A Review of Diesel Exhaust Toxicity and Public Health: Looking Down the Road in North America

By

Dr Christopher Baker

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Queen's University, Department of Family Medicine.
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Abstract

Introduction

Air pollution is an important public health matter, with associated cardiovascular and respiratory morbidity and mortality. Diesel exhaust is a significant contributor to air pollution and one of the most commonly encountered atmospheric toxins. There is expected to be a significant increase in the use of diesel powered passenger vehicles in North America in the near future. This work aims to review the literature available on the health effects of human exposure to diesel exhaust and consider the potential health implications of more diesel powered passenger vehicles in North America.

Methods

A literature search of electronic databases Web of Science, PubMed, CINAHL, EMBASE and Medline was conducted using the following terms: Diesel OR Diesel Exhaust OR Diesel Emissions OR Diesel Particulate AND Health. Filters for appropriate journals and article types were applied. Titles and abstracts were then reviewed with inclusion and exclusion criteria applied.

Results

A total of 39 original peer-reviewed articles met both inclusion and exclusion criteria. The bulk of controlled human exposure studies examine pulmonary function, vascular tone, inflammation and surrogate markers of cardiovascular health following diesel exhaust exposure. The majority of studies observed a negative health impact following diesel exhaust exposure. There is considerable heterogeneity in study design.

Discussion and Conclusion

There is evidence from human exposure studies that diesel exhaust negatively impacts respiratory and cardiovascular functioning. Induction of both local and systemic inflammation as well as impaired vascular endothelial functioning and fibrinolysis may be contributing factors. There is expected to be a significant rise in the number of diesel powered vehicles in North American and subsequently increased diesel exhaust exposure. New clean diesel technology emissions are considerably different than traditional engines and challenge the ability to apply current scientific findings to predict future trends. More research is needed on the human health impacts of exposure to new technology diesel exhaust. Primary care physicians should be aware of this prospective risk as well as the potential health implications of exposure.

Introduction

In December of 1952 nearly 4,000 premature deaths occurred in London England due to atypical weather. Interestingly, this was not the result of dramatic or stormy weather. There were no gale force winds and no frigid cold temperatures recorded. Rather, there was only a brief period of colder than normal weather and altered wind patterns. These changes however resulted in a dramatic collection of industrial air pollution covering the city. While only brief, lasting just four days, review of government medical records would eventually reveal and attribute 4,000 premature deaths to the smog and an additional 100,000 hospitalizations (1). Since the London fog of 1952 interest in the impact of air pollution on morbidity and mortality has steadily grown (2). There now exists a considerable body of evidence documenting the deleterious health impacts of air pollution (3).

Awareness of the health implication of air pollution is an increasingly important public health matter. The World Health Organization (WHO) estimates that globally air pollution is responsible for approximately 3 million premature deaths annually (5). Future projections by the WHO indicate that an increasing proportion of the global population is predicted to dwell in urban centres. As air pollution is known to be more severe in cities than rural areas, this directly translates into a greater percentage of the population being exposed to a known health hazard. Prospectively then, understanding the dynamic relationship between human health and air pollution will be an increasingly valid issue.

Air pollution is the introduction of matter into the atmosphere and consists of both gaseous and particulate matter (5). Particulate matter (PM) is defined as material "suspended in the air in either liquid or solid form" and has traditionally been the focus of air pollution related research due to it repeatedly being identified as the culprit responsible for health implications (3,6,7). In fact, the United Nations Environment Program identified particulate matter air pollution as the most serious air pollution issued faced by most cities (8).

Particulate matter air pollution varies considerably in size and is often divided into sub categories based on particle diameter. Coarse PM has a diameter range of 2.5-10 µm (PM10), fine particulate matter has a diameter of less than 2.5 µm (PM2.5) and ultrafine PM has diameter of less than 0.1µm (PM0.1).

Coarse PM10 is able to enter the human airways but bulky enough that the vast majority will deposit in the upper and larger airways. Fine PM2.5 is small enough to penetrate the entire respiratory tree and can deposit all along the tract to the alveoli. Ultrafine PM0.1 is considered penetrating enough to traverse the entire airway and is believed by many scientists to deposit systemically by entering the circulation though the alveolar capillary membrane network (9,10). This is however a relatively novel concept and currently lacks research to better support it (6,11). PM over 10 µm in diameter are considered too large to penetrate human airways enough to cause a significant biological impact and are generally not studied. The majority of coarse PM10 production is attributed to mechanical processes like agriculture, industry and natural erosion (9). Fine PM2.5 is largely the product of fossil fuel consumption and is composed mostly of sulphates, nitrates as well as organic and inorganic carbon. Due to its ability to penetrate the human airways and high particle number by volume, PM 2.5 is thought to be responsible for the majority of health related impacts of air pollution (3,6).

