High-temperature, controlled incineration and thermal treatment of contaminated soils, sediments, and wastes at Superfund sites are often preferred methods of remediation of contaminated sites under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 and related legislation. Although these methods may be executed safely, formation of toxic combustion or reaction by-products is still a cause of concern. Emissions of polycyclic aromatic hydrocarbons (PAHs); chlorinated hydrocarbons (CHCs), including polychlorinated dibenzo-p-dioxins and dibenzofurans; and toxic metals (e.g., chromium VI) have historically been the focus of combustion and health effects research. However, fine particulate matter (PM) and ultrafine PM, which have been documented to be related to cardiovascular disease, pulmonary disease, and cancer, have more recently become the focus of research. Fine PM and ultrafine PM are effective delivery agents for PAHs, CHCs, and toxic metals. In addition, it has recently been realized that brominated hydrocarbons (including brominated/chlorinated dioxins), redox-active metals, and redox-active persistent free radicals are also associated with PM emissions from combustion and thermal processes. In this article, we discuss the origin of each of these classes of pollutants, the nature of their association with combustion-generated PM, and the mechanisms of their known and potential health impacts. Key words: cardiovascular health, environmental health, fine and ultrafine particulate matter, persistent free radicals, respiratory health, thermal remediation. Environ Health Perspect 114:810–817 (2006). doi:10.1289/ehp.8629 available via http://dx.doi.org/ [Online 26 January 2006]
form and oxidation state. Few, if any, organic components of the feed-stock survive direct contact with the flame, and other than soot, only minimal organic by-products are formed (Dellinger and Taylor 1998; Oppelt 1986). Thus, the vast majority of the observed pollutants in the effluent must be originating from chemistry occurring outside the flame. In fact, most of the pollutants are probably formed in the high-temperature, postflame zone or at even lower downstream temperatures as a result of surface-mediated reactions. In the most general sense, the mechanisms of pollutant formation and destruction are expected to be relatively consistent within a zone. This “zone model” allows for classification of the reactions occurring within a given zone (Dellinger and Taylor 1998) (Figure 1).

**Zone 1, the preflame, fuel zone.** This zone is characterized by a wide range of temperatures (from near ambient to 1,200°C), residence times on the order of 0.1 sec, and low excess air conditions. Because this zone occurs at the front end of the device, it creates new reaction intermediates by several low-energy, unimolecular reaction pathways such as hydrocarbon chloride elimination and carbon–halogen bond rupture that react further in the downstream zones.

**Zone 2, the high-temperature, flame zone.** This zone is characterized by temperatures of 1,000–1,800°C, at which essentially every organic compound will undergo complete conversion to its most thermodynamically stable end products, namely, carbon dioxide, water, hydrochloric acid, and nitric oxide. Under local pyrolysis conditions, soot is the dominant product. The flame zone generates large quantities of vaporized metals and chlorine that are very important reactants in subsequent zones. Observed organic pollutants are likely due to flow paths that pass through the periphery of the flame or flow eddies of poor fuel/air mixing (Cundy et al. 1989). These flow paths represent destruction “failure modes” of the flame and generate pockets that are more properly described as high-temperature thermal zones—that is, zone 3.

**Zone 3, the postflame thermal zone.** This is a chemistry-rich zone where various types of radical–molecule reactions occur. It is characterized by temperatures of approximately 600–1,100°C, residence times of a few seconds, and both oxygen-rich and oxygen-depleted regions. Experimental and modeling studies indicate that most pollutant formation in this zone occurs in oxygen-depleted pockets of poor waste–air mixing (Chang DPY et al., unpublished data; Cundy et al. 1989; Russell et al. 1989). Within this zone, most of the PAHs, higher-molecular-weight CHCs, brominated hydrocarbons (BHCs), and mixed bromo/chloroaromatics (XHCs) are formed by molecular growth pathways. This zone may also be where metals vaporized in the flame zone are condensed to ultrafine PM.

**Zone 4, the gas-quench, cool zone.** This zone exists downstream of the flame and postflame zones and is characterized by either gradual or rapid quenching of the gas temperature. Residence times are long, > 10 sec, and oxygen concentrations vary from oxygen-depleted zones to combustion in upstream zones, to oxygen-rich zones that air in-leakage occurs. Partially oxidized products such as formaldehyde, chloroformaldehyde, and phosgene form by radical–oxygen association reactions (Russell et al. 1989). Nitrated products form via radical–molecule addition reactions involving NOx generated in the flame zone (Schuetzle and Perez 1983). Hydrocarbons and chlorocarbons may also be partially oxidized in this zone, resulting in emissions including oxy-PAHs and oxychloro-PAHs (Rubey WA et al., unpublished data).

