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EDITORIAL

Air Pollution in the Metropolis: A Lurking Health Trap

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ABSTRACT

Strong evidence has accumulated from epidemiological and observational studies for a close association between several different air pollutants and adverse health effects, particularly for the residents of metropolitan areas. Although our understanding of the pathophysiological mechanisms involved remains incomplete, there are abundant data which link short-term exposure to air pollution, due to high concentrations of particulate and gaseous matter, toxic metals and aldehydes, with a significant increase in acute cardiopulmonary mortality, particularly in certain high-risk subsets of the population and with an acute increase in hospital admissions for cardiovascular and pulmonary diseases. Furthermore, there is also convincing evidence that prolonged exposure to elevated levels of air pollutants is responsible for chronic ill effects that significantly reduce overall life expectancy. Thus, it is of paramount importance for regulatory agencies to force the implementation of relevant regulations and quality standards in order to protect the health of the population at large. Specific guidelines should also apply for activity restriction for vulnerable and high-risk persons, such as the very young and the elderly, and those with known cardiopulmonary disease or diabetes mellitus.

KEY WORDS: *air pollution; smog; particulate matter; gaseous pollutants; toxic metals; aldehydes; cardiovascular disease; asthma; cardiopulmonary disease*

ABBREVIATIONS
CVD = cardiovascular disease
CO = carbon monoxide
DNA = deoxyribonucleic acid
EPA = Environmental Protection Agency
EU = European Union
IMT = intima-medial thickness
MI = myocardial infarction
NO_2 = nitrogen dioxide
O_3 = ozone
PM = particulate matter
SO_2 = sulfur dioxide
WHO = World Health Organization

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INTRODUCTION

According with the 2013 Update of Heart Disease and Stroke Statistics of the American Heart Association, mortality data showed that cardiovascular disease (CVD) as the listed underlying cause of death accounted for 32.3% of all deaths in 2009, or ≈1 of every 3 deaths in the United States.[1] CVD any-mentions constituted 54.6% of all deaths that year. On average, >2150 Americans die of CVD each day, an average of 1 death every 40 seconds. CVD currently claims more lives each year than cancer and chronic lower respiratory disease combined. More importantly, CVD is rapidly becoming a major cause of death worldwide, and current projections indicate that between 1990 and 2020, the proportion of worldwide deaths from CVD will increase from 28.9% to 36.3%.[2] Traditional risk factors, comprising hypercholesterolemia, hypertension, smoking and diabetes as modifiable and age, gender and heredity as nonmodifiable risk factors, have been associated with the development of CVD, but a considerable percentage of patients afflicted by CVD have no established risk. Mechanisms of thrombosis and inflammation have been recently added to the predisposing risk factors,[3] however, we are still left with important determinants of CVD that currently remain

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unknown.[2] Furthermore, the development of CVD appears to be the result of an intricate interplay among genetic and environmental factors.[4,5] With regards to the influence of the environment, it is only recently that the significant contribution of ambient pollutants to the development of CVD has begun to be appreciated.[5] The cardiovascular, lung and other organ toxicity of pollutant exposure has been increasingly recognized.

PARTICULATE MATTER

In December 1952, a smog disaster occurred in London, with a subsequent substantial increase in mortality associated with the increase in air pollution.[6] There was an alarming increase in cardiovascular and respiratory deaths. The increase was greatest in the elderly. Hospital admissions were increased for both respiratory and cardiovascular diseases. In India, the worst civilian pollution crisis was the 1984 Bhopal Disaster.[7] Leaked industrial vapors from the Union Carbide factory killed more than 25,000 people and estimates for ensuing injuries vary anywhere from 150,000 to 500,000. To date, a plethora of studies have linked air pollution with daily mortality.[5] Thus, the role of environmental pollutants in producing heart, lung and other organ diseases has begun to emerge and to be seriously discussed as a new risk factor.[2,4,5,8-12]

Common sources of air pollution include particulate matter (PM), ozone, nitrogen dioxide (NO_2), and sulfur dioxide (SO_2).[5] Both indoor and outdoor air pollution have caused approximately 3.3 million deaths worldwide. Children aged <5 years that live in developing countries are deemed the most vulnerable group. According to the World Health Organization (WHO), 2.4 million people die each year from causes directly attributable to air pollution. Epidemiological studies suggest that more than 500,000 Americans die each year from cardiopulmonary disease related to breathing fine particle air pollutants. Worldwide more deaths per year are linked to air pollution than to motor vehicle accidents. A 2005 study by the European Commission calculated that air pollution reduces life expectancy by an average of ~9 months across the European Union (http://en.wikipedia.org/wiki/Air_pollutants).[13] Causes of deaths mainly relate to cardiopulmonary diseases.