The emissions from Diesel fuelled engines are some of the most commonly encountered atmospheric toxins, and by mass are considered the primary source of PM2.5 air pollution (12,13). Originally invented in 1892 the diesel fuel compression engine is reliable and durable, making it the power source of choice for buses, trucks and locomotives (12). Diesel powered automobiles also get an average 30-40% better fuel economy then their gasoline equivalents. This economy has lead the diesel engine to extreme popularity in places such as Europe where 37% of all new vehicles sold (as high as 62% in France), are diesel powered (14). However, diesel engines produce considerably higher emission levels and on an equal horsepower basis result in exhaust production that contains roughly 100 times more particulate matter then a gasoline fuelled engine (15).

As the health impacts of particulate matter air pollution are well documented (3,6), this would suggest that there may be considerable public health consequences related to diesel engine use.

The role of diesel exhaust (DE) as a public health issue becomes increasingly obvious when considered as a population attributable fraction (PAF). PAF is a useful method to quantify public health issues since it not only considers the strength of association between a risk factor and disease, but also the prevalence of exposure. Particulate matter, including diesel exhaust, is ubiquitous and essentially unavoidable to the individual. This makes DE extremely important by virtue of high population exposure (6). Primary care physicians should be aware of this importance as well as the potential health implications of exposure.

By contrast to what is seen in Europe, only about 1% of passenger vehicles in North America were diesel powered in 2010 (16). However, with the rising price of fossil fuels and increased quality and efficiency of diesel powered cars it is expected that a significantly larger proportion of North America's passenger vehicle fleet with be diesel powered. Recently Cadillac, General Motors, Ford, Jeep, Nissan, Mercedes,Mazda, BMW, Porsche and Audi have announced the introduction or expansion of diesel powered cars to be introduced through the 2013-2014 automotive year (16). The sale of diesel powered cars rose 35% through 2011 and a further 30% in 2012. In fact, diesel auto sales have increased in 22 or the past 23 months. In the next year the number of diesel vehicle sold in North America should double from 20 to 40 models available. That number is expected to increase to 60 by 2017. Sales of diesel vehicles currently account for approximately 3% of new vehicles sold in North America, and are expected to rise as high as 12.5% by 2018 (16,17) . In essence, it is expected there will be significantly more diesel powered vehicles operating in North America in the near future. The potential health impacts of this increase in diesel powered vehicles and their subsequent emissions are an important topic of public health concern and not yet well understood.

This works aims to:

1. Review the Literature and current evidence concerning the human health impacts of diesel exhaust (DE) exposure.

And with this,

2. Consider the potential public health implications of increasing diesel emissions in North America secondary to increasing numbers of diesel powered passenger vehicles.

Methodology

A literature search was carried out using the following criteria.

Web of Science, PubMed, CINAHL, EMBASE and Medline were searched using the following terms:

"Diesel OR Diesel Exhaust OR Diesel Emissions OR Diesel Particulate AND Health"

- Initial results yielded over 12,000 hits.

The following filters where applied to further refine search results:

Research articles from peer reviewed journals.

Exclusion of Journals concerned with subjects other then Medicine, Public Health, Environmental Health, Biology or Physiology.

Refined Search criteria yielded 197 hits.

Titles and abstracts where then scanned to apply the following inclusion/exclusion criteria.

Inclusion Criteria	**Exclusion Criteria**
Original articles	*In Vitro* studies
Peer reviewed Journals	Animal model studies
Studies involving human testing	Studies of air pollution other than diesel exhaust
Directly examines diesel exhaust exposure	Studies examining occupational exposures
Inhalation exposure studies	Ambient air pollution studies

Human controlled exposure studies were chosen as an inclusion criteria because they provide some of the most relevant data in assessing the health impacts of diesel exhaust exposure. These projects directly study human subjects, generally use well defined exposure concentrations and protocols and precisely measure health outcomes.

Upon completion a total of 39 original peer-reviewed articles met both inclusion and exclusion criteria. Due to considerable variation study design, meta-analysis was not attempted.

Results

The vast majority of articles obtained may be characterized as those either considering cardiovascular or respiratory consequences of diesel exhaust exposure. One study was identified examining neurological impacts of exposure; however as an outlier it is not discussed here (18). Similarly, several studies which examined the relationship between diesel exhaust and cancer were also identified. However, these were epidemiological studies and almost exclusively examining occupational exposure levels that would not be applicable to the general population. As such these articles were also omitted from discussion.