**Zone 5, the surface-catalysis, cool zone.** This zone is fundamentally different from the other four zones in that one must now consider the effects of surfaces at temperatures between 200 and 600°C. Reaction times for gas–surface reactions are a few seconds for entrained particulate or hours for deposited particles. PCDD/Fs have been shown to be formed in zone 5 (Altwicker et al. 1992; Gullett et al. 1994; Lomnicki and Dellinger 2003a, 2003b). However, many more pollutants potentially form as a result of surface catalysis via pathways including CHCs, BHCs, and XHCs; polybrominated dibenzo-p-dioxins and dibenzofurans (PBDD/Fs) and PXDD/Fs; partially oxidized hydrocarbons and CHCs (i.e., carbonyls, alcohols, organic acids, epoxides); and nitro-PAHs, oxy-PAHs, and oxychloro-PAHs (Addink et al. 1995; Lomnicki and Dellinger 2003a, 2003b; Wehrmeier et al. 1998). Most of the reactions necessary to form these products require a transition metal catalyst (Lomnicki and Dellinger 2003a, 2003b; Pieters et al. 1984).

We now suspect that the zone 2 and 3 reactions that form nanoparticles of soot/fly ash also transform metals into catalytically active forms and catalyze the formation of new toxic by-products in zone 5. Once formed in zone 5, the pollutants are emitted into the atmosphere because temperatures are too low to result in their destruction.

Incinerators and accidental fires contain all these zones. Thermal destruction devices contain only zones 3, 4, and 5. Thermal describers consist of low-temperature components of zone 3 as well as zones 4 and 5. Catalytic oxidizers consist of zones 4 and 5 only. The omission of zone 2 in most ways increases the probability of pollutant emissions by allowing all of the waste to react in zones 3–5, rather than destroying a large portion of it in the flame zone. Unfortunately, nonincineration, thermal technologies, and fires are not subject to the same strict testing and regulatory scheme as are incinerators. Consequently, most emissions of toxic combustion by-products from these sources remain uncontrolled.

The nature of emissions: precursors and thermal reactions. We must be concerned with not only the level of emissions but also their toxicity and bioavailability as determined by the form in which they are emitted. However, the problem is not intractable, for three reasons: a) Only a limited number of products form from the direct oxidation or pyrolysis of a given compound; b) in addition to by-products from specific precursors, full-scale emissions characterizations and pilot-scale and laboratory studies have shown that there are certain “ubiquitous” by-products that form regardless

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**Figure 1.** Combustor reaction zones. Zone 1, preflame, fuel zone; zone 2, high-temperature, flame zone; zone 3, postflame, thermal zone; zone 4, gas-quench, cool zone; zone 5, surface-catalysis, cool zone. PBDD/Fs, polybrominated dibenzo-p-dioxins and dibenzofurans. Reaction products from upstream zones pass through downstream zones and undergo chemical modifications, resulting in formation of new pollutants. Zone 2 controls formation of many “traditional” pollutants (e.g., carbon monoxide, sulfur oxides, and nitrogen oxides). Zones 3 and 4 control formation of gas-phase organic pollutants. Zone 5 is a major source of PCDD/Fs and is increasingly recognized as a source of other pollutants previously thought to originate in zones 1–4.
of the waste being burned; and c) the conditions under which pollutant-forming reactions occur are well defined within the zone theory of pollutant formation.

These principles suggest that characterization of toxic combustion by-products may be studied in a systematic scientific manner. In addition to PAHs that are formed in virtually every combustion source, we now believe that the principal classes of pollutants from the combustion/thermal degradation of hazardous wastes are: a) fine and ultrafine PM, b) CHCs/BHCs, and c) persistent radicals.

**Fine and ultrafine PM.** Ultrafine PM, or nanoparticles, is formed largely by combustion sources as primary PM emissions or as secondary particles formed by atmospheric chemical reactions of combustion emissions of sulfur and nitrogen oxides (Donaldson et al. 1998). Nanoparticles are not efficiently captured by air pollution control devices, are transported over long distances, and penetrate deep into the respiratory system, all of which enhance the potential negative health impacts (D'Alesio et al. 1999; Kauppinen and Palkanen 1990).

Metals are vaporized in the flame zone and subsequently nucleate to form small metal nanoparticles or condense on the surfaces of other nanoparticles in transit to the postflame (thermal reaction) zone (Figures 1, 2). Under pyrolytic or oxidative pyrolysis conditions at temperatures above approximately 600°C (zone 2), the metal seed nuclei promote reactions with gas-phase organic species to form a carbonaceous layer, resulting in nanoparticle growth (zones 2 and 3). Below approximately 600°C, under primarily oxidative and oxidative pyrolysis (thermal reactions in the presence of trace quantities of oxygen) conditions, the metal nuclei or surface-condensed metals initiate formation of new gas-phase and PM-associated pollutants (zones 3–5).

Elemental carbon (mostly soot) and organic carbon (the myriad of organic chemicals) account for more than half of these particles. Although approximately 80% of the organic carbon is extractable, only 12% is chemically resolved (Rogge et al. 1993). PAHs, oxy-PAHs, alkanes, organic acids, and macromolecular species similar to humic acid make up most of the identified chemicals. These airborne particles also contain percents (e.g., iron, potassium, silicon) and part-per-million (e.g., copper, nickel, zinc) concentrations of transition, alkali, and other toxic metals. Redox-active metals (e.g., iron and copper) and organics (e.g., PAHs, oxy-PAHs, and semiquinones) have been implicated in the biological activity of airborne fine and ultrafine PM (Carter et al. 1997; Costa and Dreher 1997; Kennedy et al. 1998; Smith et al. 2000). Unfortunately, the organic fraction remains largely uncharacterized, and there are few to no data on speciation of metals and the presence of metal-organic complexes that undoubtedly exist in these particles.

