ABSTRACT
Despite the great medical advances, cardiovascular disease remains one of the major causes of mortality worldwide, especially in industrialized countries. It develops as a result of countless complex interactions between genetic factors such as those related to age, sex, family history, weight, and post-menopausal status in women; and to environment-related factors such as cigarette smoking, alcohol use, eating habits, physical activity, and others. For more than a decade, several epidemiological studies have demonstrated the existence of a consistent association between air pollution and increased risk for cardiovascular events, that is, not only cardiovascular death, but also acute myocardial infarction and arrhythmias. Experimental studies in different animal species, observational studies in humans, as well as in vitro cellular and acellular models attempt to elucidate the probable biological mechanisms that lend plausibility to these associations, but they fail to do it clearly, since the severity and progression of cardiovascular disease are much more affected than is its induction. However, some effects resulting from the exposure to different air pollutants have been evidenced and the most significant of which involve pulmonary and systemic inflammatory response, blood clotting disorders, promotion and potentiation of the atherosclerotic process, and cardiac autonomic dysfunction.

Keywords: Air pollution/adverse effects; Cardiovascular diseases/etiology

INTRODUCTION
Since the first half of the 20th century, air pollution has been a serious problem in industrialized urban centers. Episodes of excessive air pollution caused increased number of deaths in some cities of Europe and the United States, which made the world’s scientific community turn their eyes to this issue, and brought about questions on the adverse effects on human health, thus leading to the search for answers. One of the first and well-documented episodes occurred in a small industrial valley of Meuse River, Belgium\(^1\). From December 1 to 5, 1930, heavy smog caused more than 60 deaths, a mortality rate ten-fold higher than normal, and hundreds of people developed respiratory diseases frequently accompanied by worsening of heart failure.

In October 1948, there was the Donora event\(^2\), also an industrial valley in Pennsylvania, where combustion by-products from local industries remained over the town due to the occurrence of temperature inversions that hindered their dispersion, and caused approximately 14,000 residents to experience some type of clinical sign; 400 hospitalizations and 20 deaths were recorded. However, the most dramatic event occurred in London, England\(^3\). In the winter of 1952, the impossibility of dispersion of a stagnant air mass with high concentrations of sulfur dioxide and ambient particulate that lasted four
to five days, resulted in approximately 4,000 deaths, and although respiratory causes had been accounted for the relative increase in mortality, the number of deaths from cardiovascular causes was quite significant, from then on, it was clear that both lung and heart are affected by pollution.

Aware of the London event, the US Congress, in 1955, released approximately five million dollars for studies on the health and economic impact of air pollution. In Europe, in 1956, the English Parliament assigned to the local authorities the task of controlling the areas at greater risk of accumulation of black smoke emitted by the houses, forcing the replacement of the charcoal system for electricity, gas, or diesel oil. Later, the “Clean Air Acts” was implemented, extending the air pollutant emission control to industries\(^{(3)}\).

Since then, the evidences of the human health impact of pollution have been obtained through a variety of epidemiological studies (cross-sectional, cohort, observational, case-control studies) conducted in different countries, proving a strong association with increased cardiorespiratory morbidity and mortality\(^{(4-6)}\), especially in groups of susceptible individuals such as the elderly and children\(^{(7-8)}\), particularly when associated with chronic exposure\(^{(6,9)}\). More recently, persistence of these associations with low pollutant concentrations and short-term exposure has been demonstrated\(^{(10-11)}\). This knowledge has influenced the improvement of control actions, especially in developed countries.

### CLASSIFICATION OF AIR POLLUTANTS

Technological advances have allowed the recognition of urban and non-urban air pollution as a complex mixture of components with different physical and chemical characteristics, namely gases, liquids, and particulate material, derived from a variety of sources; and its classification according to the chemical composition, particle size, emitting source, and mode of release into the indoor and outdoor environments (Chart 1).

Primary pollutants are those emitted directly into the atmosphere, whereas secondary pollutants are those resulting from chemical reactions with other pollutants or atmospheric gases. This distinction is important because reducing the precursor does not necessarily lead to a proportional reduction in the secondary pollutant. For instance, ozone levels may paradoxically increase when nitrogen oxide emission is reduced.