The high susceptibility of cardiovascular tissues to environmental pollutants is clearly underscored by a report indicating that the hearts of rats exposed to environmental *tobacco smoke* garner as many DNA adducts as the lung.[14] However, while DNA lesions in the lung diminished upon discontinuation of exposure, no significant DNA repair could be noted in the myocardium, indicating a higher susceptibility of the heart to deleterious effects of environmental toxins.[14] There is also strong evidence that exposure to ambient air particulate matter produces oxidative stress-induced DNA damage. Related biomarkers and individual exposure monitoring may be useful tools for risk stratification.[15]

Besides tobacco smoke, other pollutants (particulate and gaseous matter, metals, aldehydes) have also been found to affect cardiovascular tissues. The most convincing data come from studies examining the effects of ambient particulate matter on heart disease and CVD mortality. These data indicate a link between the levels of air particulates and CVD, implying that pollutants can adversely affect the cardiovascular system.

It has been demonstrated consistently that both *respirable particles* (<10 μm in diameter; particulate matter-PM_{10}) and *fine particles* that reach the deep lung (<2.5 μm; $PM_{2.5}$) increase mortality.[2,5] The estimation is that each 10 $\mu g/m^3$ elevation in the PM_{10} level increases the relative rate of death from all causes by 0.4–1% and each 10 $\mu g/m^3$ increase in long-term average $PM_{2.5}$ is associated with a 4% increased risk of all-cause mortality and a 6% increased risk of cardiopulmonary mortality. Both PM_{10} and $PM_{2.5}$ can reach the alveoli, while the *ultrafine particles* (<0.1 μm in diameter) can also pass into the systemic circulation and cause extrapulmonary toxicity.

Several studies have shown that increased PM_{10} and $PM_{2.5}$ concentrations are associated with an increase in cardiovascular hospital admissions due to both ischemic heart disease and congestive heart failure.[2] Exposure to elevated $PM_{2.5}$ levels have also been linked to a temporal (within a few hours and 1 day) triggering of acute myocardial infarction (MI).[16] There are reports of air pollution causing an increase in heart rate, reduction of heart rate variability and an increase in the incidence of cardiac arrhythmias.[17,18] A likely explanation may be related to a cumulative multifactorial effect of particulates on hemostatic, vasoconstrictive, and autonomic factors leading to increased electrical instability and triggering of acute coronary syndromes in a susceptible population.[2] In addition to triggering of acute events, PM exposure can also induce chronic and sustained cardiovascular damage, such as an increase in atherosclerosis and vulnerable atherosclerotic plaque formation, chronic inflammation and thrombogenesis, all contributing to increased cardiovascular mortality (Fig. 1).[4,5,19]

Systemic inflammation markers (interleukin 6 /IL-6, fibrinogen, and C-reactive protein) were correlated with concurrent levels of air pollution in a prospective longitudinal study of 1,003 MI survivors, performed in 6 European cities (2003 – 2004).[19] The investigators collected hourly data on particle number concentrations, mass concentrations of particulate matter (PM) <10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$), gaseous pollutants, and meteorological data at central monitoring sites in each city. Pooled results showed an increase in IL-6 when particle number concentrations were elevated 12–17 h before blood withdrawal (% change of geometric mean, 2.7). Five-day cumulative exposure to PM_{10} was associated with increased fibrinogen concentrations (% change of arithmetic mean, 0.6). Results remained stable for smokers, diabetics, and patients with heart failure. The authors concluded that their results might provide a link between air pollution and adverse cardiac events, as they observed an immediate thrombo-inflammatory

