

## CLINICAL REVIEW

# The Toxicity of Diesel Exhaust: Implications for Primary Care

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**Diesel fuel and the products of its combustion represent one of the toxins most commonly encountered by people living in both urban and rural areas of the world. As nations become more heavily populated, there will be increasing reliance on diesel fuel to power mass transportation and commercial vehicles, as well as heavy machinery involved in construction, farming, and mining. The majority of patients who present to urban primary care clinics and emergency departments will have had significant chronic exposure to diesel exhaust because most use and/or live near busy streets and highways. Furthermore, those who operate or work or live near diesel-powered machinery will have even more toxic exposure. Primary care physicians should be aware of the acute and chronic deleterious clinical effects of diesel exhaust. In this article we review the toxicity and myriad health problems associated with diesel exhaust. (J Am Board Fam Med 2008;21:55–62.)**

The compression-ignition diesel engine was invented by Rudolph Diesel in 1892 as an alternative to the spark-ignition gasoline engine.<sup>1</sup> The engine's popularity expanded because it had excellent fuel economy and durability and it required less maintenance. Diesel is the fuel of choice for use in mass transportation vehicles such as trucks, buses, and trains. Diesel fuel and the products of its combustion represent one of the most common toxins to which people living in both urban and rural areas of the world are exposed. On an equal horsepower basis, diesel exhaust is 100 times more toxic than gasoline exhaust, even when carbon monoxide is considered.<sup>2</sup> The Environmental Protection Agency estimates truck exhaust accounts for 20% of all vehicle-produced microscopic soot and 30% of all smog-causing chemicals in the United States.<sup>1</sup> As for passenger cars, fewer than 1% of new American cars have diesel engines. In contrast,

diesel engines power 37% of all new cars sold in Europe, with rates as high as 62% in France.<sup>3</sup> One reason for this discrepancy is the suboptimal quality of diesel fuel sold in the United States; roughly half of the supply has been found to be below the standards recommended by equipment manufacturers.<sup>1</sup>

The majority of patients who present to urban primary care clinics and emergency departments may have had a potentially significant chronic exposure to diesel exhaust because many of them live near busy streets and highways. In Japan and Europe, epidemiologic surveyors have demonstrated high acute and chronic respiratory disease morbidity rates from occupational and proximity exposure to diesel exhaust.<sup>4</sup> The National Institute for Occupational Safety and Health estimates millions of workers are occupationally exposed to the combustion products of diesel fuel in their respective workplaces. Diesel exhaust is a complex mixture of toxic compounds with wide variability of deleterious effects in human and animal studies. This represents a significant limitation to epidemiologic research on diesel exhaust because the over-reporting of exposure may affect study outcomes.<sup>5</sup> Thus, no standard for exposure limits exists at this time.

Patients most likely to be in proximity to diesel exhaust on the job and thus suffer from occupational exposure include (1) shipping, receiving, and

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**Table 1. Potential sources of clinically significant exposure to diesel exhaust**

Roads and highways
Truck stops or distribution points
Construction sites
Railway depots or proximity to trains
City streets near bus and truck routes
Gas stations
Vehicle repair and maintenance shops
Tunnels
Toll stations
Bridges
Parking structures, garages, or lots
Fire stations
Airports
Bus stations
Boat harbors and docks
Mines

loading dock workers; (2) bus, truck, and forklift drivers; (3) railroad workers; (4) mine workers; (5) diesel engine repair and maintenance garage workers; (6) construction site, tunnel, and bridge workers. In 2006 the California Air Resources Board estimated that diesel exhaust pollution directly accounts for 2400 deaths and, annually, nearly 3000 hospital admissions for respiratory and cardiac-related diseases, at a total cost of \$19 billion.<sup>6</sup> Besides on-the-job exposure to diesel exhaust, patients may be exposed to diesel exhaust from myriad and commonplace sources (Table 1). Primary care physicians should be aware of the acute and chronic deleterious health effects from diesel exhaust and its potential to exacerbate other chronic disease states. We thoroughly searched medical and scientific literature databases to identify those articles that specifically addressed the relationship between diesel exhaust pollution and illness. Here we review the myriad health problems associated with this commonly encountered substance.

