

Population and Environment: selected issues

Urbanization & Environment: trends and
patterns in contemporary Brazil

Heloisa S.M. Costa e Roberto L.M. Monte-Mór

Migration and the Environment: a view from
Brazilian Metropolitan Areas

Haroldo da Gama Torres

Population and Water Resources in Brazil

Roberto Luiz do Carmo

Indigenous Lands and Peoples: recognition,
growth and sustenance

Marta Azevedo e Fany Ricardo

Health Effects of Ambient Levels of Air Pollution

Paulo H. N. Saldiva, Alfésio Luiz Braga e Luiz
Alberto Amador Pereira

Population and Sustainable Consumption in Brazil

Donald Sawyer

Tourism and Environment in Brazil

Maria Tereza D.P. Luchiari e Célia Serrano

Agrarian Reform, Population and Environment

Juarez Brandão Lopes e Danilo Garcia Prado

Health Effects of Ambient Levels of Air Pollution

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Introduction

The knowledge that air pollution promotes adverse health effects is not new. In the 13th century, Edward I of England punished with hanging and torture those who burned coal in excess in the winter in London, because of resulting bad air. In fact, this was probably the first (and bloody) Clean Air Act of the history of mankind. In the first half of the 20th century the episodes of severe air pollution in the Meuse Valley in Belgium (1) and London (2) were so clear in demonstrating acute health effects of air pollution that they promoted public awareness and the promulgation of laws regulating emissions from stationary sources. In consequence of such measures, air pollution decreased in most of the large Western urban centres attaining levels below the air quality standards. The problem of urban air pollution and health was considered solved by most of those involved in regulatory agencies. Physicians dismissed this arena, and, by the 1980's, the relationship between air pollution and health was a quest for ecologists without solid scientific grounds. However, studies made in the late 80's provided evidence that air pollution causes adverse health outcomes, even when not surpassing the safety levels prescribed by regulatory air standards. In the last 20 years, hundreds of papers have been written in many parts of the globe, reporting acute and chronic health effects of air pollution. The revision of such huge amount of data is beyond the scope of the present paper. Our chapter plans to conduct the reader across some basic questions on the topic that deserves further attention:

- . What is the magnitude of the health effects of air pollution?
- . What are the main acute outcomes?
- . What are the consequences of prolonged exposure to atmospheric pollution?
- . What are the possible mechanisms responsible for the observed health effects?

To achieve the aforementioned objectives, this chapter will touch on concepts of epidemiology, pathology and cell and molecular biology. In the sake of clarity, complicated medical wording will be deliberately avoided, focusing the text on the transmission of the main core of information, rather than approaching the theoretical grounds of each type investigation. Those interested in broader treatment will find in the references sources of more detailed information.

Measuring health effects of air pollution: the ability of epidemiology in determining acute health effects

Epidemiologists are responsible for characterising health effects of air pollution. In this chapter, we will discuss data obtained by means of three types of studies. The largest amount of information in this area was obtained by following a given community across a defined period of time and correlating changes in measures of air pollution to variations of an estimator of health – usually mortality or morbidity counts. This type of epidemiological design is known as **time-series study**. Another way of getting useful information on air pollution effects is by comparing two or more communities living in areas with different pollution backgrounds, in a **cross-sectional study**. Finally, we will discuss data derived by the follow-up of a group of individuals, living in an area with a special profile of pollution or exhibiting a peculiar health condition that makes them more susceptible to the action of air contaminants. This approach is known as **cohort study** (if a population is the subject of investigation) or a **panel study** (in the case that a group of individuals is being studied). Of course, these three epidemiological designs are not mutually exclusive. They may be combined to increase the power of the study. For example, it is possible to incorporate a time-series within a cross-sectional study, or follow a group of patients with chronic bronchitis (panel study) in different communities.

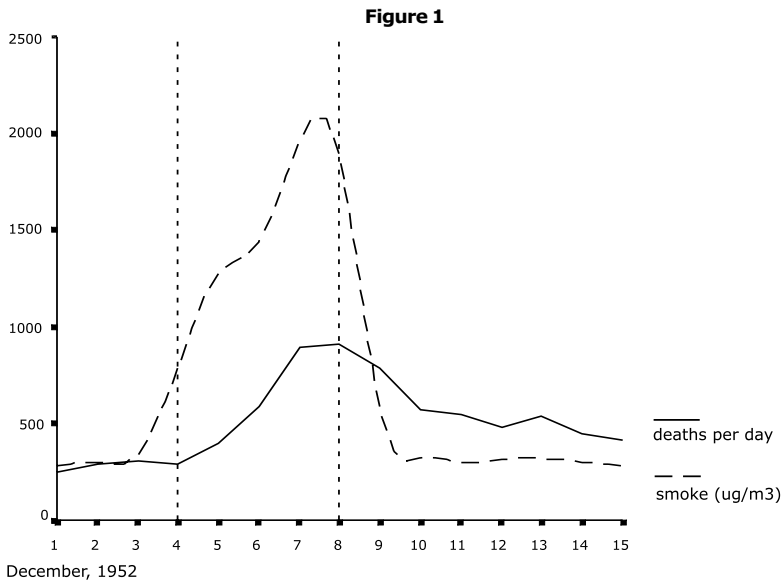


Figure 1: Daily death counts in London during the first half of December 1952. During the period of the 4th to 8th of December (vertical dashed reference lines), a period of severe atmospheric stagnation and fog occurred leading to an accumulation in the air of substances derived from combustion of coal and oil, amidst a humid environment. In day following this phenomenon, there was a sharp increase in the number of deaths, which dropped when the thermal inversion vanished, although not returning to baseline levels, at least until the 15th (figure based on data reported by Logan (2))