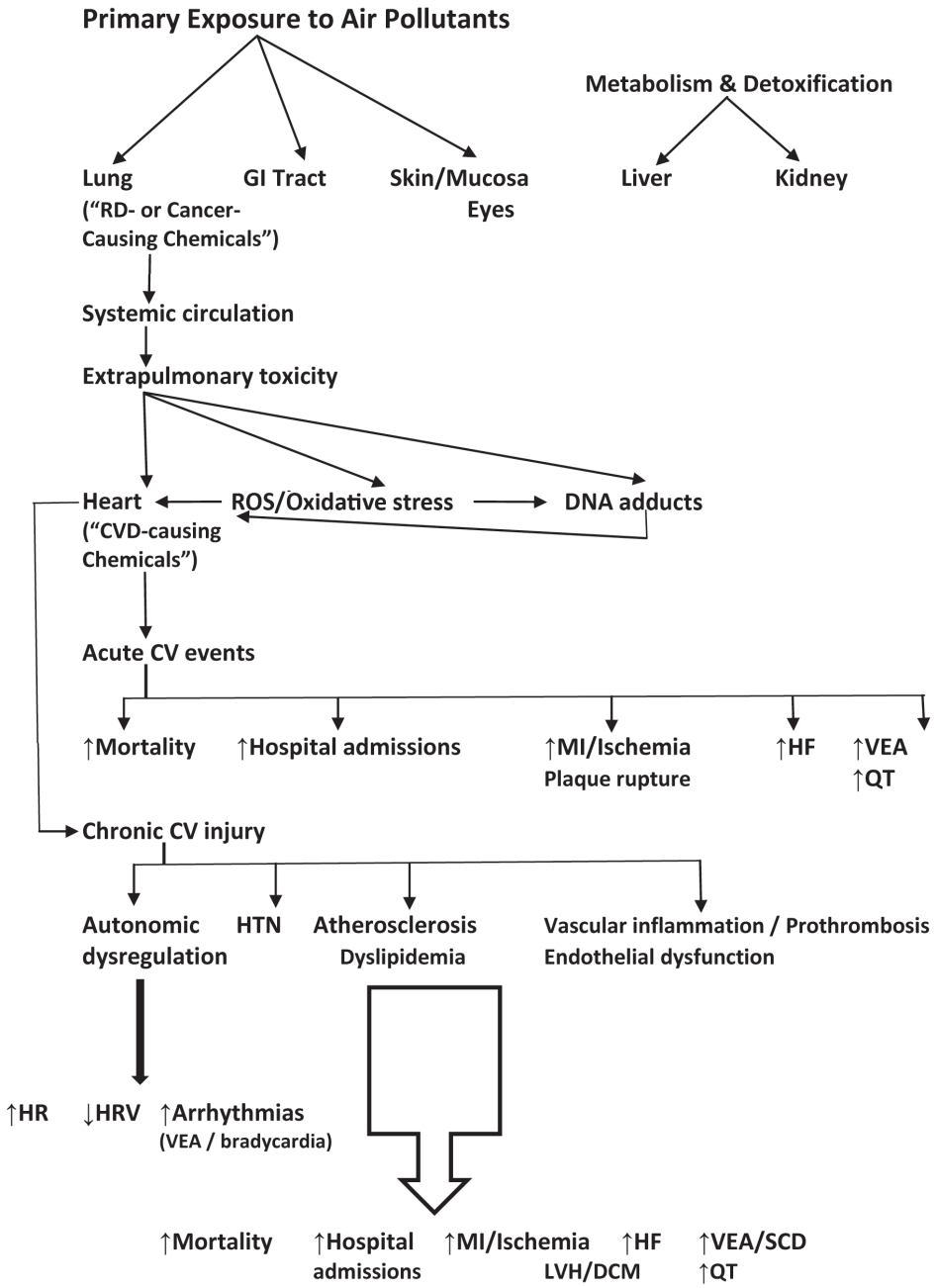

FIGURE 1. Possible pathophysiology of air-pollutant ill effects (focus on CVD). CV = cardiovascular; CVD = cardiovascular disease; DCM = dilated cardiomyopathy; GI = gastrointestinal; HF = heart failure; HR = heart rate; HRV = heart rate variability; HTN = hypertension; LVH = left ventricular hypertrophy; MI = myocardial infarction; RD = respiratory disease; ROS = reactive oxygen species; SCD = sudden cardiac death; VEA = ventricular ectopic activity.

response to particle number concentrations as reflected by increased IL-6 and fibrinogen levels.[19]