### Diesel Exhaust Composition

There are many components of diesel exhaust, including (1) carbon monoxide and carbon dioxide; (2) nitrogen oxides; (3) sulfur oxides; (4) hydrocarbons; (5) unburned carbon particles (soot); and (6) water.<sup>2</sup> Exhaust from diesel engines is considered to contribute to more than 50% of ambient particulate matter with a mass median aerodynamic diameter less than 10  $\mu\text{m}$  (PM<sub>10</sub>), greatly contribut-

ing to overall air pollution. For fine particulate matter with a diameter below 2.5  $\mu\text{m}$  (PM<sub>2.5</sub>) and ultra-fine particles with a diameter below 0.1  $\mu\text{m}$ , this contribution is even higher.<sup>1</sup> These carbon particles are small enough to be inhaled and deposited in the lungs but have a large surface area. Organic compounds from diesel exhaust with known toxic and carcinogenic properties, such as polycyclic aromatic hydrocarbons (PAH), adhere easily to the surface of the carbon particles and are carried deep into the lungs.<sup>4</sup> The majority of these particles tend to be found in the greatest concentration within the immediate vicinity of busy streets or highways.<sup>7,8</sup> Diesel engines emit other toxic compounds in disproportionately higher concentrations than gasoline engines, including nitrogen oxides, sulfur oxides, ozone, formaldehyde, benzene, and smaller organic molecules. Diesel engines also produce 26% of the total nitrogen oxides in outdoor air. Nitrogen oxides are a major contributor to ozone production and smog. More attention has been focused on the hundreds of different types of organic molecules created from the high-compression ratios of diesel engines because many are highly toxic.<sup>1</sup> A summary of the composition of diesel exhaust and its biological effects are detailed in Table 2.

### Cardiac Effects

Acute coronary syndrome (ACS) and other thrombotic effects have been associated with acute exposure to diesel exhaust.<sup>9,10</sup> A recent study by Mills and associates evaluated men with previous myocardial infarction who were exposed to diesel exhaust during moderate exercise. Significant ST-segment depression was noted, as well as diminished release of endothelial tissue plasminogen activator.<sup>11</sup> Possible mechanisms to explain these results include diesel exhaust-induced coronary vasoconstriction, transient thrombus formation, carbon monoxide exposure, and altered myocardial energetics.<sup>12</sup> Another recent study of 1816 postmenopausal women with long-term exposure to air pollution, of which diesel exhaust represented a significant proportion, concluded there was an increased risk of cardiovascular disease and death proportional to the level of exposure.<sup>13</sup> One European study group examined the association between exposure to diesel exhaust and hospital admission for ischemic heart disease in 8 cities and found that

**Table 2. Composition, breakdown, and carcinogenicity of diesel exhaust**

Gas-Phase Emission Components	Atmospheric Reaction Products	Biological Impact
Carbon dioxide	-	Global warming
Carbon monoxide	-	Asphyxiation
Nitrogen oxides	Nitric acid, ozone	Respiratory tract irritants, acid rain
Sulfur dioxide	Sulfuric acid	Respiratory tract irritant, acid rain
<b>Hydrocarbons</b>		
Alkanes	Aldehydes, alkyl nitrates, ketones	Respiratory tract irritants
Alkenes	Aldehydes, ketones	Respiratory tract irritants, mutagenic and carcinogenic
<b>Aldehydes</b>		
Formaldehyde	Carbon monoxide, hydroperoxyl radicals	Carcinogenic
Higher aldehydes (eg, acetaldehyde, acrolein)	Peroxyacyl nitrates	Respiratory tract and eye irritants, plant damage
Monocyclic aromatic compounds (eg, toluene)	Hydroxylated-nitro derivatives	Carcinogenic
Benzene	Nitro-PAH	Mutagenic and carcinogenic
<b>Particle-phase emission components</b>		
Elemental carbon	-	Nuclei adsorb organic compounds
Inorganic sulfate and nitrate	-	Respiratory tract irritant
Hydrocarbons (C14-C35)	Aldehydes, ketones, and alkyl nitrates	Unknown
PAH	Nitro-PAH and nitro-PAH lactones	Mutagenic and carcinogenic

PAH, polycyclic aromatic hydrocarbons; C, carbon.