We will begin to explore some practical examples of how epidemiology contributed for the understanding of the relationship between air pollution and human health. Perhaps, the most illustrative example of ecological time series is that published by Logan (2) in the *Lancet* in 1953. Figure 1 is based on the data of this study and shows the temporal variation of the daily deaths in London in December 1952.

Without the need of any sophisticated statistical witchcraft, Logan (2) clearly demonstrated that people might die immediately after an increase in air pollution. Those who died in this period were mostly those with prevailing pulmonary and cardiac diseases and children. Moreover, this study indicated that the time lag between increase in pollution and mortality is very short, in this case not exceeding one day. Interestingly enough, although mortality events decreased in parallel with the lowering of air pollution, the number of deaths did not reach the baseline levels, suggesting that episodic periods of air pollution may have a residual effect that lasts weeks, at least. Fortunately, today air pollution in urban centres does not exhibit such high levels as those of London in the fifties. In fact, Logan's study reporting the results of such dramatic natural toxicological experiment contributed significantly for establishing procedures of air pollution control.

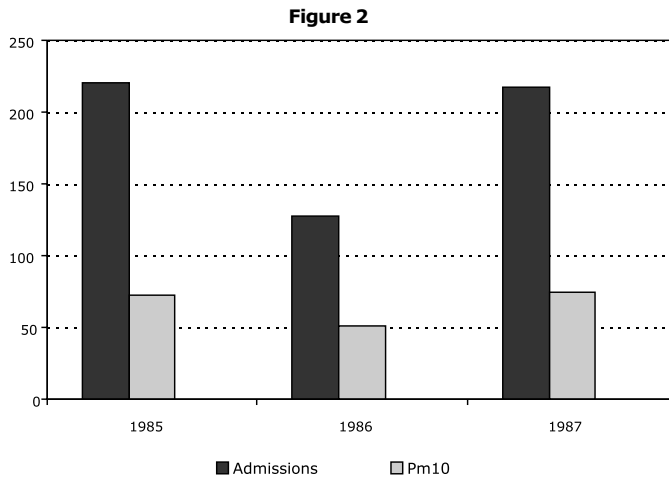


Figure 2: Variations of particles with aerodynamic diameter smaller than 10mm (Pm10) and daily hospital admissions due to respiratory disease before (1985) and during (1986) the closure of a steel mill in Utah Valley and after (1987) its return to operation (modified from Pope (3)).

Pollution levels decreased as consequence of regulatory policies, but does it mean that its health impacts have disappeared? A study done by Pope in Utah Valley (3) demonstrated that pollution is still a topic of major concern (Figure 2).

In this work, Pope (3) follows the ambient levels of atmospheric particles small enough to penetrate into the lungs (aerodynamic diameter below 10mm)

in Utah Valley before and after the closure of a steel mill (years of 1985 and 1986, respectively). A significant decrease of ambient particles was observed during the closure, indicating that this source of combustion particles contributed significantly to ambient pollution in the area. After the reopening of the steel plant, particle concentrations returned to their historic levels. Respiratory admissions followed the levels of particles with a surprising coherence, now in a range of concentration within an order of magnitude smaller than those of London in 1952. The paper of Pope (3) took advantage of another natural experiment – the closure of a significant source of air pollution – to show that even low levels of particles affect adversely human health.

Both aforementioned studies reported significant effects of air pollution on human health, but in conditions that were quite exceptional. In Logan's study (2), a dramatic increase in pollution levels was followed by an evident increase in mortality. In Pope's study (3), the cleaning of the atmosphere of particles produced by a major pollution source permitted the recognition of a marked drop in respiratory morbidity. The two works were made possible because rare events occurred. Fortunately, the increasing sophistication of statistical tools and the availability of increased computer power created the conditions to perform time-series studies without any exceptional conditions. By computing daily data of air pollution and health outcomes within a relatively long period, it is possible, by means of multivariate statistical models, to determine the short-term effects of air pollution on health. The example of some studies made in São Paulo can perhaps help to understand this approach.