A study examined the association between air pollution and cardiovascular hospital admissions for persons aged 65 years and older in the Detroit, Michigan, metropolitan area during the years 1986–1989.[8] Particulate matter with an aerodiameter of ≤10 μm (PM_{10}) was associated with daily admissions for ischemic heart disease (relative risk-RR = 1.018, for an interquartile range (32 $\mu g/m^3$) increase in pollution). SO_2, CO, and ozone made no independent contribution to

ischemic heart disease admissions. Both PM_{10} (RR = 1.024) and CO (RR = 1.022, for an interquartile range (1.28 ppm) increase in pollution) showed independent associations with heart failure admissions. [8]

In a prospective cohort study (Multi-Ethnic Study of Atherosclerosis - MESA), investigators examined the associations between the progression of the intima-medial thickness (IMT) of the common carotid artery, as an indicator of atherosclerosis, and long-term $PM_{2.5}$ concentrations among 5,362 participants completing two ultrasound examinations.[20] The authors found that among persons with a mean annual progression of 14 μm/y, 2.5 μg/m^3 higher levels of residential $PM_{2.5}$ during a 2.5-year follow-up period were associated with 5.0 μm/y greater IMT progressions among persons in the same metropolitan area. Although significant associations were not found with IMT progression without adjustment for metropolitan area (0.4 μm/y per 2.5 μg/m^3), all of the 6 areas showed positive associations. Greater reductions in $PM_{2.5}$ over follow-up for a fixed baseline $PM_{2.5}$ were also associated with slowed IMT progression (22.8 μm/y per 1 μg/m^3 reduction). The authors concluded that higher long-term $PM_{2.5}$ concentrations are associated with accelerated atherosclerosis as indicated by increased IMT progression and that greater reductions in $PM_{2.5}$ are related to slower IMT progression.[20]

In a study analyzing data obtained from the American Cancer Society, the risk factor data for approximately half a million adults were linked with air pollution data for metropolitan areas throughout the USA and combined with vital status and cause of death data through the year 1998.[10] The results indicated that fine particulate and sulfur oxide–related pollution were associated with all cause, lung cancer, and cardiopulmonary mortality. Each 10-μg/m^3 elevation in fine particulate air pollution was associated with approximately a 4%, 6%, and 8% increased risk of all-cause, cardiopulmonary, and lung cancer mortality, respectively. The authors concluded that long-term exposure to combustion-related fine particulate air pollution is an important environmental risk factor for cardiopulmonary and lung cancer mortality.

OTHER AIR POLLUTANTS

The composition of air particulates is variable and depends on geographic location, season, local climate, presence of industrial compounds, and traffic status. Particulates consist of products of combustion, airborne material from the earth crust, biological material (pollen, bacteria, viruses, and endotoxins), metals (e.g., Fe, V, Ni, Cu, Zn, Pb, Mn), inorganic compounds (oxides, nitrates, and sulfates), polyaromatic hydrocarbons, ethers, amines, nitriles, carboxylic acids and aldehydes .

METAL TOXICITY

Toxic metals contained in the inhaled particulate matter can be transported to many extrapulmonary sites where they may generate reactive oxygen species and induce oxidative stress. Toxicity has been ascribed to vanadium (V), nickel (Ni), copper (Cu), iron (Fe), and zinc (Zn). Chromium (Cr), mercury (Hg), and cadmium (Cd) contained in particulate matter are also deemed toxic as studies show that environmental exposure to these metals results in their deposition in the heart and blood vessels, and that the cardiovascular tissues are significant targets of metal toxicity.[2]

The European community has issued regulations for the emissions of elements of highest concern which include arsenic, cadmium, cobalt, chromium, copper, mercury, manganese, nickel, lead, tin, and thallium. Minute amounts of some of these elements are necessary for humans (cobalt, copper, chromium, manganese, nickel) but toxic in larger concentrations, while others are carcinogenic or toxic to several systems, e.g. central nervous system (manganese, mercury, lead, arsenic), kidneys or liver (mercury, lead, cadmium, copper), skin, bones, or teeth (nickel, cadmium, copper, chromium). Heavy metal pollution most commonly arises from the purification of metals or electroplating. Rubber tires on road surfaces release cadmium, lead and zinc in tiny particulates as dust.

Exposure to cadmium is associated with arterial hypertension and increased aortic resistance.[2] Furthermore, an increase in the incidence of heart failure in Japanese inhabitants of an area polluted by cadmium has been reported.[21] Long-term arsenic exposure is associated with peripheral vascular disease and with an increase in the incidence of ischemic heart disease.[22] Interestingly, marked increases in myocardial trace element concentration have been observed in cases of idiopathic dilated cardiomyopathy.[23] These observations underscore the association of metal pollutants in air particulates or drinking water with CVD risk.