patients 65 years and older had a significantly increased risk of ACS after exposure to diesel pollution.<sup>14</sup> In a study performed in a major European city, Peters et al determined that exposure to traffic, with its high levels of diesel exhaust, was associated with the onset of myocardial infarction within 1 hour. They concluded the time spent in traffic was consistently linked with an increased risk of myocardial infarction.<sup>15</sup>

Diesel exhaust particles (DEPs) have been shown to be cardiotoxic in animal studies. Minami and colleagues demonstrated in a guinea pig model that DEPs had a negative inotropic effect, induced arrhythmias, and caused sudden cardiac death.<sup>16</sup> Another animal study by Sakakibara et al determined that DEP-induced cardiotoxicity could not be prevented with propranolol, atropine, verapamil, diltiazem, diphenhydramine, indomethacin, superoxide dismutase, or catalase.<sup>17</sup> Diesel exhaust induces heart rate variability, ventricular arrhythmia, a significant decrease in left-ventricular systolic pressure, and an increase in left-ventricular end-diastolic pressure in animal models.<sup>18,19</sup> It is postulated that DEP produces superoxide radicals, which cause irreversible myocardial damage leading to cardiac arrest.<sup>20</sup>

DEPs also have been shown to induce immunoglobulin E synthesis and cause histamine release.<sup>21</sup> Histamine is a potent coronary vasoconstrictor and platelet and thrombin activator, and it up-regulates P-selectin on endothelial cell surfaces.<sup>22</sup> A high incidence of serious cardiac arrhythmias was noted in patients with implanted cardioverter defibrillators who had significant exposure to air pollution.<sup>23</sup> Zanobetti and Schwartz reported that diabetics have twice the risk of ACS-related admission because of particulate air pollution exposure.<sup>24</sup> Another study from Finland found that patients undergoing serial cardiac exercise testing had a higher incidence of ST-segment depression during days of high particulate air pollution.<sup>25</sup> Progression of atherosclerosis has also been linked to air pollution exposure.<sup>26</sup>

Occupational hazards may also be a factor in development of coronary artery disease. Finkelstein et al, after controlling for smoking, reported higher incidence of ischemic heart disease in heavy equipment operators chronically exposed to DEPs.<sup>27</sup> It may then be important for primary care physicians to inquire about occupational or environmental exposure to diesel exhaust from patients presenting with chest pain and dyspnea. For patients whose

ACS was indeed precipitated by acute exposure to diesel exhaust, it will be important to counsel them about avoiding diesel fumes in the future.

## Pulmonary Effects

DEPs have been demonstrated to increase the production of inflammatory cytokines such as interleukin 1 $\beta$ , interleukin 8, and granulocyte-macrophage colony-stimulating factor from cyclo-oxygenase stimulation in bronchial epithelial cells.<sup>28</sup> This in turn results in decreased adhesion between cells, reduction of structural integrity, and inhibited repair. Pulmonary damage incurred from DEP exposure may resemble that caused by bacterial endotoxin.<sup>29</sup> Asphyxiation from diesel exhaust is more likely to be caused by acute lung injury from soot particles, nitrogen dioxide, and sulfur dioxide than by carbon monoxide. This is different from gasoline exhaust, which contains 28 times more carbon monoxide than diesel exhaust.<sup>30</sup> Nevertheless, in patients with significant acute and/or chronic diesel exhaust exposure, carbon monoxide levels should be checked. In the absence of deliberate exposure, elevated carbon monoxide levels may represent a marker for serious exposure to diesel exhaust and should be further investigated. Patients with reactive and/or obstructive airway diseases such as asthma and emphysema may have their underlying disease exacerbated as a result of exposure to diesel exhaust.<sup>31–33</sup> Visits to the emergency department for pulmonary complaints have been shown to increase during periods of severe air pollution.<sup>34</sup> One possible explanation is DEPs combining with atmospheric allergenic molecules to create even more inflammatory allergens.<sup>35</sup> Admission rates for pediatric asthma exacerbation have been shown to be higher in areas with greater-than-average diesel emissions.<sup>36</sup> DEPs have been shown to directly induce degranulation of mast cells with subsequent histamine release.<sup>37</sup> Histamine release-induced by exposure to DEPs may result in allergic conjunctivitis, rhinosinusitis, pharyngitis, laryngitis, and chronic cough.<sup>38</sup> Macrophages, the first line of immunologic defense within the lung, are severely impaired from exposure to high concentrations of DEPs, resulting in an increased risk of bacterial and viral bronchitis and pneumonia.<sup>39</sup> Although no relevant clinical studies have been published, primary care physicians may consider the inclusion of antihistamines in addition to  $\beta$ -agonists and corticoste-

roids for the care of patients with acute exacerbation of reactive airway disease precipitated by diesel exhaust exposure.