Cardiac

It has long been suspected that traffic related air pollution, including diesel exhaust, is associated with cardiovascular morbidity and mortality (19). Our search results yielded several articles which provide a possible explanation for this association which has been implicated in many epidemiological studies. Altered blood pressure control has been postulated as a possible mechanism explaining the relationship between air pollution and DE. In a double blind cross over study in 2012 Cosselman and colleagues noted an increase in the systolic blood pressure of patients exposed to DE. The rise was mild but considered significant and persisted for several hours post exposure (20). The results of this study are congruent with others which demonstrated similar findings (21,22). It is interesting to consider that as the authors highlighted the resulting blood pressure rise was mild, but their test subjects were relatively young and healthy. In a more vulnerable group, the results may have been more dramatic (20).

There have been a considerable number of studies investigating the relationship between DE and vascular function. In 2005 Mills and colleagues conducted a double blind cross over study on human subjects evaluating vascular tone and fibrinolysis in response to diesel exhaust exposure.

Both variables were subsequently noted to be significantly impaired in those patients transiently exposed to diesel exhaust. This was the first study directly showing inhaled DE can impair vascular function in humans and at particle concentrations applicable to the public (22).

Similarly, in 2009 Lundback and colleagues demonstrated transient arterial stiffness after brief DE exposure (23). Subsequent studies of similar design have gone on to find similar results of impaired vascular function, specifically endothelially mediated tone, at both varying concentrations of DE exposure (24) and varying post exposure time frames with significant vascular impairment noted to persist up until at least 24 hours post exposure (25). And recent studies have highlighted that nitric oxide endothelial mediated vascular function may be selectively impaired with DE exposure (26,27,28). Collectively these studies represent an interesting body of work. Endothelial dysfunction is widely considered the earliest pathological process involved in atherosclerosis (29) and an important predictor of future cardiovascular events (30,31). With this in mind studies demonstrating endothelial dysfunction in subjects post DE exposure provided an interesting suggestion as to link DE with cardiovascular morbidly and mortality.

The likely relationship between DE exposure and cardiovascular complications was further highlighted by Mills and colleagues in 2007. In a double blind cross over study, subjects with a history of myocardial infarction were noted to display ST depression on ECG monitoring after being exposed to DE (32). In 2013, Krishnan and colleagues observed significantly more pronounced increases in hemoconcentration and impaired thrombocytosis in patients with metabolic syndrome exposed to DE than in otherwise healthy subjects (33). The results of these studies not only suggest an important relationship between DE exposure and cardiovascular events but also demonstrate them in particularly vulnerable groups of patients (32,33). These results may be considered increasingly valid in the context of increasing burden of patients with chronic disease, including cardiac pathology.

It is important to acknowledge that not all studies evaluating the health impacts of diesel exhaust on human health have yielded supportive results. In 2010 Mills et al set out to evaluate the effects of diesel exhaust exposure on heart rate variability in human subjects. Heart rate variability, or the variation in the interval between consecutive heart beats, is considered to be an important indicator of autonomic function and indicator of cardiovascular morbidity and mortality (34). In their double blind cross over study no significant changes in heart rate or variability were noted in the 52 volunteers. These results lead the authors to conclude that diesel exhaust does not seems to affect heart rate variability nor would autonomic dysfunction seem to be the link between air pollution and cardiovascular morbidity and mortality (35).

Respiratory

Epidemiological studies have reported associations between ambient particulate matter, traffic pollution and diesel exhaust and increase respiratory disease exacerbations, decreased pulmonary function, worsening allergies and asthma (36-41). Pulmonary, and perhaps systemic, inflammation has been implicated as a mechanism by which these symptoms manifest. However it was not until recently that evidence from direct human exposure studies were available to investigate these links.

In 1999 Salvi and colleagues exposed human volunteer subjects to either DE or filtered air and compared blood tests, bronchoscopy with biopsy and lung function tests pre and post exposure. Interestingly, researchers observed no change in lung function, but noted significant rises in white blood cells, cytokines and inflammatory markers in both lung (indicating pulmonary inflammation) and blood samples (indicating systemic inflammation) (42). In 2000 a subsequent study by the same group revealed increase in transcription levels of many pro-inflammatory cytokines in endobronchial biopsy samples after DE exposure (43). Subsequent studies have observed similar results of increased serum inflammatory markers and genetic transcription levels (44-46).

Collectively the authors concluded that DE exposure at concentrations applicable to the real world cause obvious pulmonary and systemic inflammation (42,43).

