

Controlled human exposures to diesel exhaust

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Summary

Diesel exhaust is a complex mixture of gaseous and particulate compounds resulting from an incomplete combustion of diesel fuel. Controlled human exposures to diesel exhaust and diesel exhaust particles (DEP) have contributed to understanding health effects. Such acute exposure studies of healthy subjects to diesel exhaust and DEP demonstrate a pro-inflammatory effect in the lung and systemically but only at higher concentrations (with a threshold dose approximating $300 \mu\text{g}/\text{m}^3$). Unexpectedly, there appears to be a lack of an inflammatory response to diesel exhaust and DEP in asthmatic individuals. Controlled human exposure studies of cardiovascular effects show that, comparable to other particle-associated exposures, diesel exhaust has a capacity to precipitate coronary artery disease. In addition, there is a relationship between diesel exhaust and DEP exposure and vascular endpoints; these effects in diesel exhaust may be diminished with removal of DEP. Many extra-pulmonary health effects of diesel exhaust exposure, including systemic inflammation, pro-thrombotic changes, and cardiovascular disease, are considered consequent to pro-inflammatory events and inflammation in the lung. Future research will focus on the relative importance of diesel exhaust components, potential interactions between components and other pollutants, effects in sensitive individuals, and effects of longer or repeated exposures.

Key words: *vehicle emissions; air pollution; particulate matter; asthma; oxidants*

Introduction

Diesel is the fuel of choice for use in vehicles of mass transportation including lorries, buses, and trains. Combusted diesel exhaust (DE) is a complex mixture of gaseous and particulate compounds resulting from an incomplete combustion of diesel fuel. While over 100 substances have been identified in DE [1], major components include nitrogen and sulfur oxides, carbon monoxide (CO), organic compounds (including aromatic and alkane substances), and particles [2]. Relative to those using gasoline, diesel engines emit higher concentrations of nitrogen and sulfur oxides, particle numbers, and organic molecules [2]. Diesel exhaust particle (DEP) is usually <25% of the emission

mass and composed of elemental carbon (50–75% of the mass depending on engine age, technology, fuel characteristics, and operating conditions), organics (19–43%), sulfates, nitrates, and metals. Approximately >95% of DEP is fine ($\text{PM}_{2.5}$) while ultrafine particle can account for up to 20% of the total mass. The ultrafine component of DEP always constitutes the majority of the total particle number [3]; particles of this size present an enormous surface area allowing absorbance of compounds and subsequent transport into the distal portions of the lung.

DEP concentrations in ambient air are employed as a measure of exposure to DE. DEP mass in ambient PM is variable approximating zero in rural areas to 35% of PM_{10} in urban areas. The mean DEP exposure in the United States is calculated to be $2 \mu\text{g}/\text{m}^3$ but can be greater in both vehicles and the immediate vicinity of major streets and highways where it can approach $20\text{--}25 \mu\text{g}/\text{m}^3$ [4–6]. Areas of significantly increased DE exposure along transportation avenues have been described with DEP concentrations $>100 \mu\text{g}/\text{m}^3$ (up to a maximum exposure of approximately $350 \mu\text{g}/\text{m}^3$ with the duration being seconds) during simulations of a vehicle with a 2006 diesel engine driving by [7].

Recent changes in diesel engines have altered exhaust characteristics [8, 9]. Newer engines emit reduced CO, organics, and nitrogen oxides, [10]. In addition, ambient air DEP concentrations are lower now than in the past due to improvements in diesel-engine technology. While there is evidence that DEP mass is lower in the exhaust of newer engines, studies suggest that nanoparticle emissions may not be decreased.

Controlled human exposures to diesel exhaust

Controlled human exposures refer to human investigation which places either healthy subjects or patients in a chamber into which an exogenous agent is introduced. Such studies have contributed to understanding pollutant-induced health effects and, relative to epidemiological and other forms of investigation, provide several advantages (table 1) [11, 12]. Subsequently, controlled human exposures have generated much knowledge about the underlying mechanisms of how air pollutants affect the body. There are also limitations of this methodology (table 1). While it is recognised that controlled human exposures employ