**Emissions of CHCs and BHCs.** The combustion and thermal reactions of CHCs are of particular interest because a) they constitute most of the toxic components of hazardous wastes, b) they are often quite refractory, and c) they form other highly toxic aliphatic and olefinic CHCs, chlorinated PAHs, and PCDD/Fs.

Trichloroethylene produces a wide range of by-products, including hexachlorobenzene, chlorinated PAHs, and the perchlorinated analogue of the highly carcinogenic butadiene (Avakian et al. 2002). CHCs also form as by-products in zone 5 by surface-mediated reactions. This finding, along with the resistance of CHCs to oxidation, suggests that the formation of PAHs and chlorinated PAHs (CIPAHs) may be more facile in halocarbon combustion systems than in hydrocarbon systems.

Numerous research studies have definitively demonstrated that PCDD/Fs are formed in almost any combustion or thermal device if there are sources of carbon and chlorine along with a transition metal to catalyze chlorination and condensation reactions (Dellinger and Taylor 1998; Froese and Hutzinger O 1996). Three general pathways of formation have been proposed: a) de novo formation (200–500°C), in which carbon in soot or fly ash acts as reagent to form PCDD/Fs by chlorination/oxidation of “dioxin-like” structures that inherently exist in a carbon matrix (Altwicker 1996; Hell et al. 1997; Huang and Buekens 1996; Stieglitz 1998); b) transition-metal, surface-catalyzed formation (200–500°C) from PCDD/F precursors such as chlorinated phenols and chlorinated benzenes (Altwicker 1996; Froese and Hutzinger O 1996; Ghiorishi and Altwicker 1996; Lomnicki and Delliger 2003a, 2003b); and c) gas-phase, radical–molecule reactions (˃600°C) of chlorinated phenols, chlorinated benzenes, and polychlorinated biphenyls (Lenoir et al. 1998; Louw and Ahnokhai 2002). Field studies suggest that gas-phase pathways are responsible for about 30% of total PCDD/F emissions, with the remainder due to surface-mediated pathways. Any source containing a hydrocarbon, a transition metal, and a source of chlorine (organic or inorganic) will form PCDD/Fs if the temperature is ever raised above 200°C (Altwicker 1996; Froese and Hutzinger M 1996; Ghiorishi and Altwicker 1996; Lomnicki and Delliger 2003a, 2003b).

There is a growing recognition that BHCs, including PBDD/Fs, are formed and emitted during the thermal treatment of brominated flame retardants in fabrics and plastics and electronic materials (E-materials and E-wastes), frequent contaminants at Superfund sites. Until recently, BHCs have received little attention primarily because of difficulty of analysis, lack of available analytical standards, and a paucity of health effects data. However, recent findings suggest that brominated flame retardants as well as PBDD/Fs are highly toxic (Lenoir et al. 2001). Computer motherboards contain an incredible amount (~50% per unit) of bromine (Sakai et al. 2001). Analysis of the effluent from an E-waste incinerator reveals that the effluent contains 4.6–7.6 mg of copper per dry standard cubic meter (dscm). This is significant because it is well established that copper catalyzes the formation of PCDD/Fs from CHCs in combustion systems, and the same catalytic behavior is expected from BHCs. Recent experimental studies have shown that BHCs, PBDD/Fs, XHCs, and PXDD/Fs are formed from combustion of...
Aqueous extracts of combustion-generated PM generate free radicals, we examined samples of fine PM is combustion, and these sources damaging superoxide and hydroxyl radicals. We believe that the source of this damage is a surface-associated semiquinone-type radical. Semiquinones are relatively nonreactive with O$_2$ due to resonance stabilization (Berho and Leclaux 1997; Wiater-Protas and Louw 2001). When a semiquinone is adsorbed on a surface, additional stability may be imparted to the radical if the adsorption site is an electron acceptor (Kodomari et al. 1988). The presence of semiquinone-type radicals on combustion-generated PM is significant and suggests a previously unrecognized origin of the health effects attributed to fine PM.

**Health Effects of Toxic Combustion By-products**

**Routes of exposure and distribution: size matters.** Combustion of hazardous wastes results in pollution that exists in a gaseous, liquid, and/or solid particle state suspended in air. A crude characterization of suspended pollutants uses the mean diameter of the suspended particles and varies from a few nanometers to several micrometers. The coarse fraction of suspended airborne pollutants originates from windblown dust, crushing and grinding operations, materials handling, and/or atmospheric abrasion of even larger particles. The aerodynamic diameter of inhalable coarse PM ranges from 2.5 to 10 µm (i.e., PM$_{10}$). Combustion, on the other hand, typically generates smaller PM < 2.5 µm in diameter (i.e., PM$_{2.5}$). Finally, ultrafine PM, or nanoparticles, form both in combustion sources and in atmospheric processes through condensation and molecular growth pathways and are <100 nm (i.e., PM$_{0.1}$) in diameter.