In the beginning of 1990's, the municipality of São Paulo created a program to provide daily mortality data, by using a central that collects death certificates and codifies them using the International Code of Diseases. This program – PROAIM – produces daily outputs of mortality in São Paulo in electronic media. São Paulo also has a network of fourteen stations of air pollution measurements maintained by the State Sanitation Agency (CETESB), which gives daily concentrations of PM₁₀, CO, O₃, SO₂ and NO₂. These data allow the modelling of daily mortality as function of air pollution data, taking into account other confounding variables like season of the year and weather variables. One advantage of the modelling of daily data is that it offsets the interference of important determinants of respiratory and cardiovascular mortality, such as smoking, indoor air pollution and nutrition, among others. In fact, it is difficult to conceive that, for instance, people will smoke more or less because today is a polluted day. In other words, the variability of pollution is independent of the variability of individual health or environmental conditions. Another advantage of the daily ecological time series is that it uses secondary data, *i.e.*, data sets that were already produced. This condition makes this approach very inexpensive and affordable for developing countries. The main limitation of this kind of study is that it is efficient only for the determination of acute health effects of air pollution.

Perhaps, the presentation of the basic results of a study performed in São Paulo may help the reader to get the basics of the daily time series approach. The first epidemiological study of our group presented the effects of air pollution on daily mortality of people over 65 years of age for the period 1990-1991, using secondary data produced by the PROAIM and CETESB (4).

Figure 3 depicts the coefficients relating mortality in elderly people with the month of the year (4). According to the model, mortality exhibits a strong seasonal behaviour. When taking January as reference, our model predicted that July exhibits an excess of about 30 deaths per day; December presenting a negative effect of about 10 deaths/day in comparison to January.

Figure 3

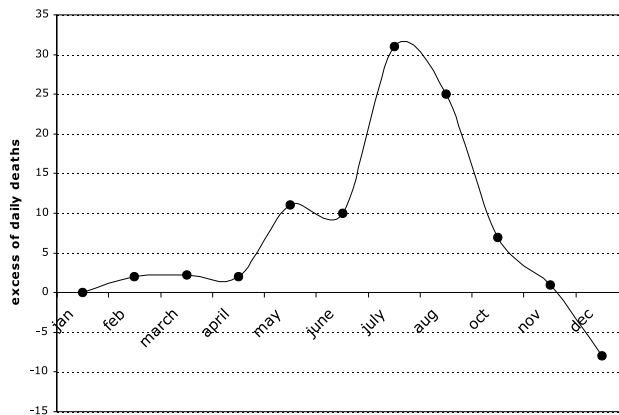


Figure 3: Estimated seasonal effect on daily mortality of elderly people in São Paulo for the period 1990-1991 (4).

The significant seasonal effect on mortality indicates that is quite important to incorporate parameters for control such phenomenon when modelling daily mortality in São Paulo. Since air pollution in São Paulo also increases during winter, the use of a seasonal controlling parameter avoids attributing all the mortality increase observed in colder months only to pollution.

Weather also affects mortality in São Paulo. As demonstrated in Figure 4, there is a sharp increase in mortality in days preceded by cold temperatures.

After adjusting the model, using several predictive variables (weather, seasonal effects, day of the week), a significant effect of air pollution on mortality remains. Figure 5 shows the dose-response relationship relating mortality of elderly people with the levels of PM10 of the preceding day. A straight dose-response function is observed, meaning that:

a) There is no significant safety threshold in the relationship relating air pollution to mortality, even for levels quite below air quality standards. Using the 20% of the days with lower pollution levels, the days with higher levels of air pollution causes an increase of mortality of about 12%

b) The time lag between increase in air pollution and increased mortality is very short, within a range of few days.

Using the time-series approach, it is possible to evaluate the "size" of the effect of air pollution on human health. Figure 6 presents the percentage of deaths attributable to air pollution in São Paulo in two different periods: 1991-1994 and 1996-2000.

Figure 4

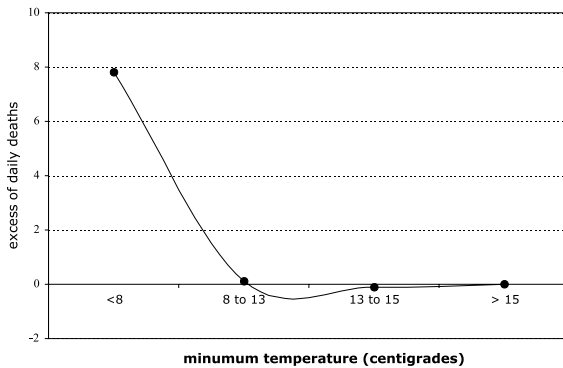


Figure 4: Coefficients relating mortality of elderly people in São Paulo to the minimum temperature of the preceding day. There is a sharp increase in mortality when temperature drops below 8°C. (4)

Figure 5

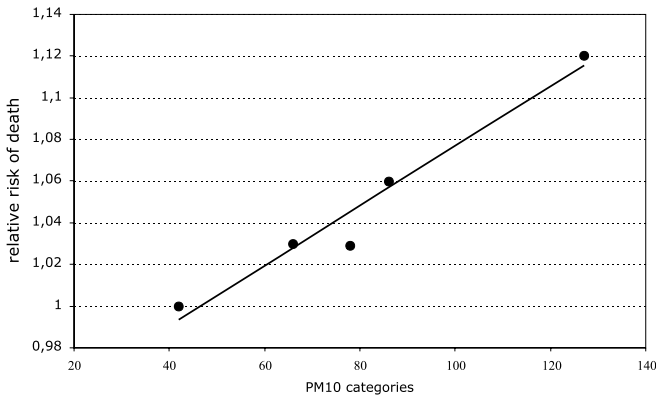


Figure 5: Dose-response curve relating mortality in elderly people during the period 1990-1991 in São Paulo to PM10 levels of the preceding day (4).