particle concentrations which can be more relevant to ambient levels than those in animal studies, they frequently use doses which are high relative to ambient concentrations in order to increase detection of an effect while guaranteeing safety for the subject. In past investigations, DEP concentrations used in controlled human exposures approached one to two orders of magnitude greater than average environmental exposures of the general population (e.g., 300 vs. 3 $\mu\text{g}/\text{m}^3$ respectively). Controlled human exposures often focus on a single air pollutant; a scenario that is rarely achieved in real life. The observed biological effects of a controlled human exposure are frequently small and the signal to noise ratio can be unfavourable. Short one-time exposures (which usually are a few hours) make it difficult to relate a “no effect” result to true environmental exposures which, in contrast, are both prolonged and repetitive. Study endpoints for controlled human exposures can frequently be limited to samples that are easily accessible, e.g., symptoms, examination, blood, urine, pulmonary function tests, electrocardiographic indices, sputum, breath condensate, and sometimes bronchoscopy specimens (bronchoalveolar lavage fluid, bronchial brushing

and endobronchial biopsy). Finally, it is rather complex, if not impossible, to extrapolate the changes in endpoints obtained during controlled human exposures to those employed in epidemiological studies (e.g. mortality and hospital admissions for chronic obstructive pulmonary disease).

In controlled human exposures frequently conducted in environmental health, human volunteers and patients are exposed either sequentially or at random to filtered air and a pollutant of interest. Exposures may employ DE, woodstove emissions, ozone, nitrogen oxides, sulfur oxides, carbon monoxide, resuspension of particles collected on filters, emission source and ambient particles (e.g., DEP and concentrated ambient particles), surrogate particles (e.g., carbon black), and combinations of these. Exposures can be performed in a concentration-related manner if subjects can be scheduled for repeated visits. Additionally, another advantage for the controlled experiment is an ability to perform time-dependent analyses; that is, the exposure can be turned on and off at specific intervals and the human response can then be assessed for pharmacokinetic parameters. Classical pharmacokinetic (PK) and physiologically based pharmacokinetic (PBPK) models for blood, breath, and urine biomarkers can be developed to explore biological variability due to metabolism and to provide a framework for exposure reconstruction for estimating previous exposures based on current biomarker measurements [13, 14]. Although such models could also be constructed from observational data in humans or from animal experiments by inferring various partition coefficients and rate constants, the controlled chamber experiment serves as the gold standard for assessing pharmacokinetic parameters.

Controlled human exposures at the United States Environmental Protection Agency employ DE generated from an idling 6-cylinder, 205 hp, 5.9L-displacement diesel engine (fig. 1A) in a vehicle located outside of the Human Studies Facility (Chapel Hill, North Carolina). Diesel fuel is purchased as a certified fuel and the same lot is used for the duration of the study. DE is introduced into the exposure chamber (1.83 m x 1.83 m x 2.44 m) after a 1:30 dilution with clean and humidified air to yield a feedback-regulated concentration of 100 to 300 $\mu\text{g}/\text{m}^3$ (fig. 1B). In the exposure chamber, the volunteer alternates between sitting (15 minutes) and exercising (15 minutes) on a recumbent bicycle ergometer for two hours. The chamber temperature and humidity are controlled to approximately $22 \pm 2^\circ\text{C}$ and $40 \pm 10\%$ respectively. DEP is controlled in real time using a tapered element oscillating microbalance to measure the chamber concentration. The particle number concentration and the number size distribution are also measured. The particle concentration is verified by weighing filters obtained using a versatile air pollution sampler. In addition to these measures of particle size and mass, environmental measurements are numerous during the exposure (table 2). Health endpoints routinely obtained before and after controlled human exposures can include symptoms (with a computerised questionnaire), changes in physical examination, indices in blood, urine, breath condensate, exhaled breath, sputum, and bronchoalveolar lavage. Pulmonary function tests, heart rate variability, and Holter exams can also be repeatedly performed before and after



Figure 1

Diesel exhaust is collected from an idling truck parked outside the building (A). This is diluted with filtered air and introduced through piping into an exposure chamber (B).

the exposure. Bronchoscopy is frequently included to obtain evidence of an effect by the DE.