In the urban atmosphere, the particulate material (PM) is divided into three categories according to the particle size, and it differs as to the origin, chemical composition and physical characteristics. These categories are as follows:

- **coarse particulate**: particles with aerodynamic diameter from 2.5 to 10 \(\mu\)m. They are mechanically produced by the break-up of larger particles from industrial activity; in roads, they come from the soil (road dust, for instance, brake and tire dust); construction debris; biological material, such as pollen and bacteria; agricultural processes;
- **fine particulate**, with aerodynamic diameter lower than 2.5 \(\mu\)m. It is usually formed from the combustion process including motor vehicles, wood burning, plantation or forest burning, and some industrial processes. The major precursor gases are sulfur dioxide (SO\(_2\)), nitrogen oxides (NO\(_x\)), ammonia (NH\(_3\)), and volatile organic compounds;
- **ultrafine particles**: with aerodynamic diameter lower than 0.1 \(\mu\)m. They are produced by metal condensation or high-temperature vaporization of organic compounds (fossil fuel combustion). They are usually composed of nitrate, sulfate, carbon, ammonia, and metal traces;
- **total suspended particulate (TSP)**: represents the pool of several particulate material usually exceeding 10 \(\mu\)m in diameter, sometimes reaching up to 50 \(\mu\)m in diameter.

The particles in the inhaled air selectively deposit in the respiratory tract according to their size, so that the coarse particles (PM\(_{2.5}\)) are able to penetrate the upper airways, whereas only the fine (PM\(_{10}\)) and ultrafine particulate are able to penetrate up to the pulmonary alveoli. To make the idea of the size of different particulate matters clearer, Brook et al.\(^{(12)}\) compared these pollutants to infectious agents and cells, and showed that TSP has dimensions ranging from the

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**Chart 1. Classification of air pollutants**

<table>
<thead>
<tr>
<th><strong>A. Regarding the mode of emission into the atmosphere</strong></th>
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<tbody>
<tr>
<td>1. Primary pollutants: pollutants emitted directly into the atmosphere, for example: sulfur dioxide (SO(_2)), some types of nitrogen oxide (NO(_x)), carbon monoxide (CO), and particulate material.</td>
</tr>
<tr>
<td>2. Secondary pollutants: pollutants that are formed in the atmosphere as a result of chemical reactions with other pollutants and gases, such as ozone (O(_3)).</td>
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<tr>
<th><strong>B. Regarding the origin (indoor or outdoor environment)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Indoor pollutants</td>
</tr>
<tr>
<td>(a) Sources: combustion of products such as wood, in cooking activities; particle resuspension; building supplies; air conditioner; tobacco smoke; heating; and biological agents.</td>
</tr>
<tr>
<td>(b) Products: CO, carbon dioxide (CO(_2)), aldehydes, alcohol, ketones, alkalis, microbial agents, and organic dusts.</td>
</tr>
<tr>
<td>2. Outdoor pollutants</td>
</tr>
<tr>
<td>(a) Sources: industrial, commercial, urban, regional, natural, agricultural.</td>
</tr>
<tr>
<td>(b) Products: SO(_2), NO(_x), PM, benzene.</td>
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</tbody>
</table>

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<tr>
<th><strong>C. Regarding the type of pollutant</strong></th>
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<tbody>
<tr>
<td>1. Gaseous: SO(_2), NO(_x), CO, benzene, aldehydes, 1,3-butadiene</td>
</tr>
<tr>
<td>2. Particulate: Total Suspended Particulate (TSP), coarse particulate material (PM(<em>{2.5})), fine particulate material (PM(</em>{10})), and ultrafine particles (UFP &lt; 0.1 (\mu)m)</td>
</tr>
</tbody>
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\(\text{PM}_{10}\): 10 \(\mu\)m in diameter, sometimes exceeding 10 \(\mu\)m in diameter.
thickness of a hair thread to those of a cell, that is, below vision limit (between 5 and 10 µm). PM$_{2.5}$ is comparable to the size of bacteria (1 µm), whereas ultrafine particles have dimensions close to those of viruses (0.1 µm), or even molecules (0.01 µm).

As from the 1960’s, the United States of America established air quality standards specifying the pollutants that would be controlled. To make this control effective, the US Environmental Protection Agency – EPA was created, with powers to determine the technical criteria for the control of substances considered toxic, based on their health effects. The following substances were selected: ozone (O$_3$), sulfur dioxide (SO$_2$), nitrogen dioxide (NO$_2$), carbon monoxide (CO), and inhalable particles – PM$_{10}$. In 2006, the control of PM$_{2.5}$ atmospheric levels was included (Chart 2). Nowadays, it is also possible to follow the environmental levels of different pollutants in several US regions using data constantly updated and made available by the US EPA, via website.