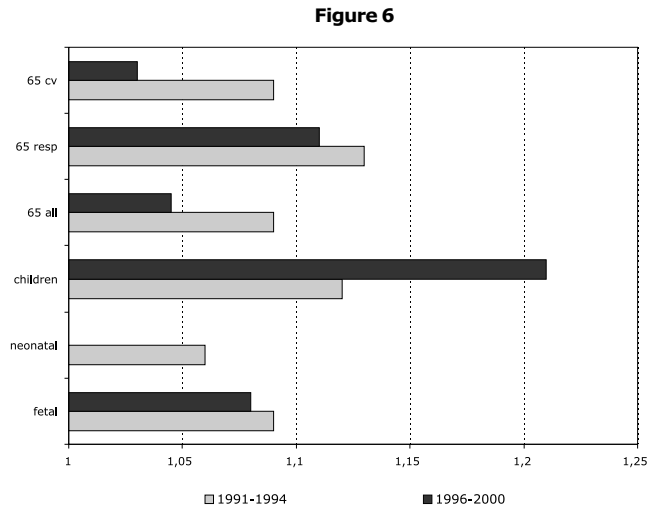


Figure 6: Percentage increase in mortality attributed to air pollution in São Paulo for different age groups and health outcomes, measured in two periods: 1991-1994 and 1996-2000.

Who are the individuals in a population who suffer the most with air pollution?

From the studies already presented, it is clear that people with chronic respiratory diseases – chronic bronchitis, emphysema and asthma –, elderly people and children represent preferential targets of air pollution. Recent studies are increasing the range of susceptible individuals to air contamination. In this chapter, we will address two groups who have been recognised to be victims of air pollution: people with cardiovascular diseases and fetuses. In addition, we will discuss some aspects about how socio-economic factors may act as modifiers of air pollution toxicity in poor communities.

Air pollution and cardiovascular diseases: The observation that there is a short time lag between increase in air pollution and mortality leads, intuitively, to the fact that some of these fatalities attributed to air pollution could be of cardiovascular origin (5). Coherent with this concept, Schwartz (6) examined the location of deaths associated with air pollution, reporting that the greatest relative increase in pollution-associated deaths in Philadelphia, Pennsylvania, USA, was for “dead on arrival” deaths. This finding supports that many people who died on high pollution days exhibited a very rapid deterioration of their health, a clinical picture compatible with cardiovascular events. In a recent work undertaken in 10 American cities (7), a significant association between PM10 and cardiovascular deaths was detected. Interestingly enough, this study demonstrated that the time lag between increase of air pollution and death is different for cardiovascular and chronic respiratory diseases. As shown in Figure 7, mortality due to chronic

obstructive pulmonary diseases (COPD) was related to the air pollution of the two preceding day, whereas deaths caused by myocardial infarction were more strongly associated with pollution levels of the concurrent day.

Figure 7 also shows that the relative excess of deaths attributable to air pollution is greater for COPD than for MI. However, since the number of people who die due to MI is significantly higher than due to COPD, it is clear that cardiovascular mortality is clearly a significant end-point when studying adverse health effects of air pollution.

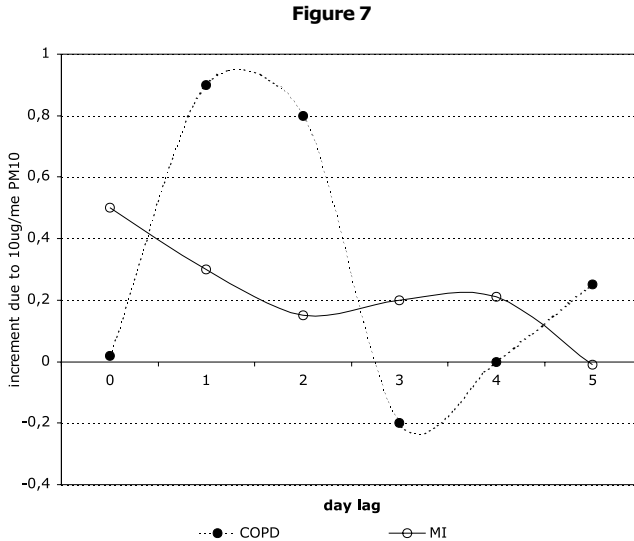


Figure 7: Excess in daily mortality (%) due to an increase of 10 mg/m^3 of PM_{10} in a study performed in 10 American cities (8). The x-axis represents the structure of lags of air pollution, ranging from 0 to the previous 5th day, in decrements of 1 day. COPD: chronic obstructive pulmonary disease; MI: myocardial infarction (modified from reference 7).

