallergens. As noted above, considerable evidence that exposure to DEP can enhance allergic responses has been reported from animal studies. Although no such studies have been conducted in humans with allergic asthma, controlled human exposure studies of subjects with allergic rhinitis have been reported. Diaz-Sanchez and colleagues, using nasal challenge to DEP, have documented enhanced allergic inflammatory responses to ragweed as well as enhanced sensitisation to a neoantigen.^{20,21} Moreover, they reported that variants in two antioxidant enzymes, glutathione S-transferase μ and π , are associated with increased risk of DEP enhancement of allergic nasal inflammatory responses.²²

Whether the primary mechanism by which diesel emissions affect asthma is through an effect on immune regulation or not, greater understanding of the contribution of this pollutant mixture to traffic-related asthma morbidity is needed. Control strategies can be better designed if mechanistic knowledge is available. If the major effect of diesel exhaust on individuals with asthma is merely to induce mild bronchoconstriction, then the current approach of promoting cleaner diesel engines with reduced DEP emissions may be sufficient. However, new technology engines may produce more nitrogen oxides and ultrafine particles. These pollutants may have effects other than mild bronchoconstriction. Continued support of research on the health effects of diesel exhaust, especially from newer engines, is warranted.

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