Many substances in diesel exhaust, such as ozone, can contribute to lung tissue destruction. Ozone is formed from nitrogen oxides, which diesel engines emit in disproportionately higher amounts compared with catalytic converter-equipped gasoline engines. Many of the hydrocarbon molecules emitted by diesel engines, such as PAH, are quite toxic to the lung. Living in areas with high DEPs accelerates pulmonary disease. Chronic exposure to DEPs is associated with an increased risk for the development of asthma. Churg et al compared postmortem lung histology of nonsmoking inhabitants of Mexico City, Mexico, with those of Vancouver, British Columbia, Canada.<sup>40</sup> The lungs of the Mexico City inhabitants were significantly more diseased, with smaller airways consistent with an obstructive pattern and ultra-fine particles embedded in the airway mucosa. A similar study comparing young, recently deceased patients in Los Angeles and Miami found higher levels of pulmonary centriacinar inflammation in the Los Angeles residents.<sup>41</sup> A large study of children demonstrated a significant decrease in the forced expiratory volume in 1 second (FEV1) in those patients living in areas with high concentrations of DEPs.<sup>42</sup> Another pediatric study concluded a dose-dependent inverse association exists between the carbon content of airway macrophages and FEV1 for children living in urban areas with significant diesel exhaust exposure.<sup>43</sup> Workers in enclosed spaces such as mines and ships are especially at risk from DEP-induced pulmonary disease. Jorgensen and Svensson reported that underground miners had productive cough and frequent respiratory infections,<sup>44</sup> and Wade and Newman attributed asthma in train crews to diesel exhaust.<sup>45</sup>

## Cancer

In 1989, the International Agency for Research on Cancer concluded that there is sufficient evidence for the carcinogenicity of diesel exhaust in experimental animals but limited evidence for carcinogenicity in humans. In 1990, California identified diesel exhaust as a substance known to cause cancer. Diesel exhaust particles have been shown to directly damage DNA and result in carcinogenesis in several animal lung studies.<sup>46</sup> Diesel exhaust parti-



cles have been shown to generate reactive oxygen species, which lead to oxidative stress and DNA damage. PAH associated with diesel exhaust are genotoxic, forming PAH-DNA adducts and resulting in mutation and DNA strand breakage.<sup>47</sup> Occupational studies of railroad workers, heavy equipment operators, and truck drivers have demonstrated a significantly higher-than-normal incidence of death from lung cancer.<sup>48,49</sup> A more recent case-control study of occupational diesel exhaust exposure in Montreal, Quebec, Canada found a limited association with lung cancer in both smokers and nonsmokers.<sup>50</sup> Gustavsson et al reported that workers exposed to combustion products had a higher incidence of esophageal cancer.<sup>51</sup> In a study by Guo et al, human exposure to DEPs was associated with a higher risk of ovarian cancer but not with esophageal, testicular, or urinary tract cancers or leukemia.<sup>52</sup> A possible causal relationship between DEPs and multiple myeloma was reported by Lee et al.<sup>53</sup>

### Hypertension

A link between hypertension and diesel exhaust exposure seems to exist, based on several studies.<sup>54–57</sup> Transient hypertension has been associated with brief periods of severe pollution and is possibly related to the effect of DEPs on cardiovascular autonomic control. This sudden increase in blood pressure may be a cofactor in the development of myocardial ischemia precipitated by diesel exhaust exposure. At levels encountered in an urban environment, inhalation of dilute diesel exhaust impairs regulation of vascular tone and endogenous fibrinolysis.<sup>58</sup>