Controlled exposure studies for selecting exposure surrogates and biomarkers

Biomarkers are valuable tools for quantifying chemical exposures in epidemiological studies. Yet, applications of biomonitoring for DE exposure assessment have been limited because: 1) DE is a complex and dynamic mixture; 2) traditional exposure surrogates for DE (i.e., EC and PM) do not lend themselves to analysis in biological media; and 3) chemical constituents of DE that can be measured as biomarkers are often ubiquitous environmental pollutants. In a previously discussed controlled exposure study [15], a suite of volatile aromatic compounds, volatile and semivolatile PAHs, and particle-bound PAHs in chamber air was measured (both "control" air and 100 µg/m³ DEP plus combustion gases) and evaluated as potential DE exposure surrogates [16]. The goal of this analysis was to identify and critically evaluate promising biomarkers of DE exposure for use in epidemiological studies. First, airborne concentrations of individual analytes in DE were studied to identify prominent species. In general, volatile aromatic compounds (e.g., benzene, toluene, ethylbenzene, xylenes (BTEX) and styrene) stood out as the most abundant analytes, followed by volatile and semivolatile, PAHs (e.g., naphthalene and phenanthrene), and then particle-bound PAHs (e.g., chrysene and benzo(a)pyrene). Next, enrichment from the DE source was quantified using the ratio of analyte levels in DE to those in clean (purified and filtered) air. Ratios were largest for the particle-bound PAHs, followed by the volatile and semivolatile PAHs, and then the volatile aromatic compounds. The volatile and semivolatile PAHs, specifically naphthalene and phenanthrene, were selected for additional evaluation since they were both abundant in DE (compared to the particulate PAHs) and highly differentiated with respect to clear air

(compared to the volatile aromatic compounds). Pairwise comparisons showed significant correlations between naphthalene, phenanthrene and organic constituents of DE, namely total organics, total volatile and semivolatile PAHs, and total particle-bound PAHs.

Based on these results, a follow-up analysis was performed of PAH levels (including those of naphthalene and phenanthrene) in blood samples of these study subjects collected before, immediately after, and 24 hr after exposure to DE [16]. Results showed no effect of the controlled DE exposure on blood PAH levels. Thus, a 2 hour exposure to 100 µg/m³ DEP and associated combustion gases did not affect circulating levels of blood PAHs in the study subjects. This suggests that the controlled exposure levels were too low to elicit an increase above "background" levels stemming from environmental sources. There is also some possibility that PAH levels were either transiently elevated and then absent at 24 hours or not yet detectable at 24 hours. Future controlled studies of DE exposures may identify a threshold for distinguishing biomarkers of DE exposure from those of background/ambient sources and also optimal kinetics for sampling.

Pulmonary effects of controlled exposure of healthy subjects to diesel exhaust

Gaseous and particulate components of air pollution initiate an inflammatory response in humans [17, 18]. This inflammation was considered essential in the mechanistic pathways of injury, including pulmonary and cardiovascular disease, following air pollution exposure. Since it is a constituent of ambient air pollution, it was anticipated that DE, and DEP, would contribute to a comparable set of biological effects. Epidemiologic investigation associated indices of both traffic-related air pollution and DE exposure with adverse human health outcomes including pulmonary inflammation, exacerbations of asthma, lung infections, and cardiovascular effects [19–23]. Accordingly, investiga-

Table 1: Strengths and weaknesses of controlled human exposure studies.

Strengths	Weaknesses
Well-defined exposure concentrations.	Small subject numbers.
Clear durations of exposure.	Generally short term effects only.
Control of confounding exposures.	Usually cannot expose the most sensitive population.
Employment of a number of distinct health endpoints.	Lack of control for recent exposure.
Predetermined inclusion and exclusion criteria to possibly minimise variability.	
Inclusion of potentially susceptible populations (e.g., elderly, diabetics, and individuals with chronic obstructive pulmonary disease, asthma, and cardiovascular disease).	
Use of controlled exercise to increase dose and shorten exposure duration.	
Access to instrumentation not feasible to employ in field studies.	

Table 2: Common environmental measurements obtained during controlled human exposure to diesel exhaust.

Exposure chamber temperature
Relative humidity
Nitrogen dioxide
Nitric oxide
Sulfur dioxide
Carbon monoxide
Total hydrocarbons
Particle mass concentration
Particle number concentration
Particle size

tion using controlled human exposures to DE and DEP was undertaken.