In Brazil, governmental authorities’ concern over the issues related to air pollution is relatively recent. In 1990, the National Environment Council (Conselho Nacional de Meio Ambiente, CONAMA) adopted air quality standards based on the US Environmental Protection Agency, with less strict criteria for primary standards, and did not include PM$_{2.5}$ (13).

**Chart 2. Air quality standards for the major pollutants according to the US Environmental Protection Agency (EPA)**

<table>
<thead>
<tr>
<th>Pollutants</th>
<th>Primary standards</th>
<th>Averaging time</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM$_{10}$</td>
<td>50 µg/m$^3$</td>
<td>Annual arithmetic mean</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>15 µg/m$^3$</td>
<td>Limit level for 24 hours</td>
</tr>
<tr>
<td>PM$_{2.5}$</td>
<td>35 µg/m$^3$</td>
<td>Limit level for 24 hours</td>
</tr>
<tr>
<td>O$_3$</td>
<td>0.12 ppm (225 µg/m$^3$)</td>
<td>Maximum hourly average</td>
</tr>
<tr>
<td>SO$_2$</td>
<td>0.03 ppm (80 µg/m$^3$)</td>
<td>Annual arithmetic mean</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>9 ppm (10 µg/m$^3$)</td>
<td>Maximum 8-hour average</td>
</tr>
<tr>
<td>CO</td>
<td>35 ppm (40 µg/m$^3$)</td>
<td>Maximum level in 1 hour</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>0.053 ppm (100 µg/m$^3$)</td>
<td>Annual arithmetic mean</td>
</tr>
</tbody>
</table>

Source: http://www.epa.gov. Final Revisions to the National Ambient Air Quality Standards for Particle Pollution (Particulate Matter). Updated in September 21, 2006

**EVIDENCES OF CARDIOVASCULAR ADVERSE EFFECTS PRODUCED BY DIFFERENT AIR POLLUTANTS**

Increased rates of hospital admissions and daily mortality for cardiovascular diseases related to the air pollutant mass have been demonstrated by several authors worldwide. In those with chronic lung and heart diseases, these rates are even higher (14).

In 1994, Schwartz showed that air pollution is primarily associated with non-hospital deaths represented by sudden deaths, many of which for arrhythmia and myocardial infarction (15), and verified an increase by 1.06 (95% CI = 1.03-1.10) in the relative risk for mortality for each 100 µg/m$^3$ increase in TSP levels, and even higher relative risks for cardiovascular disease (1.08) and for the elderly population (1.09) (16).

The adverse effects of high levels of fine inhalable particles, the PM$_{2.5}$, were the object of the Harvard Six Cities Study, which involved six US cities and showed a clear association with hospital admissions of cardiovascular causes and, to a lesser extent, with chronic obstructive pulmonary disease (COPD) (17). These findings were also confirmed for the coarse particulate, the PM$_{10}$, in the National Morbidity, Mortality and Air Pollution Study (NMMAPS), the largest longitudinal study ever conducted, involving a variety of environments in 90 different American cities, and which resulted in positively associated high PM$_{10}$ levels with cardiorespiratory mortality and hospital admissions for pneumonia, worsening of cardiovascular diseases and of chronic obstructive pulmonary disease (COPD) in patients older than 65 years (4).

Five thousand individuals living close to heavy-traffic roads in the Netherlands were followed up for eight years, and a higher association with cardiorespiratory mortality was found for this group in comparison with individuals who live in regions with less environmental pollution (9).

Cardiovascular ischemic complications such as the activation of the atherosclerotic process, exacerbation of cardiac symptoms due to arrhythmias, increased heart rate, decreased heart rate variability, significant conditions for the risk of sudden death, and worsening of heart failure were related to acute increases in pollutant concentrations (13, 18-20). These findings suggest the possibility of the occurrence of the cardiac autonomic control, being affected due to the pollutant (fine particulate) toxicity directly in the heart (21).

More recently, increased risk for mortality and increased hospital admissions, both for stroke, were demonstrated and related to chronic and acute exposures to air pollution (22).

Another key issue is the strong association between the particulate material and the levels of gaseous pollutants (CO, NO$_2$, SO$_2$, and O$_3$). A study including 29 European cities (10) concluded that in the cities with the highest NO$_3$ levels, the positive association for overall mortality and PM$_{10}$ was significantly higher. The same has been demonstrated for cardiovascular mortality (20).