### Neurotoxicity

Volatile hydrocarbons such as PAH attach to DEPs and are rapidly absorbed through the lungs into the central nervous system. A possible association between chronic DEP exposure and Parkinson's disease has been explored because DEPs have been shown to decrease the number of dopaminergic neurons in the brain tissue of mice.<sup>59</sup> Another study group demonstrated that brain inflammation induced by DEPs resulted in histopathologic changes similar to those seen in patients with Alzheimer's disease.<sup>60</sup> The result of chronic DEP exposure may affect learning ability, coordination, memory, and judgment in both children and adults.<sup>61</sup> Kilburn

demonstrated slowness of response, memory loss, and disordered sleep suggestive of neurobehavioral impairment in workers whose occupations involved significant indoor diesel exhaust exposure. Abnormalities such as visual field defects, delayed blink reflex latency, and balance impairment, as well as impaired recall memory, problem solving, and perceptual motor speed tests were also detected.<sup>62</sup>

### Perinatal Health and Infertility

Several worldwide studies have linked diesel exhaust exposure to low birth weight in infants, premature births, congenital abnormalities, and elevated infant mortality rate.<sup>63–66</sup> DEPs caused a significant decrease in adult sperm production and a diminished number of Sertoli cells in an animal model.<sup>67</sup> Other studies have shown aberration of sex hormone production and effect in chronically exposed female rats, with increased levels of testosterone and subsequent masculinization.<sup>68</sup> Pregnant rats exposed to DEPs had higher rates of spontaneous abortions. There are few human epidemiologic studies, but one study demonstrated a negative effect of DEPs on human sperm motility.<sup>69</sup> Another compound isolated from DEPs, 4-nitrophenol (PNP), has been identified as a vasodilator. One study group demonstrated that PNP has estrogenic and antiandrogenic activities in vivo, leading to sterility.<sup>70</sup> The accumulation of PNP in air, water, and soil may be one factor in the increasing incidence of sterility in humans and animals, but epidemiologic studies are pending.

### The Future

In 2001 the Environmental Protection Agency proposed the Heavy-Duty Engine and Vehicle Standards and Highway Diesel Fuel Sulfur Control Requirements, to be implemented by 2008.<sup>1</sup> The production and distribution of low (<30 parts per million) sulfur content diesel fuel, which is widely available in Europe, is one of the most significant changes in policy. This cleaner diesel fuel is viewed as being essential to reducing tailpipe emissions from large trucks and buses; the current sulfur content prevents pollution control equipment from working properly.<sup>71</sup> After-treatment devices such as diesel particulate filters, traps, and nitrogen oxide-reducing catalysts are also being implemented. One study found that buses using diesel and compressed natural gas as well as clean diesel fuel and

**Table 3. Unexplained signs and symptoms and potential diesel exhaust exposure**

Chest pain
Arrhythmia
Dyspnea
Cough
Rhinitis
Conjunctivitis
Bronchospasm
Laryngitis
Neoplasm
Impotence
Hypertension
Headache
Dizziness
Insomnia
Memory loss
Dementia

particulate traps were superior to standard diesel buses with regard to emissions.<sup>72</sup> A new generation of diesel engines developed for Europe should become available in the United States in the near future. The Environmental Protection Agency has issued a Notice of Proposed Rulemaking to implement onboard diagnostic systems to monitor diesel exhaust emissions on heavy-duty engines used in highway vehicles over 14,000 pounds by 2010. Individual states are also implementing “No Idling” policies with regard to diesel-powered vehicles that are not in active use.

## Conclusions

As populations continue to grow worldwide, the expansion of mass transportation and the construction of new buildings for housing and commerce will occur concomitantly. Until alternative energy sources are fully developed and implemented, reliance on diesel fuel will increase. Acute and chronic exposure to diesel exhaust will continue to be a problem in the United States. This will ultimately increase the number of patients presenting to urban primary care clinics and emergency departments with cardiopulmonary disease, neurological disorders, and adverse perinatal events. If new regulations and technology to reduce DEP emissions are fully implemented and prove to be effective, this outcome may be averted. The omnipresence of diesel exhaust in urban areas may lead the clinician to preclude its query in the patient’s history. A

plethora of unexplained signs and symptoms may be caused by diesel exposure (Table 3). Although no specific screening guidelines exist, primary care physicians should question patients about potential exposure to diesel exhaust and be familiar with its myriad deleterious health effects.

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