Several studies subsequently expanded on these works. In 2000 Nordenhall and colleagues conducted exposure studies and monitored sputum neutrophil levels in serial fashion to establish time kinetics of inflammatory response to DE exposure. Significant rises were noted in all test subjects up to 6 hours post exposure with some subjects showing significant rises as late as 24 hours (47). Pourazar and colleagues noted during their 2004 human exposure study that DE induced a significant pulmonary rise in pro-inflammatory Interleukin 13 and Sehlstedt and colleagues observed marked eosiniphilia in endobronchial biopsies of humans exposed to DE (48,49). Jointly these works suggest a clear pulmonary and systemic inflammatory response when exposed to DE.

It has been suggested in many epidemiologic studies that PM air pollution, including DE, is thought to worsen existing respiratory disease. With this in mind, many researchers postulate that the observed pulmonary inflammation generated in healthy subjects on DE exposure would be exaggerated in patient with asthma. Several studies have attempted addressing this. In 2001 airway responsiveness and airway resistance were both noted to increase significantly in asthmatic subjects following DE exposure. The author's considered these results particularly noteworthy since test subjects were permitted to continue using inhaled corticosteroids (50).
Interestingly, in Stenfors and colleague's 2004 study comparing asthmatic vs non-asthmatic response to inhaled DE a similar pattern of increased airway resistance was noted. However sampling of test subject airways revealed cellular and chemical signs of inflammation only in the non-asthmatic individuals (51). These results of a surprising lack of inflammatory response in asthmatics to DE exposure were subsequently confirmed by Kongerud and colleagues in 2006 and Behndig and colleagues in 2010 (52,53). These preliminary results highlight that much is yet to be understood regarding DE exposure and human health.

It is important to note that while the majority of human exposure studies have observed signs of significant inflammation, there are several well designed studies which did not. In 2000 Nightengal and colleagues conducted double blind exposure study and monitored spirometry, cardiovascular vitals and peripheral blood markers of inflammation, all of which did not show a significant response when subjects were exposed to DE (54). In a 2004 study researchers determined that DE exposure had "no significant effect on healthy" airways (55). And a human exposure study conducted by Behndig and colleagues in 2010 concluded that there is likely a threshold for PM exposure after noting different levels of inflammatory response from various sections of the respiratory tree (56).

Cross examination of the existing human exposure studies concerning pulmonary inflammation to DE reveals what is likely a dose dependent response. Many of the studies which found less consistent or no significant inflammatory response were conducted using protocols with DE concentrations of 200 or 100 $\mu g/m^3$. This is in contrast to the majority of studies showing significant inflammation in response to exposure with the standard 300 $\mu g/m^3$ concentration. This is further highlighted by the 2013 study of Xu and colleagues who noted that by increasing subject exposure time, from the standard protocol of 1 to 3 hours, (using 300 $\mu g/m^3$ concentration) pulmonary inflammation could be noted as early as 75 minutes and thus suggesting a dose dependent response (57).

Discussion

While the available results from diesel exhaust human exposure studies are fairly limited, there do appear to be some emerging trends. It seems clear that controlled exposure to diesel exhaust is able to generate both pulmonary and systemic signs of an inflammatory response in human subjects. Similarly, diesel exhaust exposure appears to negatively impact vascular endothelial functioning and impair fibrinolysis.

These trends may even be part a mechanism that could lead to significant cardiovascular pathology, although it would seem premature to conclude that at this point. Finally, in review of the results thus far it would seem that there is likely a particulate level concentration threshold at which these effects begin to manifest. This may be at a particulate count of approximately 300 $\mu g/m^3$ as studies using this exposure level produced the most consistent results. However, it should be kept in mind that all the available exposure studies used a relatively brief exposure period of 1-2 hours. As Xu and colleagues (2013) demonstrated there are signs of a time and dose dependent response to diesel exhaust exposure, and thus lower particulate concentrations may induce a response over longer periods of exposure, as could be experienced in the daily environment (57). Study results to date are however limited and do not lend well to broad interpretations. There does appear to be clear evidence of negative health impacts from diesel exhaust exposure, but to what extent and by what mechanisms are yet to be fully understood.

Predicting the health implications of increasing diesel powered vehicles on the road in North America poses several interesting challenges. Firstly, is the question of how useful the available body of scientific evidence will be to predict this transition? As stated above the results do not lend well to broad interpretations. However there is the even broader consideration of how applicable the evidence is in the context of recent changes in diesel emissions. Prior to 1988, diesel exhaust emissions were essentially unregulated. Since then there have been increasingly stringent emission standards leading to significant changes in emission levels. To differentiate the compositional changes, it has been suggested that pre-1988 DE be called “traditional DE”, 1988–2006 DE be labelled “transitional DE”, and post-2006 DE referred to as “clean” or “new technology DE” (58).