In Brazil, the Experimental Air Pollution Laboratory of University of São Paulo School of Medicine, headed by Professor Paulo Hilário Nascimento Saldiva, who is the pioneer in the study on the human health impact of air pollution, and has conducted epidemiological studies, experimental studies in different animal species, and observational studies for more than three decades,
Due to the variability of the chemical profiles of the ambient particles, the most important components have not been positively determined, although the most common constituents are known. Experimental studies with rats suggest that adverse biological responses to PM are more related to the emitting-source-dependent particulate composition and to weather conditions, than to the particle mass\(^{27-29}\).

Many transition metals (iron, copper, vanadium, zinc, chrome, cobalt, cadmium and nickel) have been suggested as potential agents inducing the inflammatory response to the particulate matter, since they more constantly associate with smaller particles and exhibit a great oxidative potential\(^{27}\). The free radicals generated in the oxidative process play a key role in the pathogenesis of many pulmonary diseases and, more recently, the cardiac oxidative effect has been considered by many authors as a risk factor for the occurrence of dysfunction of the cardiac autonomic regulation and, consequently, for the occurrence of arrhythmias, changes in the heart rate variability, vasoconstriction, arterial thrombosis and heart failure\(^{18-20,29}\). Studies with rat models have demonstrated increased oxidative stress in the heart after particle inhalation\(^{24}\).

Although a considerable amount of data relates the coarse and fine particulate to adverse health effects, very little is known about the ultrafine particles (< 0.1 \(\mu\)m), which are more abundant, potentially more toxic, and, to date, with no standardization for the control of their levels in the ambient air. More recently, in an attempt to explain the rapid adverse effects seen in the cardiovascular system, such as acute myocardial infarction, a few hours following exposure to pollution\(^{11,18-19}\), many authors have postulated the possibility of ultrafine particles being able to rapidly cross the pulmonary epithelial barrier toward the circulation, thus leading to direct effects on the cardiovascular system and blood\(^{22}\), with higher toxicity than PM\(_{2.5}\) and PM\(_{10}\) because they contain higher concentrations of transition metals and reductant chemicals.

However, despite all the evidences shown in countless studies, the exact biological mechanism or mechanisms responsible for the adverse health effects have not been fully identified. Factors depending on the recipient, such as genetic and comorbidity factors, as well as the composition and aerodynamic characteristics of the particles, play an important role in the pathogenesis of particle-induced inflammation. The possible biological mechanisms associating air pollution with heart disease are listed in Chart 3, and involve the direct effect on the cardiovascular system and blood, and/or indirect effects mediated by pulmonary oxidative stress as well as by pulmonary and systemic inflammatory response.
CONCLUSIONS

To date, the literature on the analysis of the biological effects of the exposure to air pollution has strongly suggested the existence of a cardiac toxicity mechanism. Even without fully understanding the stages that involve this process, this hypothesis seems to corroborate the unquestionable epidemiological findings that relate air pollution to increased cardiovascular morbidity and mortality. Surprisingly, little attention has been given to environmental factors that could influence inflammation levels, oxidative stress, and cardiac autonomic regulation, thus increasing the cardiovascular risk. Therefore, the identification of the toxicity of several air pollutant constituents (both chemical and biological), and of the basic mechanisms (local and systemic mediators, cellular and molecular signaling, pathways, and the toxin-specific metabolism) affecting atherogenesis, vascular function, heart rate variability, and induction of thrombosis is worth being further investigated through basic research.

Also important is that the initiative of PM$_{2.5}$ level reduction promoted by the US Environmental Protection Agency in 2006 be widely adopted: that primary standards for the control of ultrafine particles be established, both in the 24 hours and annual means, since the latter are considered the most hazardous for the cardiovascular system and are, up to the moment, free of any type of control action; that pollutant levels considered “safe” to be established for individuals free of any type of control action; and, pollutant levels belonging to cardiovascular event risk groups; and, mainly, that governmental authorities be aware of the need for improving urban vehicular traffic conditions.

REFERENCES

3. Quality of Air Mean Quality of Life. Revisions to the National Ambient Air Quality Standards for Particle Pollution (Particulate Matter). [Internet]. [cited 2006 Sep 21]. Available from: http://www.epa.gov