The mechanisms by which air pollution causes cardiovascular mortality still remains unclear, but some good clues are already available. Epidemiology contributed in providing some lines of investigation in this area. One of the more important epidemiological studies on the pathogenesis of cardiovascular mortality induced by air pollution was done by Peters et al (8), by doing a panel study of patients with implanted cardioverter defibrillators. Those patients are at high risk of developing a fatal cardiac arrhythmia, up to a point of having implanted in their bodies a system that is activated when a potentially severe disturbance of cardiac rhythm occurs. These devices possess a memory that can tell the investigator when the arrhythmia happened. In this study, nitrogen dioxide (NO_2) and $\text{PM}_{2.5}$ (particulate matter with aerodynamic diameter less than $2.5 \text{ }\mu\text{m}$) concentrations of the preceding two hours were associated with defibrillator discharges due to ventricular arrhythmias, as demonstrated in Figure 8. These results indicate that air pollutants may promote sudden changes of cardiac rhythm, with potential of causing death.

Figure 8

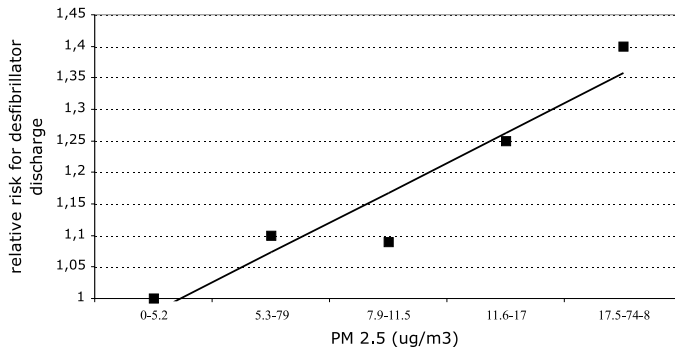


Figure 8: Relative risk of defibrillator discharge as a function of the concentration of PM2.5 of the preceding 2 hours (modified from reference 8).

The finding that air pollution interferes with cardiovascular function up to a point of causing death generated a series of studies aimed to better characterise what type of cardiovascular disease is more affected and the mechanisms responsible for the adverse cardiovascular effects induced by inhaling contaminated air. Those interested in having more detailed information about the epidemiologic and panel studies already performed in this field are encouraged to go to excellent review studies available in the literature (9-11). We will come back to the possible mechanisms of pollution-induced cardiovascular toxicity further on.

Figure 9

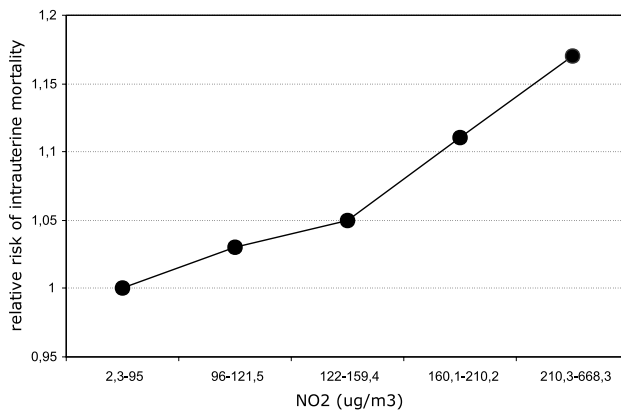


Figure 9: Dose-response relationship of the association between risk of intrauterine mortality and NO2 for the city of São Paulo (modified from reference 14).

Air pollution and fetal health: There is growing evidence that the effects of air pollution can be manifested in intrauterine life. Recent studies have reported that pregnancies conducted in areas with higher levels of pollution present a significant risk of low birth weight (12), and birth defects (13). A significant association between intrauterine mortality and air pollution was observed by Pereira et al in São Paulo (14), as shown in Figure 9.

Pereira et al (14) found a linear association between the levels of **carboxyhemoglobin** in the blood of umbilical cord of infants delivered to non-smoking mothers and ambient levels of carbon monoxide, after adjusting the model for passive smoking (Figure 10). Such findings are indicative that ambient pollutants may reach the fetus and promote adverse health effects.