GASEOUS POLLUTANTS

Sulfur and nitrogen oxides are emitted into the atmosphere primarily from the burning of fossil fuels. Thus, air pollutants are produced in the form of particulate matter (sulfates, nitrates) and related gases (nitrogen dioxide-NO_2, sulfur dioxide-SO_2 and nitric acid). Nitrogen oxides also will interact with volatile organic compounds to form ozone (http://www.epa.gov/oar/aqtrnd99/chapter7.pdf).[24] Atmospheric carbon monoxide (CO) and nitrogen dioxide (NO_2) levels have been shown to be associated with hospital admissions for ischemic heart disease and with an increased risk of inducible ischemia at exercise tests in patients with stable coronary artery disease.[2,5] Increased risk of cardiovascular morbidity and mortality on CO or SO_2 exposure has been documented by several epidemiological studies.[25,26] Ozone is an additional copollutant, which can induce pulmonary inflammation and edema, or may confer a bradycardic effect.

A French study (AMI registry - the Toulouse MONICA Project) examined the relationship between short-term expo-

sure to air pollutants and the occurrence of acute MI (1997-1999) in individuals 35 to 64 years of age by measuring hourly concentrations of SO_2, NO_2, and O_3.[27] After adjustment for temperature, relative humidity, and influenza epidemics, the relative risks (RRs) (for an increase of 5 μg/m^3 of O_3 concentration) for acute MI occurrence were significant for the current-day and 1-day-lag measurements (RR, 1.05; P=0.009; and RR, 1.05; 95% CI, 1.01 to 1.09; P=0.007, respectively). Individuals 55 - 64 years of age with no prior history of ischemic heart disease were the most susceptible to develop an acute MI (RR, 1.14). NO_2 and SO_2 exposures were not significantly associated with the occurrence of acute MI. The authors concluded that observational data confirm that short-term ozone exposure within a period of 1 to 2 days is related to acute MI in middle-aged adults without previous heart disease, whereas NO_2 and SO_2 are not.[27]

On the other hand, Bell et al indicated that the gaseous pollutants NO_2 and CO are exhibiting the strongest and most consistent associations with emergency department visits.[11] Similarly, Forastiere et al have examined the association between hospital admissions in Rome related to coronary disease and ambient air pollution including CO, NO_2, PM, and ultrafine particles. They found the strongest associations for CO and ultrafine particle concentrations for fatal and nonfatal hospitalization for acute MI.[12] Finally, during a follow-up of MI survivors in 5 European cities, all pollutants, including CO, NO_2, PM, and ultrafine particles, were associated with increased risk of hospital readmissions.[9]

ALDEHYDES

Several aldehydes such as crotonaldehyde, glyoxal, glycoaldehyde, and hydroxybenzaldehde are important constituents of $PM_{2.5}$, and are considered responsible for mediating cardiotoxicity. Other volatile aldehydes may be PM copollutants.

Aldehydes are present in high concentrations in automobile exhaust and smog and are generated during combustion of organic material in any form (coal, wood, paper, or cotton). They constitute 1 - 2% of the volatiles generated from automobile exhaust and the burning of fossil fuels. Cigarette smoke contains 50–70 parts/million acrolein, and 0.04– 2.2 parts/million acrolein has been detected near petrochemical plants. In addition, acrolein and related aldehydes are also present in high abundance in several food substances, and their concentration is particularly high in fried foods and reheated oils. With the exception of metals, aldehydes are the major toxic substances in drinking water. Over 36 different aldehydes are found in drinking water, of which acrolein and endrin have been classified as the two highest priority pollutants.

Strong evidence suggests that aldehydes may confer adverse cardiovascular effects.[2] Direct exposure to high concentrations of unsaturated aldehydes is cardiotoxic. They may be arrhythmogenic by causing prolongation of the Q-T interval, and may elicit vasopressor and hypertensive effects. Chronic changes in cardiovascular tissues on aldehyde exposure may lead to cardiac hypertrophy, hypercholesterolemia and plaque formation. Occupational exposure to aldehydes could also induce cardiovascular changes. Increased risk of atherosclerotic heart disease has been reported in plant workers producing formaldehyde, as well as a higher incidence of heart disease in undertakers, embalmers, and perfumery workers, all linked to aldehyde exposure. Finally, the high concentration of aldehydes in cigarette smoke raises the possibility that some of the adverse cardiovascular effects of smoking are related to aldehyde toxicity.