Particles are deposited in the respiratory tract, and deposition is directly proportional to aerodynamic diameter of the particles (Figure 3). PM$_{10}$ deposits mainly in the upper respiratory tract and may be cleared by mucociliary actions. PM$_{2.5}$ and PM$_{0.1}$ penetrate the alveolar regions of the lung, where the ultrafine PM rapidly penetrates the epithelium (Oberdorster 2001). Clearance of fine and ultrafine PM is mediated mainly by phagocytic activity and particle dissolution (Wagner and Foster 1996).

The ability of PM$_{0.1}$ to translocate to the pulmonary interstitium suggests that these particles have a significant impact on the health of other organ systems (Nemmar et al. 2001). Indeed, studies using radiolabeled 2,3,7,8-tetrachlorodibenzo-p-dioxin ([3H]TCDD) have clearly demonstrated that inhalation, ingestion, or dermal absorption results in major tissue deposits of [3H]TCDD in the liver and fat (Diliberto et al. 1996) and suggest that multiple routes of exposure occur and that these exposures lead to multiple organ and systemic effects.

Ambient air pollution is a complex mixture of volatiles and particulates arising from various sources, including vehicular exhaust, flaring of hydrocarbons at refineries, coal burning at power plants, and thermal treatment of hazardous wastes at Superfund sites. A larger number of epidemiologic studies have documented associations between air pollution, specifically PM$_{2.5}$ and PM$_{0.1}$, and acute health effects (Burnett et al. 2000; Ostro et al. 1996; Peters et al. 2001; Pope et al. 1999). However, very little is known about the health effects associated with exposure to the by-products produced from the combustion of hazardous wastes. Thus, the following discussion is primarily based on a review of recent literature addressing the effects of air pollution on health effects.

**Pulmonary effects. Decreased lung function.** Increases in ambient air pollution result in increased hospital admissions for numerous respiratory end points, including decreased lung function [i.e., reductions in peak flow and declines in forced expiratory volume in 1 sec (FEV$_1$)], cough, and exacerbations of pulmonary disease states such as asthma and chronic obstructive pulmonary disease (Boezen et al. 1998; Pope 2000; Schwartz 1994; Timonen and Pekkanen 1997; Vedral et al. 1998). Interestingly, stratifying the results of some of these studies for sex demonstrated an increase in asthma attacks in girls compared with boys (Brunekeef et al. 1997; Oosterlee et al. 1996; Van Vliet 1997). However, none of these reports even postulates as to why females may be more susceptible to air pollution than are males.

**Inflammatory responses.** Exposure to airborne PM has been shown to elicit an acute inflammatory response (i.e., an influx of neutrophils and other inflammatory cells in the airway lumen and release of proinflammatory cytokines) in the lung (Carter et al. 1997; Fuji et al. 2001; van Eeden 2002). Effects of air pollution on pulmonary function are observed in various animal models, including rats, mice, and dogs (Henderson et al. 1988; Hiura et al. 1999; Nel et al. 2001; Saldiva et al. 1992). In a recent study, normal rats exposed to concentrated ambient air particles (PM$_{2.5}$) for 3 consecutive days demonstrated a dose-dependent increase in pulmonary inflammation, as measured by increased neutrophil numbers in the bronchoalveolar lavage fluid (Saldiva et al. 2002). These data were supported by histopathology demonstrating an
acute inflammatory response characterized by an influx of neutrophils into the central areas of the pulmonary acinus, hyperplasia of the alveolar epithelium, and macrophage accumulation in the alveolar spaces.

**Immune responses.** Data further suggest that ambient air pollution has the ability to modulate immune responses due to certain respiratory viral infections. PM\textsubscript{10} exposure has been shown to interfere with the replication of respiratory syncytial virus (Kaan and Hegele 2003) and to lead to a decreased production of proinflammatory cytokines (Vincent et al. 1997), whereas exposure of rhinovirus-infected epithelial cells to moderate levels of air pollutants led to enhanced generation and release of proinflammatory cytokines (Spannhake et al. 2002). Although conflicting, these data suggest that air pollution modulates pulmonary inflammation due to certain viral infections in vivo and may be important in the exacerbation of respiratory inflammatory disease states such as asthma and chronic obstructive pulmonary disease.

Numerous epidemiologic studies have demonstrated increased mortality associated with increased levels of PM. On high-pollution days, the numbers of deaths due to respiratory viral infections such as pneumonia were disproportionately high (Schwartz 1994). In fact, hospitalization admissions for preschool age children and elderly individuals were elevated almost 2-fold in communities where PM\textsubscript{10} levels were above the 24-hr and annual National Ambient Air Quality Standards of 65 and 150 µg/m\textsuperscript{3} (Dockery and Pope 1996).