Controlled human exposure to DE increased both neutrophils and B lymphocytes in bronchoalveolar lavage (BAL) of healthy volunteers 6 hours following a 1 hour exposure (with moderate intermittent exercise) to diluted whole DE (with mean DEP equivalent to $300 \mu\text{g}/\text{m}^3$) [24]. Lavage concentrations of histamine and fibronectin were similarly elevated. Biopsies confirmed an influx of neutrophils, mast cells, and T lymphocytes into the bronchial wall as well as elevated expression of adhesion molecules defining a lung inflammatory response. In addition to the lung, neutrophils were elevated in the peripheral blood supporting a systemic inflammation. Increased mRNA and protein expression of pro-inflammatory mediators were observed in cells resident in the lower respiratory tract [25]. These results were in agreement with an investigation (double-blind, randomised, and crossover) of 10 healthy, non-smoking volunteers exposed to resuspended DEP (mean DEP of $200 \mu\text{g}/\text{m}^3$) without the associated gases for 2 hours which demonstrated increased sputum neutrophils and sputum myeloperoxidase 4 hours later; however, there was no evidence of a systemic inflammation [26]. In addition to sputum induction and phlebotomy, endpoints in this study included serial spirometry and measurement of pulse, blood pressure, exhaled carbon monoxide, and methacholine reactivity at 0 to 4 and 24 hours after exposure. There were no changes in cardiovascular parameters or lung function following exposure to DEP but levels of exhaled CO as a marker of effect (i.e., heme oxygenase function) were increased and maximal at 1 hour. In a third investigation using controlled human exposure, fifteen healthy subjects exposed to DE (mean DEP of $270 \mu\text{g}/\text{m}^3$) showed evidence of lung inflammation on bronchoscopy [27]. There was an increased expression of p-selectin and vascular endothelial adhesion molecules in bronchial mucosal biopsies and elevated numbers of eosinophils in the BAL 6 hours after exposure. It was suggested that disparities between the results of this study [27] and that of prior investigation may reflect engine load [24]. Normal, healthy subjects exposed to DE (mean DEP of $200 \mu\text{g}/\text{m}^3$) for 2 hours at rest showed an activation of an inflammation pathway (proteasome activity) in peripheral white blood cells [28]. All of these studies support pro-inflammatory events in the lung following human exposure to DE or DEP.

There have also been controlled human exposure studies showing an absence of an effect of DE and DEP exposure on lung inflammation. Twenty-five healthy subjects exposed to diluted whole DE ($100 \mu\text{g}/\text{m}^3$) demonstrated increased symptom prevalence and bronchoconstriction with increased values of airway resistance [29]. Spirometry failed to reveal any changes and there was no evidence of an inflammatory response on bronchoscopy with BAL 6 hours later. An increased concentration of reduced glutathione was evident in the airways. Among 15 non-smoking, healthy volunteers, exposure to DE ($300 \mu\text{g}/\text{m}^3$) for 1 hour had no effect on bronchial expression of interleukin (IL)-10 and IL-8 in airway epithelial cells [30]. Results of a third study showed that 18 hours after exposure of healthy subjects to DE ($100 \mu\text{g}/\text{m}^3$) for 2 hours, there was inflammation in the airways (increased neutrophil numbers, IL-8,

and myeloperoxidase concentrations in bronchial lavage and elevated increased neutrophils and mast cells in bronchial mucosa) but not in the alveolar compartment [31].

As a result of epidemiologic investigation documenting a worsening of asthma following exposure to DE [19, 21–23, 32, 33], asthmatics were included in controlled human exposures. In one study, a group of 14 non-smoking, atopic asthmatics (treated with inhaled corticosteroids) were exposed to DE ($300 \mu\text{g}/\text{m}^3$) for 1 hour [34]. While all participants were hyperresponsive at baseline, there was increased airway responsiveness (i.e., methacholine challenge) 24 hours following DE exposure. There was also an increase in airway resistance and elevated levels of sputum interleukin-6 but no changes in sputum levels of eosinophil cationic protein, myeloperoxidase and interleukin-8 and sputum differential cell counts. A second controlled human exposure to DE and DEP $108 \mu\text{g}/\text{m}^3$ for 2 hours similarly did not demonstrate an inflammatory response among asthmatics [35]. While healthy volunteers had airway neutrophilia, lymphocytosis, and lavage interleukin-6 and -8 concentrations 6 hours after the exposure, asthmatics showed no response. In a third study focused on asthmatic subjects, there was a lack of inflammation following exposure of subjects with mild to moderate disease to DE (mean DEP of $100 \mu\text{g}/\text{m}^3$) for 2 hours [36]. In contrast, healthy subjects showed increased neutrophil numbers, myeloperoxidase, and IL-6 in the bronchial wash and submucosal neutrophils on biopsy 18 hours after the same exposure.