Figure 10

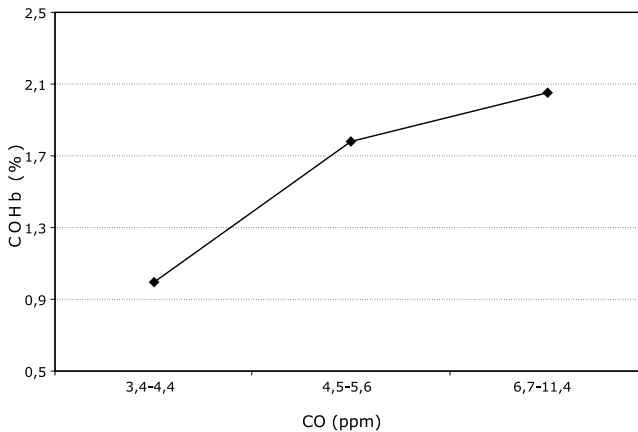


Figure 10: Adjusted coefficients relating **carboxyhemoglobin** and ambient CO in the umbilical cord in pregnancies of non-smoking women, adjusted for passive smoking (14).

Socio-economic factors as modifiers of pollution effects: In the previous topics, we focused on specific diseases (COPD and cardiovascular pathologies) or age groups (elderly people, children and fetuses) as susceptible groups to the effects of air pollution. However, it is plausible to propose that socio-economic factors may modify the coefficients relating air pollution and disease. There are several reasons for that. In São Paulo, people who live in slums have a greater indoor penetration of outdoor pollution, thus augmenting the exposure. Accessibility to health services, perception of disease, nutritional and health conditions are factors that may interfere significantly with the susceptibility to airborne toxins. A recent study performed by Martins et al (15) in São Paulo provided solid evidence to support the fact that socio-economic factors are important modifiers of air pollution effects. In this study, the authors conducted a time-series study in different areas of the city and measured the association between air particles and mortality of elderly people, adjusted for several seasonal and weather variables. The

increase in mortality due to an inter-quartile increase in PM₁₀ was not similar across the areas investigated, exhibiting significant associations with several estimators of socio-economic conditions (Figure 11). These results suggest that air quality criteria should probably be adapted in different parts of the world, taking into account local socio-economic indicators.

Figure 11

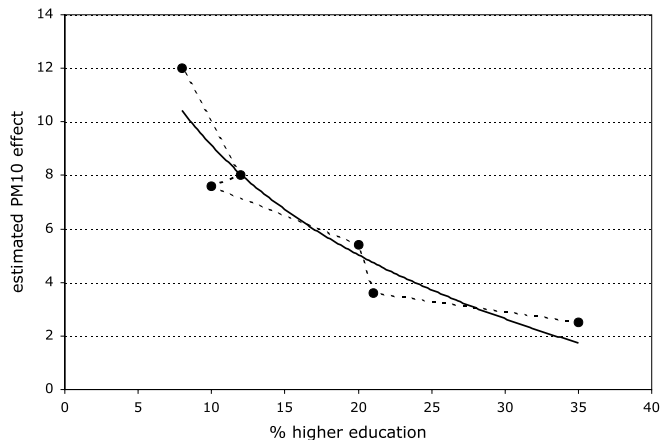


Figure 11: Estimated increase in mortality of people over 65 years of age for an inter-quartile increase of PM₁₀, computed in 6 areas of the city of São Paulo with different levels of education. It is evident that PM₁₀ effects decrease as the level of education of those communities increases (modified from the reference 15).

Epidemiological evidences of chronic effects of air pollution

The idea that air pollution causes chronic health effects is intuitive. The demonstration by different groups that there are acute effects of pollution on health makes it almost impossible to imagine that acute injuries to our bodies made over years of exposure occurs without presenting their costs. However, the demonstration of chronic effects of pollution by epidemiological methods is not so simple as for acute effects. We mentioned previously that most of the present knowledge about the health effects of air pollution has been produced by time-series studies. This approach has the advantage of being relatively unaffected by events other than pollution that affect human health as well. Although very powerful in determining acute health effects, time-series studies are not suited to evaluate chronic health effects. The simple cohort studies may be employed for such purpose, but have limitations because one should take into consideration that the observed differences among different communities can be affected by other factors – cultural, geographic, nutritional, socio-economic, for instance – rather than by pollution alone. Usually, large cohort studies, by following communities over a long period of time, gave the strongest evidences of the chronic effects of pollution. These studies take long to be accomplished (usually,

decades) and represent an investment of millions of dollars. In our opinion,, the best research on cohorts in the literature focusing on the chronic effects of air pollution are those conducted by the Harvard group (16) and by Pope, et al, using data collected by the American Cancer Society (ACS) (17). These studies showed conclusive evidence that chronic exposure to air pollution significantly impairs human health. The Harvard Six-Cities study (16) was based on a 14- to 16-year prospective follow-up of more than 8,000 adults living in six U.S. cities. It controlled for individual differences in age, sex, cigarette smoking, education levels, body mass index, and other risk factors. Cardiopulmonary mortality was significantly associated with mean sulfate and fine particulate concentrations over the years of the study period. The ACS study linked individual risk factor data from the American Cancer Society, Cancer Prevention Study II (CPS-II), with national ambient air pollution data (17). The analysis used data for more than 500,000 people who lived in up to 151 different U.S. metropolitan areas and who were followed from 1982 through 1989. It controlled for individual differences in age, sex, race, cigarette smoking, and other risk factors, and evaluated the association of adjusted mortality with two indices of long-term exposure to combustion-source particulate air pollution, mean sulfate, and median fine particles. Both indices of combustion-source particulate air pollution were associated with overall mortality and, especially, with cardiopulmonary mortality. Both studies, using two different data sets, gave the same basic results, *i.e.*, air pollution is significantly associated with decreased life expectancy due to cardiopulmonary diseases. For descriptive purposes, we present in Figure 12 the effects of smoking and air pollution detected in both studies.