Several studies support these findings. In one such study, human alveolar macrophages (AMs) were isolated and subsequently exposed to PM. The AMs showed significant decreases in a number of receptors important for host defense such as CD11b and CD11c (important for phagocytosis of opsonized pathogens) and CD29 (important in neutrophil recruitment). Within 3 hr of exposure, the ability of AMs to generate reactive oxygen species (ROS; important in the killing of microorganisms) was markedly reduced, and within 18 hr, significant declines were observed in the phagocytic ability of AMs (Becker and Soukup 1998). More recent studies confirm that exposure to airborne particles from combustion of residual oil (residual oil fly ash (ROFA)) may alter AM function. For example, ROFA instilled into the trachea of rats before infecting them with *Listeria monocytogenes* results in an increase in the phagocytic ability of AMs, decreased bacterial killing, and increased mortality (Antonini et al. 2002). These results correlated with a significant decrease in the production of nitric oxide by AMs. The demonstrated suppression of host defense mechanisms against *L. monocytogenes* is not specific to ROFA or PM, but has also been observed on exposure to sulfur-related air pollution, leading to long-term respiratory effects and to changes in AM-mediated particle clearance mechanisms (Kreyling et al. 1999).

Although the above studies agree with numerous other studies on ROFA and bacterial infectivity (Antonini et al. 2002; Hatch et al. 1985), they disagree with assessments of infectivity using other PM samples (Antonini et al. 2000; Yang et al. 2002). For example, AM function (i.e., phagocytosis and production of ROS) was actually enhanced in the lungs of animals exposed to crystalline silica and subsequently infected with *L. monocytogenes* (Antonini et al. 2000). The reasons for this controversy are unclear; however, it is anticipated that the various components associated with the source of the PM are important in the observed effects.

Cumulatively, these data suggest that air pollution acts as an immunosuppressor, deflating the normal host response to pathogens and, in particular, the pulmonary immune response. Whether this is a result of decreased AM cell numbers, decreased AM phagocytic abilities, and/or diminished T-cell responses appears to depend on the chemical composition of the exposure.

**Diminished lung function growth.** Although effects on pulmonary function are obvious, long-term effects such as lung function growth in children are just being realized. Gauderman et al. (2002) followed a cohort of 1,678 fourth-grade schoolchildren from 12 different southern California communities over a period of 4 years. Each spring, a team of Children’s Health Study technicians obtained seven maximal forced expiratory maneuvers from each child as a measure of pulmonary function. Air pollution in the 12 communities was monitored for the entire study period. Air-monitoring stations recorded hourly concentrations of ozone, PM\textsubscript{10}, and nitrogen dioxide levels. PM\textsubscript{2.5} levels were obtained from 2-week filter samples. Investigators observed a negative correlation between pollution levels and pulmonary function for all pollutants examined. A significant negative correlation was observed between FEV\textsubscript{1} growth rate and acid vapor (p = 0.03). Significant negative correlations between FEV\textsubscript{25-75%} (the middle 25–75% of the FEV\textsubscript{1} maneuver) were observed for acid vapor, nitrogen dioxide, PM\textsubscript{2.5}, and elemental carbon. Despite the large number of publications in this area, no resounding theory as to how ambient PM induces pulmonary dysfunction has surfaced.

**Cardiovascular effects.** Increased cardiovascular events. Epidemiologic studies have also shown an increase in cardiovascular morbidity and mortality that is associated with increases in PM. In fact, cardiovascular death rates were higher than pulmonary death rates during peak episodes of air pollution (Pope et al. 1999). Numerous studies conducted within the United States and other countries, including Canada and Chile, have reported statistically significant, positive correlations between daily human cardiovascular events and exposure to fine PM in the atmosphere (Burnett et al. 1995; Dockery et al. 1993; Ostro et al. 1996).

Unfortunately, the epidemiologic data do not provide a clear description of the types of cardiac events observed. In fact, cardiovascular deaths in most of these studies were lumped into a single group, coronary heart disease (CHD), which was associated with increases in ambient PM concentration (Poloniecki et al. 1997; Schwartz and Morris 1995). However, CHD results from myocardial ischemia, arrhythmias, artherosclerosis, thrombosis, and/or vascular spasm. This represents a major problem in determining the underlying cause of cardiovascular mortality associated with increased PM levels. The temporal association between cardiovascular hospitalizations/mortality and ambient PM seems to be relatively short (0–3 days), suggesting that increased cardiovascular morbidity/mortality is due to myocardial ischemia (Pekkanen et al. 2002), myocardial infarcts (Peters et al. 2001), and/or ventricular arrhythmias (Peters et al. 2000), and heart rate variability (Gold et al. 2000; Pope et al. 1999). Short-term exposures (<2 hr) have been shown to increase the occurrence of myocardial infarction in people at risk of developing CHD (Peters et al. 2001). Numerous animal studies have been able to replicate most of the observed human responses to PM. These studies demonstrate that acute exposure to environmentally relevant PM induces cardiovascular effects, including changes in heart rates (Gordon et al. 1998; Pope et al. 1999); arrhythmias (Hoeck et al. 2001); electrocardiographic abnormalities (Bloch et al. 1972); cardiomyopathic changes, including inflammatory infiltrates, fibrosis, and cardiac myocyte degeneration (Kodavanti et al. 2003); and progression of atherosclerotic lesions (Suwa et al. 2002).