These controlled human exposure studies support the conclusion that exposure of healthy subjects to DE and DEP is consistently pro-inflammatory only at higher concentrations with a threshold dose approximating $300 \mu\text{g}/\text{m}^3$. The pro-inflammatory effect shows considerable variability between the different exhausts and particles employed in investigation; disparities between these studies likely reflect disparities in the DE and DEP. Exposure concentration and duration as well as the timing of bronchoscopy need to be considered when inflammatory responses are evaluated. Additional factors including engine type, engine load, fuel characteristics, and driving mode may all modify the airway inflammatory responses to DE/DEP. There appears to be a lack of an inflammatory response to DE and DEP in the lungs of asthmatic individuals.

Cardiovascular effects of controlled exposure of healthy subjects to diesel exhaust

Controlled human exposure has also been employed in defining cardiovascular effects of DE and DEP. Exposure of 20 men (with a mean age 60 years) with prior myocardial infarction to DE ($300 \mu\text{g}/\text{m}^3$) demonstrated worsening of exercise-induced ischemia [37]. Subjects had had a myocardial infarction more than 6 months prior to enrollment in this study, had been treated with primary angioplasty and stenting, and were receiving standard secondary preventive therapy. Men with unstable coronary disease, angina pectoris, history of arrhythmia, diabetes mellitus, uncontrolled hypertension, renal failure, and hepatic failure were excluded. Current smokers and men with

asthma, significant occupational exposures, or an intercurrent illness were also not enrolled in this investigation. Endpoints included vascular studies (requiring brachial artery cannulation with a 27 gauge needle), plasma tissue plasminogen activator, plasminogen activator inhibitor-1, and C-reactive protein. Myocardial ischaemia was detected on electrocardiograph during exercise in all subjects. Relative to filtered air, there was a greater decrement of ST segment during exposure to diesel exhaust and this was interpreted as an increase in the exercise-induced ischemic burden. DE did not aggravate pre-existing vasomotor dysfunction measured as endothelium-dependent (acetylcholine) and endothelium-independent (nitroprusside) vasodilatation at 6 hours after exposure. Exposure to DE did reduce the acute bradykinin-induced release of endothelial tissue plasminogen activator. There were no differences in tissue plasminogen activator, plasminogen activator inhibitor-1, leukocyte and neutrophil counts, platelet counts, and C-reactive protein. These findings in patients with prior myocardial infarction contrasted those observed in healthy subjects in which 30 healthy men were exposed to DE (300 $\mu\text{g}/\text{m}^3$) using the same exposure protocol (double-blind, randomised, crossover) [38]. DE attenuated increases in forearm blood flow induced by bradykinin, acetylcholine, and nitroprusside infusion measured 2 and 6 hours after exposure in these healthy volunteers. DE also suppressed the bradykinin-induced release in plasma tissue plasminogen activator 6 hours after exposure. Vascular dysfunction among 15 healthy volunteers 24 hours after exposure using the same protocol confirmed that DE reduced acetylcholine- and bradykinin-induced vasodilatation [39]. However, DE had no effects on endothelium-independent vasodilatation induced by either sodium nitroprusside or verapamil. DE did not attenuate bradykinin-induced increase in plasma tissue plasminogen activator.

In a fourth controlled human exposure study into the cardiovascular effects of DE, 19 healthy volunteers were exposed to DE for 1 hour [40]. Bilateral forearm blood flow and plasma fibrinolytic factors were assessed with venous occlusion plethysmography and blood sampling during intra-arterial infusion of acetylcholine, bradykinin, sodium nitroprusside, and verapamil. Compared with filtered air, DE decreased reduced vasodilatation and increased *ex vivo* thrombus formation. A particle trap reduced DEP number (from 150000 to 30000/cm³ to 30 to 300/cm³) and mass (320 ± 10 to $7.2 \pm 2.0 \mu\text{g}/\text{m}^3$) and was associated with increased vasodilatation, reduced *ex vivo* thrombus formation, and an increase in tissue plasminogen activator release. The negative effects of DE on vasomotor function, endogenous fibrinolysis, and thrombus formation were precluded by reducing DEP concentration and number with a particle trap.

These controlled human exposure studies of the cardiovascular effects of DE and DEP do not allow broad conclusions. However, it appears that, comparable to other particle-associated exposures, DE can precipitate coronary artery responses. In addition, there is a relationship between DE and DEP exposure and vascular endpoints. Maximal effects on vasomotor function were detected at 2 and 6 hours after exposure, with some prolonged effects on acetylcholine responses at 24 hours. Effects on endo-

genous fibrinolysis were only detected at 6 hours. These effects may be associated with DEP rather than gaseous components of DE.