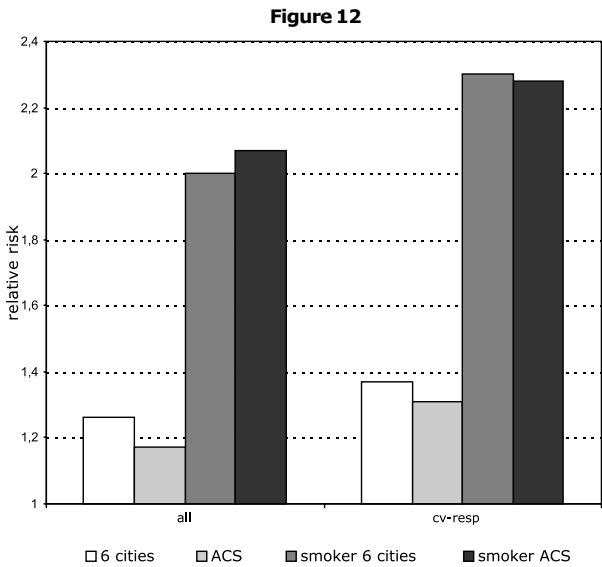


Figure 12: Relative risk of mortality due to all causes and cardiopulmonary diseases attributed to smoking and air pollution in the Harvard Six-Cities study (16) and the American Cancer Society (17) cohorts.

Possible mechanisms responsible for the adverse effects of air pollution: the role of experimental models

Despite the enormous amount of epidemiological data relating air pollution to health effects, the pathogenetic mechanisms of such association are not hitherto clarified. The identification of the mechanisms of damage may help orient strategies of air pollution control, and allow each individual to take measures to protect his/her health. In this context, experimental models can provide important information in two aspects. First, it is important to provide biological plausibility to the epidemiological studies, since population based studies measure association but not causality. Secondly, by knowing what is going on when one breathes polluted air, it would be possible to think of pollution medically, *i.e.*, to devise therapeutic interventions aimed at protecting the most susceptible segments of the exposed population.

The problem of identifying the mechanism by which air pollution damage people's health is not trivial. First, we have to consider that there is not just a single pollutant in the atmosphere of polluted cities. The exhaust pipe of a truck or a chimney of an industry emits several gases and particles together. It is quite plausible that air pollution toxicity is not dependent on a single component, but on the sum of individual components present in the air. In addition, these primary compounds react among themselves to an extent dependent upon dispersion, humidity and solar irradiation. Thus, considering the complexity of the problem, we will choose one of the components of urban air to explain how toxicologists and experimental pathologists are approaching the puzzle of determining the toxicity of urban pollution. Since most of toxicological studies identify small particles as the pollutant that exhibits the strongest associations with adverse health outcomes, we will present the experimental evidence that supports particle toxicity.

Urban air contains a variety of solid and liquid particles that vary in size, composition, and origin. Depending on their size, particles may be classified in 3 categories, namely coarse particles, fine particles, and ultra-fine particles. Coarse particles (aerodynamic diameter > 2.5 μm) are derived primarily from soil and other crust materials. Fine particles (PM_{2.5}) are derived mainly from combustion processes. Sulfate and nitrate particles are commonly generated by conversion from primary sulfur and nitrogen oxide emissions, and a varying portion of sulfate and nitrate particles may be acidic. Thus, urban particles are composed primarily by particles emitted due to combustion and those produced by gas-particle conversion including sulfates and nitrates. Ultra-fine particles (< 0.1 μm) have relatively short life in the atmosphere because they accumulate or coagulate to form larger fine particles.

After restricting our attention to particles, we will focus on the following in some basic final points:

DOES POLLUTION PROMOTES RESPIRATORY DAMAGE IN EXPERIMENTAL MODELS?

Rodents living during prolonged periods of time (3 to 6 months) in downtown São Paulo, in an area with high particle concentration, exhibit clear pathological signs that those particles penetrate in their lungs, as shown in Figure 13.

Figure 13

Figure 13: Scanning electron micrography of the nasal passages of rats kept for 6 months in a clear environment (upper panel) and a polluted area (lower panel). The cilia that covers airways and are responsible for removing pollutants deposited on airway surfaces are destroyed in the pollution-exposed animals. Particles can be seen on the airway epithelium.