**Chronic cardiovascular inflammation.** Long-term exposure studies (10 mg/m\textsuperscript{3} at 6 hr/day and 1 day/week for 16 weeks) in Wistar Kyoto rats demonstrated that PM induces both time- and dose-dependent myocardial injury (Kodavanti et al. 2003). Histopathology of the cardiac tissue revealed randomly distributed foci of inflammatory responses composed of mixed populations of neutrophils, lymphocytes, and macrophages and suggests a state of chronic active inflammation in the heart due to PM exposure. The myocardial injury was characterized by cardiac myocytes in various stages of degeneration. The degenerating cardiac tissue was
associated with fibrosis and collagen accumulation of the interventricular septum and throughout the ventricles. Interestingly, examination of the pulmonary tissue showed a dose- and time-dependent accumulation of particle-laden AMs with no associated peribronchial or perivascular inflammation or pulmonary fibrosis, suggesting that PM directly affects cardiovascular tissue. A recent study using dogs residing in polluted urban areas of southwestern Mexico City demonstrated numerous myocardial changes, including apoptotic myocytes and inflammatory infiltrates in the left and right ventricles and interventricular septum (Calderon-Garciduenas et al. 2001). Vascular changes were also noted in the dogs, including smooth muscle cell hyperplasia, deposition of PM in the media and adventitia, and microthrombi in the capillaries and small arteries and veins.

Very little is known about how PM increases the risk of cardiovascular events. One hypothesis is that inhaled PM produces an acute cardiovascular event indirectly through the induction and perpetuation of inflammatory responses in the lung. The chemokines and cytokines released during this inflammatory response travel through the blood to the myocardium, where they are known to cause myocardial dysfunction, including myocardial infarction, atherosclerosis, and decreased contractility (Abc et al. 1993; DeMeules et al. 1992; Mann and Young 1994). Indeed, a systemic inflammatory response induced by PM has been demonstrated (van Eeden 2002). This systemic response elicited cytokine release from the lungs into circulation and proliferative responses of bone marrow polymorphonuclear leukocytes. In conjunction with the systemic inflammation, it was noted that a progression of atherosclerotic plaques occurred on exposure to PM in animals susceptible to atherosclerosis.

An alternative hypothesis is that the inhaled PM is absorbed by the blood and translocated from the lung to the heart. Provocative data from a few investigators have begun to demonstrate the ability of PM$_{10}$ to penetrate deeply into the lower respiratory tract, where it is capable of producing significant systemic effects (Salvi et al. 1999), and to diffuse from the lungs into the systemic circulation (Nemmar et al. 2001). Evidence for transport of PM from the lungs into circulation was noted, although not discussed, in the canine study, which demonstrated deposition of PM in the arteriolar blood vessels (Calderon-Garciduenas et al. 2001). PM transported via the vasculature, directly or indirectly, influences the cardiac myocytes, cardiovascular functioning, and/or hemodynamics through thrombus formation or changes in rhythm.

**Genotoxicity.** Genotoxicity results in DNA mutations that affect a) only the individual’s DNA (i.e., somatic mutations), b) only the DNA of the individual’s progeny (i.e., germline mutations), or c) both the individual and its progeny. Genotoxic events are often considered the most detrimental; however, cytotoxic events also result in changes to the physiologic functioning of the organ/cell, a predisposition to develop disease, and/or cell death and organ damage.

PM$_{2.5}$ and combustion-generated PM contain exogenous free radicals that have been shown to induce DNA damage (Dellinger et al. 2001) and mutations (Demarini et al. 1991; Houk et al. 1990; Watts et al. 1992). In one study, mice chronically exposed to the ambient air pollution of downtown São Paulo for 90 days showed a significant increase in the frequency of micronuclei (an indicator of DNA damage), which was associated with increased levels of carbon monoxide, nitrogen dioxide, and PM$_{2.5}$. Similar data were observed on exposure of human bronchial epithelial cells to 1,3-butadiene (Catallo et al. 2001). Also, both cytotoxic and genotoxic mutations may lead to cancer (Vines and Hogafvel-Pursiainen 2005). Increased mutagenicity associated with combustion PM emissions appeared to depend on the incompleteness of combustion and reduced efficiency of pollution control equipment.

Investigations conducted in Hamilton Harbor, Ontario, Canada (an industrial area with two steel mills), suggest that PM from air pollution and combustion emissions is the principal factor responsible for eliciting genetic mutations (Somers et al. 2004). In particular, offspring of mice exposed to industrial combustion from Hamilton Harbor demonstrated an increased incidence (i.e., 1.5- to 2-fold higher expanded simple tandem repeat mutation rates than animals exposed to ambient air) of DNA mutation rates that were paternally derived. Intriguingly, these data are the first to implicate PM in the induction of mutations heritable by the subsequent generations (Somers et al. 2004) and imply that inhaled PM or their metabolized products are transported to germ cells (Semat and Pope 2003).