By comparison to Traditional DE, new technology DE produces about 1% the particulate matter per horsepower/hour operation (Figure 1) (59). This is a substantial reduction in particulate matter and as some authors have argued may require the recognition of NTDE as a distinct chemical entity from TDE (60). Consequently, exposure to "clean" diesel exhaust may have significantly different health implications than traditional diesel exhaust (61).

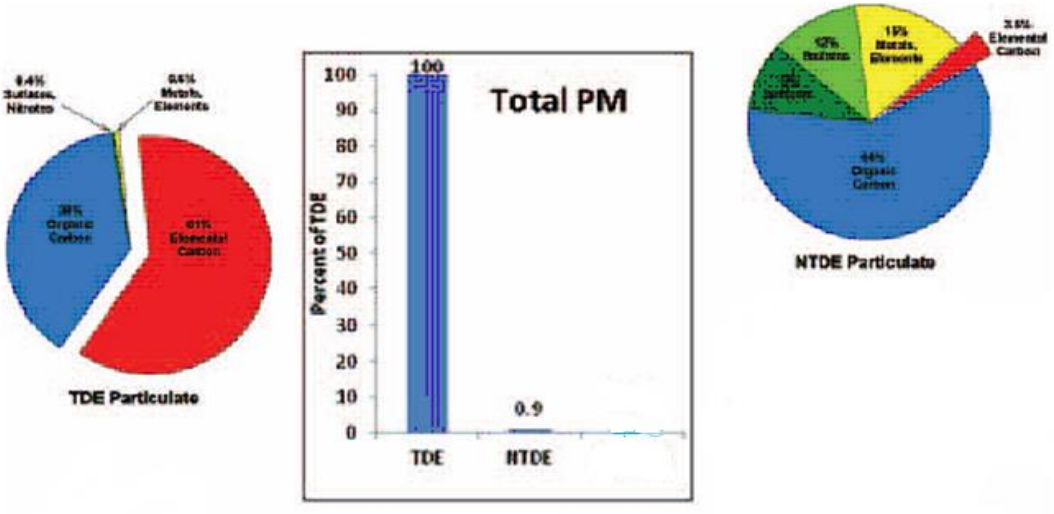

Figure 1. Graphical comparison between traditional technology diesel exhaust composition (left) and new technology diesel exhaust (right) From Cheung et al, 2009 (59).

Unfortunately, there are very few studies which have specifically examined the health effects of new technology DE, and fewer still directly involving human exposure studies (62). Our literature search yielded only a single peer reviewed human exposure study.

In 2011 Lucking and colleagues conducted a controlled human exposure study where researchers measured vascular impairment as well as *in vitro* and *in vivo* thrombus formation in 19 healthy subjects. Comparisons were made between individuals exposed to traditional diesel exhaust and to those exposed to diesel emissions generated using a particulate filter which created an exhaust mixture with a particulate matter concentration similar to that of "clean" diesel (59,63). Their results showed significantly less impairment of vascular function and a reduced elevation in thrombus formation for exposure to DE treated with particle filter (63). Although only a preliminary study on surrogate biomarkers of cardiovascular health, these results would suggest reduced adverse health outcomes upon exposure to diesel exhaust treated with a particle filter. Fortunately there are several extensive studies uniquely considering the health implications of NTDE exposure which are expected to become available in 2014 (62).

Conclusion

Collectively then the public health impact of the predicted increase in diesel powered vehicles in North America is an important topic to be aware of. Diesel exhaust is the extensively studied source of air pollution and there is a significant body of work linking exposure to a variety of adverse outcomes in humans. New technology diesel exhaust is compositionally quite different than traditionally studied exhaust, for which the majority of research relates to. More studies, and specifically those considering new diesel emissions standards are needed to further the understanding of diesel exhaust exposure and the potential human health implications, particularly in North America.

An increasingly larger proportion of the world's population is expected to dwell in urban areas. Primary care physicians should be aware of the health implications of diesel exhaust and air pollution in general. The majority of patients presenting to primary care have the potential to be both acutely and or chronically exposed to diesel exhaust. Physicians should be aware of the deleterious health effects associated with exposure, especially in vulnerable patients with chronic illness. Effects of exposure may become an increasingly relevant public health issue in North America as more diesel fuelled vehicles appear. To what extent the effects will manifest will likely vary depending on the prevalence of diesel vehicles and further understanding of new technology diesel exhaust.

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