Mechanism of pulmonary and cardiovascular effects after DE exposure

Findings derived from several studies support the concept that the biological effect of DE and DEP exposure is initiated by oxidative stress [41–47]. DEP produces reactive oxygen species in the lungs of animal models [48–51]. The oxidative stress associated with DE and DEP initiates a cascade of reactions culminating in inflammation. This includes phosphorylation-dependent cell signaling, an activation of the mitogen-activated protein (MAP) kinase cascade (ERK, p38, and Jun kinases), and release of pro-inflammatory mediators [47, 52–58]. Subsequently, the immediate response to DE and DEP is a pulmonary and systemic inflammation. Disparities between specific DEP in the capacity to induce oxidants and inflammation have been reported (e.g., forklift-generated DEP, NIST standard reference material 2975, and Japanese automobile-derived DEP show dissimilarities in biological effect). Those exact characteristics responsible for these differences are yet to be defined. However, they are likely the result of distinct physicochemical properties arising from different generation and collection conditions [59]. Generally, the capacity of DEP to produce both oxidative stress and a biological response approximates those of other combustion products such as wood stove particles [60–62].

The biological effect of DE and DEP is most frequently attributed to inflammation resulting from oxidant generation. The human controlled-exposure studies at elevated exposure levels (i.e., for DEP concentrations in the range of several hundred $\mu\text{g}/\text{m}^3$) largely support the pro-inflammatory role of DE in humans. If prolonged, such inflammation has been associated with chronic sequelae including tissue fibrosis, cardiovascular disease, and increased risk for neoplasm [63–67]. It has been postulated that specific effects of particles can be the result of a systemic distribution of those with ultrafine size [68]. Cardiovascular effects of DEP are likely to be independent of such distribution for two reasons. First, it has been demonstrated that it is not necessary to invoke such systemic distribution to provoke a biological effect since other models of human inflammation associated with an increased risk for cardiovascular disease have never been shown to necessitate this (e.g., gingivitis affects an increased risk for cardiovascular disease without a requirement for septicemia) [69]. Second, there is conflicting data on whether translocation of insoluble particles from the lung into the bloodstream of any animal model actually occurs [70].

Investigation either directly demonstrates or supports a decrease in the inflammatory response to DE and DEP among those individuals with pre-existing disease (e.g., asthmatic, chronic obstructive pulmonary disease, and chronic heart disease) [37–39]. This was not anticipated as these are the same populations which appear to be at increased risk for particle-related morbidity and mortality in epidemiological studies [71, 72]. One explanation for this inconsistency

is that individuals with chronic disease are frequently on medications which could alter the inflammatory response to DE and DEP exposure [37, 73–75]. Prominent among these medications would be the statins which affects the response to particle-associated exposures [76]. A second possibility to account for the diminished inflammatory effect in these patients is a selection bias for individuals with specific gene expression among those with chronic disease [76]. A final potential reason for disparities in the response between healthy volunteers and those with chronic illness to DE and DEP in controlled human exposures could be that disease process itself modifies the inflammatory reaction to DE and DEP exposure. In support of this, COPD patients demonstrate changes in patterns in particle deposition which can modify the response to DE and DEP exposure [77, 78]. Those with chronic inflammation may not have the ability to coordinate an acute inflammatory response to DE and DEP; this would be analogous to inflammation following infection [79]. It can be postulated that the acute inflammation benefits the individual and that the incapacity to fully initiate such inflammation in the chronically ill predicts a negative outcome.

Conclusion

The effects of DE have been investigated for their impact on human health more than any other emission source pollutant [80]. In the healthy subject, controlled human acute exposure to DE incites lung and systemic inflammation with a threshold concentration approximating 300 $\mu\text{g}/\text{m}^3$. Systemic health consequences of DE exposure are considered consequent to the primary lung inflammation and include pro-thrombotic changes and cardiovascular disease. It appears that DEP is associated with some portion of the biological effect of DE. Future research can focus on potential effects of longer or repeated exposure, effects in sensitive individuals, the relative importance of DE components, and potential interactions between components and other pollutants.

Disclaimer: This report has been reviewed by the National Health and Environmental Effects Research Laboratory, United States Environmental Protection Agency and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Agency nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

Funding / potential competing interests: No financial support and no other potential conflict of interest relevant to this article was reported.

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Figures (large format)



Figure 1

Diesel exhaust is collected from an idling truck parked outside the building (A). This is diluted with filtered air and introduced through piping (arrow) into an exposure chamber (B).