In addition to direct exposure to aldehydes, exposure to industrial pollutants that generate aldehydes has also been linked to an increased risk of cardiovascular disease. Exposure to 1,3-butadiene is associated with an increased incidence of atherosclerosis, particularly in workers exposed to butadiene in styrene-butadiene rubber polymer manufacturing plants. Similar increases in CVD risk have been suggested for workers exposed to vinyl chloride, which is metabolized via cytochrome *P*450 to its active constituent, chloroaldehyde. A 7-year study of 1,100 workers exposed to vinyl chloride monomer showed a significant increase in cardiovascular diseases, including hypertension, MI, and other circulatory disorders.[28]

STYRENE EXPOSURE

Epidemiologic studies have reported increased daily mortality and hospital admissions associated with exposure to particulate air pollution. Cardiovascular deaths constitute large part of this increased mortality. However, the reason behind this detrimental effect of air dust is not clear. It has been suggested that some substances adhering to particulates could be responsible for acute cardiovascular effects. Styrene, a volatile hydrocarbon (also known as vinyl benzene and phenyl ethane), the precursor to polystyrene and several copolymers, has been incriminated as such a deleterious substance. Styrene is widespread in ambient air emanating from industrial sources, exhaust gases of various engines, and smoke of fossil fuel combustion to name a few. Styrene concentrations may vary significantly [0.40 to 3.80 μg/m^3 (0.09–0.89 ppb)], reaching levels of 2,934 μg/m^3 in ambient air in communities near some industrial sources. Some believe that this range may be underestimated for a variety of reasons. For example, only the vaporous part is measured, while the aerosol form or that adhered to suspended particulates is not included as air samples for styrene use charcoal tube collection or passive dosimeters; styrene aerosols could also undergo physical and chemical alteration, such as vaporization and/or polymerization and if vaporization occurs after inhalation, the result would be a highly concentrated vaporous dose to the respiratory system. Finally, styrene is a highly volatile hydrocarbon, which is rapidly transformed in the atmosphere through a reaction with hydroxyl radicals. The half-life for styrene in the atmosphere is ~7 hours. Thus, styrene is not expected to undergo

extensive transportation, suggesting that styrene measured at scattered air-monitoring stations might not represent the high concentrations in the limits around styrene-emitting sources.

Styrene is highly lipophilic. Inhaled styrene is almost completely absorbed, rapidly dispersed throughout the body, and then degraded through oxidation of the side chain to soluble metabolites for final excretion. Industrial studies have found an increase in cardiovascular disease among styrene-exposed workers. A case-cohort study comprising 498 cases that died of ischemic heart disease explored a possible dose-response relation between styrene exposure and ischemic heart disease; the study also included 997 male workers employed during 1943–1984 in two styrene-butadiene rubber-manufacturing plants in the United States. [29] The study showed that recent styrene exposure was significantly associated with acute ischemic heart disease death among active workers. The relative hazard of death from acute ischemic heart disease for exposure during the most recent 2 years among active workers with 2 or more years of employment was 2.95 at a time-weighted styrene concentration of 0.2–<0.3 ppm and 4.30 at ≥0.3 ppm for the same exposure period, respectively.[29] Thus, the results of this study suggested that a chemical, like styrene, found in the air and in industrial settings, capable of getting absorbed onto particles, can be associated with an increased risk of heart disease precipitating acute cardiac events at relatively low industrial exposures.

CLINICAL EFFECTS

With regards to the health effects of exposure to air pollutants (Table 1), a few additional points need to be reviewed (http://www.csun.edu/~vchsc00b/468/).[30]

Air pollution particulates are distinguished between inhalable, respirable, and thoracic particulate matter (PM). *Inhalable* particulate matter includes particles that enter the upper airways. *Thoracic* particles enter the airways and gas exchange regions of the lungs; *respirable* particles are a subset of thoracic particles that have a high probability of being deposited in lung tissue. The smaller the particle size, the more likely it will be deposited in lung tissue where adverse effects may occur. Ultrafine particles are particularly harmful to lung tissue.