The prolonged exposure of these animals in different experiments (18-23) consistently demonstrated that air pollution promotes airway inflammation throughout the respiratory tract, increased airway responsiveness, decreased pulmonary defences and increased predisposition to develop lung tumors. Also, autopsy studies performed in young people (urban x countryside dwellers) who died because of external causes disclosed significant differences in lung histology (24) between groups. Those exposed to air pollution showed significant deposition of carbon particles in the lung parenchyma, mucus hyper-secretion with a marked shift towards production of acidic mucin by airway glands and respiratory bronchiolitis.

DOES POLLUTION PROMOTES CARDIOVASCULAR DAMAGE IN EXPERIMENTAL MODELS?

This question is of paramount importance to gather the mechanism by which air pollution causes sudden death. Recent studies, that our group participated in, demonstrated that rats with acute myocardial infarction develop premature ventricular contractions in two hours after exposure to particles (Figure 14).

These electrical abnormalities of cardiac rhythm occur within a time window that is reported in people with severe heart diseases and, perhaps, this model can help to identify how particles induce cardiac damage.

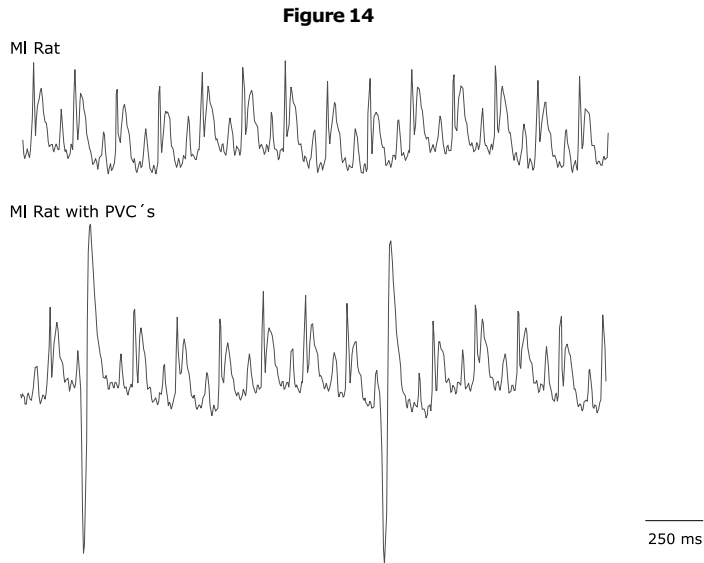
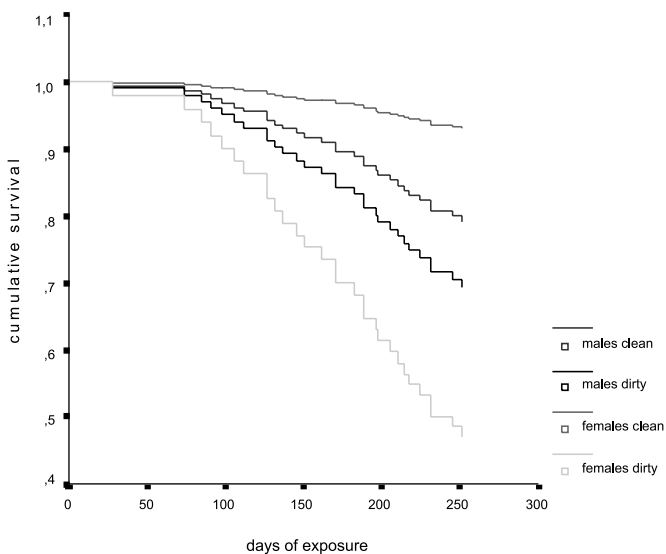


Figure 14: Electrocardiogram of rats with myocardial infarction. The lower panel shows 2 high amplitude premature ventricular contractions after 2 hours of exposure to a particle surrogate (ROFA) (25)

DOES POLLUTION REDUCE LIFE EXPECTANCY IN EXPERIMENTAL MODELS?

The determination of chronic health effects, mainly reduction of life expectancy, using epidemiologic studies takes an enormous amount of time, energy and money. The use of animals with short life spans can help scientists to test this hypothesis much more easily, since genetically similar animals can be housed in cages with identical conditions of living and feeding. Our group just finished a life-time experiment with mice living in areas with high (São Paulo, downtown) and low (Caucaia do Alto) pollution levels. The study was based on following the survival of these two groups and, when an animal dies, to perform pathologic examination of all organs to determine the cause of death. The results can be summarised in the Figure 15, which presents the graphic output of Cox's proportional hazards models relating survival rate to mice kept in the clean and dirty areas, divided by sex. Both females and males living in São Paulo presented a significant reduction of time of life. The effect was more intense in females, which have only 50% survival rate at the end of the experiment.

Figure 15**Figure 15:** Survival rates of male and female mice exposed or not to air pollution.

Final considerations

This chapter discussed some basic questions about the complex relationship between air pollution and human health. Quantitative data are presented, but augmented with some degree of subjectivity. It is almost impossible to be totally neutral about such exciting topic, thus making the authors insert their own interpretation and personal feelings. We hope that the liberty in our text has not impaired the work in its totality.

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