**Reproductive effects.** Exposure to environmental pollutants has also been linked to adverse reproductive health. Some of the effects observed include developmental changes in the male reproductive tract, including testicular abnormalities, whereas other effects include reduced fecundity (i.e., reduced sperm quality and count, levels of testosterone, and embryo implantation) (Carlson et al. 1992; Dallinga et al. 2002; Pflieger-Bruss and Schill 2000; Swan et al. 2000). Studies using organochlorines, which are found in the diet of Inuit tribes from the Arctic (Dewaillly et al. 1993), have demonstrated decreased motility and diminished viability of sperm within 2 hr of exposure. If exposure occurred during in vitro fertilization, the investigators observed diminished sperm penetration of the oocyte and slower development to blastocyst rates (Campagna et al. 2002).

Likewise, decreases in female fertility have been observed on exposure to environmental air pollution (Mohallem et al. 2005). Female mice exposed to ambient air for 4 months displayed higher incidences of implantation failure and decreases in live-born pups. These differences in fertility were significant if exposures to ambient air pollution began at an early age (i.e., 10 days after birth). Cumulatively, these studies suggest that pollutants affect implantation and reduce fertility by damaging the germline cells.

**Intrinsic properties of the host.** The health impact due to various environmental exposures is highly variable and depends on multiple parameters both intrinsic and extrinsic to the individual. For example, season and climate have been shown to have a potential role in the health impacts associated with ozone (Guo et al. 1999; Lee et al. 2003). It is also plausible that certain populations are more susceptible to adverse health effects on exposure such as the elderly, the developing fetus, or those with pre-existing disease states. Consequently, several investigators are focusing on the impact of exposure in groups of specific ages or with specific pre-existing diseases (Zanobetti et al. 2002; Zanobetti et al. 2000). It is also clear that genotypic polymorphisms exist among individuals within populations and that genetic background is an important susceptibility factor for adverse health effects on exposure to emissions. Some of the genes implicated in adverse health effects on exposure to ozone and sulfate-associated PM are toll-like receptor 4 (Kleeberger et al. 2000), proinflammatory cytokines (Ohnatsuka et al. 2000), and tumor necrosis factor-α (Yang et al. 2005). Linkage analysis data are strongly supported by experimental data demonstrating a role for these candidate genes in ozone and PM susceptibility (Choi et al. 2005; Kleeberger et al. 2000). In particular, a recent study demonstrated that variability in genes encoding enzymes that are members of the xenobiotic defense pathways determines lung cancer risk from indoor coal combustion emissions (Lan et al. 2000). Null genotypes for glutathione S-transferase M1 were associated with increased risk of lung cancer (2.3-fold increase).

**Outlook**
Understanding the relationships between the origins, mechanisms of formation, nature of emissions, biological availability, and biological activity of toxic combustion by-products will require well-coordinated interdisciplinary research by biomedical, biological, chemical, and engineering researchers. Furthermore, establishing the nature of this link will require
each group of researchers to go beyond their traditionally narrow veins of research and to integrate their understanding into a new field of research that could be referred to as health effects engineering science.

Inhalation of airborne fine and ultrafine PM has been identified as a major route of exposure to toxic combustion by-products; research should address this poorly understood area. From a combustion and environmental chemistry perspective, key research issues include the following:

- What are the properties change en route?
- What effect does exposure have on predisposition to disease states or on disease progression?
- What are the specific cellular and molecular mechanisms associated with airborne exposures?

### References

Abe Y, Kawakami M, Kuroki M, Yamamoto T, Fujii M, Kobayashi H, et al. 1993. Transient rise in serum interleukin-8 concentration during acute myocardial infarction. Br Heart J 69:324–326.

Addink R, Bakker WCM, Olie K. 1995. Influence of HCl and Cl2 on the formation of polychlorinated dibenzo-p-dioxins/dibenzofurans in a carbon/ffly ash mixture. Environ Sci Technol 29:2055–2058.

Atwood ER. 1996. Formation of PCDD/DF in municipal solid waste incinerators: laboratory and modeling studies. J Hazard Mater 47:137–161.

Atwood ER, Konduri RKNV, Lin C, Milligan MS. 1992. Rapid formation of PCDD/F in municipal solid waste incinerators. Environ Health Perspect 101:1195–1198.

Becker S, Szukup JM. 1998. Decreased cd11b expression, phagocytosis, and oxidative burst in urban particulate pollution-exposed human monocytes and alveolar macrophages. J Toxicol Environ Health A 56:455–477.

Berko F, Lessing RA. 1997. The phenotypic cellular UV spectrum and kinetics of gas-phase reactions with itself and with oxygen. Chem Phys Lett 279:289–296.

Bloch WN Jr, Lewis TR, Busch KA, Orthofer JG, Stara JF. 1972. Cardiovascular effects of polychlorinated dibenzo-p-dioxins. Experientia 28:298–303.

Burnett RT, Brook J, Dann T, Deloia C, Philip O, Calakas S, et al. 2000. Association between particulate- and gas-phase components of urban air pollution and daily mortality in eight Canadian cities. Environ Health Perspect 112:suppl 4:15–39.