Short-term high-level exposure to air pollutants results in *acute* health effects with symptoms of eye, nose and throat irritation and/or asthmatic attacks usually experienced within hours. Extreme episodes may even result in death. *Chronic* effects result from low-level, long-term exposures, with disease syndromes developing several decades later; these may include respiratory and cardiovascular disease, neurotoxic effects and cancer. Groups that are more susceptible comprise very young or aged individuals, patients with pre-existing respiratory and/or cardiovascular disease, occupationally exposed individuals diabetics and smokers.

TABLE 1. Health Effects of Air Pollution

Short-term Effects
Irritation to the eyes, nose and throat
Respiratory infections
Bronchitis
Pneumonia
Other symptoms
Headache
Nausea
Allergic reactions
Exacerbation of medical conditions
Asthma
Bronchitis
Emphysema
Triggering of
Acute myocardial infarction
Stroke
Arrhythmias
Long-term Effects
Chronic respiratory disease
Cardiovascular disease
Atherosclerosis
Hypertension
Heart failure
Arrhythmias
Prothrombotic state
Lung cancer
Other organ damage
Brain
Nerves
Liver
Kidney

Target organs for air pollutant exposure include the eye, the skin, the respiratory and cardiovascular systems, the nervous system, and the gastrointestinal and reproductive systems. Acrolein (propenal; an unsaturated aldehyde), formaldehyde and peroxyacetyl nitrate (PAN) are examples of common ambient irritants for the eye. Carbon monoxide (CO), lead and fine particles are primary pollutant candidates for cardiovascular toxicity. Carbon monoxide binds to hemoglobin to form carboxyhemoglobin which cannot release oxygen to the tissues.

Exposure to carbon monoxide (CO) may also result in central nervous system effects. There is evidence to indicate that CO exposures can contribute to heart disease, increase the risk of heart attack and premature mortality. Lead has myriad harmful effects, such as forming reactive radicals that damage the DNA, producing an inflammatory reaction, interfering with the immune system, causing anemia, hypertension, renal damage, neurotoxicity and so on. More specifically, lead is linked to CVD by promoting oxidative stress and inflammation, disrupting nitric oxide (NO) signaling pathways, altering vasoregulation and endothelial function, inhibiting fibrinolysis, and contributing to the development of hypertension.[31,32] Thus, with regards to lead exposure, the recommended threshold for lead blood level to avoid health effects, e.g., hypertension, is <7 μg/dl, while the concern level in children is >10 μg/dl. The Environmental Protection Agency (EPA) of the US has set a level of 0.15 μg/m^3 for lead in ambient air which is not to be exceeded (http://www.epa.gov/air/criteria.html).[33] The EPA has set National Ambient Air Quality Standards for 6 principal pollutants, which are called "criteria" pollutants and in addition to lead include CO, NO_2, O_3, SO_2 and particle pollution $PM_{2.5}$ and PM_{10} (Table 2). As aforementioned, premature cardiovascular mortality has been strongly associated with exposure to $PM_{2.5}$. In a case-crossover design study, the authors examined the association between ambient air pollution and 798 confirmed ventricular arrhythmias in 84 subjects among 203 patients with implantable cardioverter defibrillators. The authors found that interquartile range increases in 24-hour moving average $PM_{2.5}$ and ozone were independently associated with 19% and 21% increased risks of ventricular arrhythmia, respectively.[34]

The respiratory system has defense mechanisms that protect it from airborne particles. Nasal hairs prevent the passage of large particles into the respiratory system. Large particles are removed in the nasal turbinates and cleared from respiratory airways by the cilia-mucus escalator or by the cough/sneeze reflex. Small particles deposited in bronchioles and alveoli are removed by macrophages and the cilia-mucus escalator. However, very small particles can reach the alveoli and then transported to extrapulmonary organs and tissues. Exposure to air pollutants such as SO_2, O_3, and particles can result in

TABLE 2. Air Quality Standards: Guideline Upper Values for Air Pollutants

	WHO Guidelines		European Union Directive		EPA Standards	
Pollutant	**Short-Term Exposures**	**Long-Term Exposures**	**Short-Term Exposures**	**Long-Term Exposures**	**Short-Term Exposures**	**Long-Term Exposures**
$PM_{2.5}$	25 μg/m^3 24-hour mean	10 μg/m^3 annual mean		25 μg/m^3 (by 2015) 20 μg/m^3 (by 2020) annual mean	35 μg/m^3 24-hour mean	12 μg/m^3 annual mean
PM_{10}	50 μg/m^3 24-hour mean	20 μg/m^3 annual mean	50 μg/m^3 1-day mean	40 μg/m^3 annual mean	150 μg/m^3 24-hour mean	
O_3	100 μg/m^3 8-hour mean		120 μg/m^3 Maximum daily 8-hour mean		0.075 ppm 8-hour mean	
NO_2	200 μg/m^3 1-hour mean	40 μg/m^3 annual mean	200 μg/m^3 1-hour mean	40 μg/m^3 annual mean	100 ppb 1-hour mean	53 ppb Annual mean
SO_2	500 μg/m^3 10-minute mean	20 μg/m^3 24-hour mean	350 μg/m^3 1-hour mean	125 μg/m^3 1-day mean	75 ppb 1-hour mean	0.5 ppm 3-hour mean
Benzene				5 μg/m^3 annual mean		
CO			10 mg/m^3 max daily 8-h mean		35 ppm 1-hour mean	9 ppm 8-h mean
Lead				0.5 μg/m^3 annual mean		0.15 μg/m^3 Rolling 3 month average

CO = carbon monoxide; EPA = Environmental Protection Agency (US); NO_2 = nitrogen dioxide; O_3 = ozone; PM = particulate matter; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter; PM_{10}, particulate matter <10 μm in aerodynamic diameter; ppb = parts-per-billion; ppm = parts per million; SO_2 = sulfur dioxide; WHO = World Health Organization

asthmatic attacks. Certain air pollutants can increase the severity of infectious respiratory disease or increase the probability that infection may develop. Exposure to SO_2 and acid sulfates can cause severe irritation of the upper airways. Apart from asthmatic attacks, exposure to SO_2 can contribute to chronic bronchitis. Chronic bronchitis is a progressive disease of the respiratory airways caused by exposure to harmful substances in tobacco smoke and ambient pollution, leading to chronic inflammation, excessive mucus production, and decreased ciliary activity. Finally, long-term exposures to ozone (O_3) may decrease lung elasticity. It also appears to cause asthmatic attacks, interfere with the body's ability to defend itself from infection, and increase the risk of premature mortality.

Most evidence to support a causal relationship between exposure to atmospheric pollutants and the development of lung cancer in humans is indirect. It includes higher rates of cancer in urban non-smokers, higher rates of cancer in migrants from high-pollution areas, etc. Recent epidemiological evidence shows a direct link with exposures to fine particles. A very large percentage of regulated "hazardous" or "toxic" pollutants are known or suspected human carcinogens. Asbestos is regulated as a hazardous air pollutant as it causes human cancer and there is no known safe level of exposure.

The risk of disease from exposure to ambient air pollutants compared to tobacco smoking is relatively small from a public health standpoint, but it applies to the entire population with considerable public burden. Importantly, ambient air pollutant exposure and secondhand smoking constitute an involuntary risk and thus more likely to be regulated than voluntary risks (e.g., active smoking). Interestingly, banishment of smoking in public places in Europe has had significant effects on hospital admissions for cardiovascular disease and in particular for coronary artery disease.[35,36] The benefit was noted both in smokers and non-smokers, indicating that part of the adverse effects of secondhand smoke may be conferred via exposure to particulate matter indoors and outdoors.[37] Indeed, pathophysiological mechanisms linking active and secondhand smoking, as well as ambient air pollution with cardiovascular diseases are impressively similar.[37,38]

CONCLUSION

There is strong emerging evidence that both indoor and outdoor air quality is a modifiable risk factor for cardiovascular, pulmonary and other organ diseases, particularly for the residents of metropolitan areas. Air pollutants, including particulate and gaseous matter, metals and aldehydes, have serious health effects. Apparently, health effects of air pollution and even those of low-dose smoking and secondhand smoke, are still underestimated by decision makers around the world. Regulation of air quality needs sustained vigilance aiming at improving life expectancy. Current recommendations from the World Health organization (WHO) (global update 2005 on Air quality guidelines),[39] the European Union (EU) (Directive 2008)[40] and the US Environmental Protection Agency (EPA) (National Ambient Air Quality Standards 2011)[33] are outline in Table 2. It is of utmost importance for regulatory agencies to force the implementation of these regulations and maintain regularly monitored and updated quality standards in order to protect the health of the population at large. Specific attention should be given for activity restriction by susceptible and high-risk individuals, such as the very young and the elderly, and those with known cardiovascular and/or pulmonary disease or diabetes mellitus.

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