Burnett RT, Dales R, Krewski D, Vincent R, Dann T, Brook J. 1995. Associations between ambient particle sulfate and admissions to hospital for cardiac and respiratory diseases. Am J Epidemiol 142:15–22.

Calderon-Garcidueñas L, Gambling TM, Acuna H, Garcia R, Osanya N, Monroy S, et al. 2001. Caines as sentinel species for assessing chlorination exposure: air pollution. 1: Cardiac physiology. Toxicon 36:136–367.

Campagna C, Guillermelle C, Paradis R, Sauvage N, Saudry F, et al. 1992. Evidence for decreasing quality of semen during past 50 years. BMJ 305:609–613.

Carter JD, Ghio AJ, Samet JM, Devlin RB. 1997. Cytokine production by human airway epithelial cells after exposure to an air pollution particle is metal-dependent. Toxicol Appl Phamacol 146:180–188.

Cataló WJ, Kennedy CH, Henk W, Barker SA, Grace SC, Penn A. 2001. Combustion products of 1,3-butadiene are cytotoxic and genotoxic to human bronchial epithelial cells. Environ Health Perspect 109:220–226.

Cho HY, Jedlicka AE, Clarke R, Kleeberger SR. 2005. Role of toll-like receptor-4 in genetic susceptibility to lung injury induced by residual oil fly ash. Physiol Genom 22:108–117.

Comprehensive review of polychlorinated dibenzo-p-dioxin, and dibenzofuran in heterogeneous combustion reactions of acetylene. Environ Sci Technol 30:998–1008.

Fed GJ, Hayashi S, Hogg JC, Vincent R, Van Eeden SF. 2001. Particulate matter induces cytokine expression in human bronchial epithelial cells. Am J Respir Cell Mol Biol 25:265–271.

Guo YL, Lin YC, Sung FC, Huang SL, Ko YC, Lai JS, et al. 1999. Mechanistic aspects of the de-novo-synthesis of PCDD/PCDF on model fly ash. Arch Environ Health 25:193–194.

Guo YL, Lin YC, Sung FC, Huang SL, Lai JS, et al. 1999. Climate, traffic-related air pollutants, and asthma prevalence in middle-school children in Taiwan. Environ Health Perspect 107:1001–1008.

Henderson RF, Fickrell JA, Jones RK, Sun JD, Benson JM, Mauderly JL. 1998. Response of rodents to inhaling diluted diesel exhaust: biochemical and cytological changes in bronchoalveolar lavage fluid and in lung tissue. Fundam Appl Toxicol 39:1546–1557.

Huang H, Guevens A. 1996. De novo synthesis of polychlorinated dibenzo-p-dioxin and dibenzofuran from atmospheric combustion products. Environ Sci Technol 29:195–201.

Hiura TS, Kasubowsky M, IP, L N, Nel AE. 1999. Chemicals in diesel exhaust particles generate reactive oxygen radicals and induce apoptosis in macrophages. J Immunol 162:5582–5589.

Houk BV, Demarinis DM, Watts RR, Levey J. 1990. Toxicological evaluation of hazardous effluents and emissions using genetic bioassays. Abstr Pap Am Chem Soc 200:23-ENVR.

Huang H, Guevens A. 1996. De novo synthesis of polychlorinated dibenzo-p-dioxin and dibenzofuran from atmospheric combustion products. Environ Sci Technol 29:195–201.

Kobayashi H, et al. 1993. Transient rise in serum interleukin-8 concentration during acute myocardial infarction. Br Heart J 69:324–326.
Ingram DJE, Tapley JG, Jackson R, Bond RL, Murnaghan AR. 1954. Paramagnetic resonance in carbonaceous solids. Nature 174:797–798.

Kaestner KH. 2006. Free radicals and inhaled oxidants. Am J Respir Cell Mol Biol 35:604–612.

Koskela NN, Airaksinen MS, Tuukkanen E. 2003. Interaction between respiratory syncytial virus and particulate matter in guinea pig alveolar macrophages. Am J Respir Cell Mol Biol 28:548–554.

Koerpel AT, Oepkes D, Van Den Heuvel M, Van Schijndel RMJ, Van Es HH, et al. 2000. Synergy between rhinovirus infection and oxidant exposure enhances inflammatory response in untracheally instilled respiratory epithelial cells in vivo. Environ Res 87:5–12.

Koski T, Aalto IMO, Kallio KM. 2000. Interactions between inhaled oxidants and alveolar macrophages. Am J Respir Crit Care Med 161:1555–1562.

Koski T, Aalto IMO, Kallio KM, Liimatainen A. 2000. Synergy between rhinovirus and inhaled oxidants in the respiratory epithelium: a systematic review. J Toxicol Environ Health A 65:1435–1453.

Koski T, Aalto IMO, Kallio KM, Liimatainen A. 2000. Synergy between rhinovirus and inhaled oxidants in the respiratory epithelium: a systematic review. J Toxicol Environ Health A 65:1435–1453.