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The role of outdoor air pollution and climatic changes on the rising trends in respiratory allergy

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Evidence suggests that allergic respiratory diseases such as hay fever and bronchial asthma have become more common world-wide in the last two decades, and the reasons for this increase are still largely unknown. A major responsible factor could be outdoor air pollution, derived from cars and other vehicles. Studies have demonstrated that urbanization and high levels of vehicle emissions and westernized lifestyle is correlated with the increasing frequency of pollen-induced respiratory allergy. People who live in urban areas tend to be more affected by pollen-induced respiratory allergy than those from of rural areas.

Pollen allergy has been one of the most frequent models used to study the interrelationship between air pollution and respiratory allergic diseases. Pollen grains or plant-derived paucimicronic components carry allergens that can produce allergic symptoms. They may also interact with air pollution (particulate matter, ozone) in producing these effects. There is evidence that air pollutants may promote airway sensitization by modulating the allergenicity of airborne allergens. Furthermore, airway mucosal damage and impaired mucociliary clearance induced by air pollution may facilitate the access of inhaled allergens to the cells of the immune system. In addition, vegetation reacts with air pollution and environmental conditions and influence the plant allergenicity. Several factors influence this interaction, including type of air pollutants, plant species, nutrient balance, climatic factors, degree of airway sensitization and hyperresponsiveness of exposed subjects.

Key words: air pollution; bronchial asthma; airway hyper-responsiveness; hay fever; pollinosis; respiratory allergy; urban pollution.

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Introduction

Several studies have shown the adverse effects of ambient air pollution on respiratory health (1–8). Allergic respiratory diseases such as hay fever and bronchial asthma have indeed become more common in the last decades in all industrialized countries (9,10) and the reasons for this increase are still debated. However, despite evidence of a correlation between the increasing frequency of respiratory allergy and the increasing trend in air pollution, the link and interaction is still speculative. Interpretation of studies are confounded by the effect of cigarette smoke, exposure to indoor pollutants and to outdoors and indoors allergens. Another factor clouding the issue is that laboratory evaluations do not reflect what happens during natural exposure when atmospheric pollution mixtures are inhaled. As a consequence, even if it is plausible that ambient air pollution plays a role for the onset and increasing frequency of respiratory allergy, it is not easy to prove this conclusively. In addition, it is important to recall that an individual's response to pollution exposure depends on the source and components, as well as climatic factors. Indeed, some air pollution-related incidents with asthma aggravation do not depend only on the increased production of air pollution but rather on climatic factors that favour the accumulation of air pollutants at ground level. A study from The Netherlands (7) demonstrated that children with atopy and bronchial hyper-responsiveness are at risk of increased symptoms during episodes of air pollution .The children with bronchial hyper-responsiveness and high levels of serum total IgE had an increase in respiratory symptoms up to 139% for every 100 mcg m^{-3} increase in particulate matter. However, a potential confounding factor is the content of allergen in air during most of these episodes. There is evidence that living near roads with high levels of car traffic is associated with impaired respiratory health, since road traffic with its gaseous and particulate emissions is currently, and is likely to remain, the main contributor to air pollution in most urban settings. For every 100 km a car emits a mean value of about 1 kg of pollutants into the atmosphere . Air pollution is convincingly associated with many signs of asthma aggravation (increased bronchial hyper-responsiveness, visits to emergency departments, hospital admissions, increased use of medication) (2,8). Moreover, sensitive techniques to analyse

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TABLE 1. Rationale for the inter-relationship between agents of air pollution and allergens in inducing respiratory allergy

—	Components of air pollution can interact with pollen grains, leading to an increased release of antigens characterized by modified allergenicity.
—	Components of air pollution can interact with allergen-carrying paucimicronic particles some derived from plants and which are able to reach the peripheral airways with inhaled air, inducing asthma in sensitized subjects.
—	Components of air pollution, especially ozone, particulate matter and sulphur dioxide, have an inflammatory effect on the airways of exposed, susceptible subjects, causing increased permeability, easier penetration of pollen allergens in the mucous membranes and easier interaction with cells of the immune system. There is also evidence that predisposed subjects have increased airway reactivity induced by air pollution and increased bronchial responsiveness to inhaled pollen allergens.
—	Components of air pollution, in particular diesel exhaust particles, have and adjuvant immunologic effect on IgE synthesis in atopic subjects.

time-series data have shown that there are clear adverse effects on mortality rates from current levels of air pollution (6,11,12). In a study of six U.S. cities, after adjusting for some risk factors, a significantly increased mortality rate ratio was found in the most polluted areas compared to the least polluted city (11). Governments worldwide and international organizations such as the World Health Organization and European Union are facing a growing problem of the respiratory effects induced by gaseous and particulate pollutants arising from motor vehicle emissions.

The most abundant air pollutants in urban areas with high levels of vehicle traffic are respirable particulate matter (PM_{10}), nitrogen dioxide (NO_2) and ozone (0_3). It is estimated that more than 50% of the U.S.A. population live in areas that exceed current National Ambient Quality Standards for O_3, NO_2, sulphur dioxide (SO_2) and particulates, as monitored by the U.S. Environmental Protection Agency (1). In general, the effects of air pollutants on lung function depends on the environmental concentration of the pollutant, the duration of exposure and the total ventilation of exposed persons.

Aeroallergens derived from pollen grains lead to bronchial obstruction in predisposed subjects and pollen allergy is a frequent model used to study the interrelationship between air pollution and respiratory allergy (13–16). In other words, biological aerosols such as pollen grains (17–19), paucimicronic components deriving from leaves and stems (20) or ruptured pollen grains (21) act as aerocontaminants and can induce symptoms in predisposed subjects. They may interact with airborne contaminants and it has been suggested that air pollutants may promote airway sensitisation by modulating the allergenicity of airborne allergens (14,22). There is also evidence that the airway mucosal damage and the impaired mucociliary clearance induced by air pollution may facilitate the access of inhaled allergens to the immune system (14).

Interaction between air pollution and allergenic vegetation

Vegetation reacts with air pollution over a wide range of pollutant concentrations and environmental conditions. Many factors influence the interaction, including type of air pollutants, plant species, nutrient balance, soil conditions and climatic factors.

At low levels of exposure for a given species and pollutant, no significant effect is observed. However, as the exposure level increases, a series of potential injuries may occur such as alterations of plants (Table 1).

Components of air pollution can influence the plant allergenic content. By affecting plant growth, air pollutants can affect both the amount of pollen produced and the amount of allergenic proteins contained in pollen. A study showed that the pollen grains of plants stressed by air pollution express enhanced levels of allergenic proteins (24). Moreover, birch trees exposed to high levels of air pollutants are characterized by higher level of birch pollen antigen than pollen from birch trees, which grow in areas with lower levels of air pollution (25).

It has been also observed that exposure to 100 ppb of NO_2 adversely affect the germination of birch, alder and hazel and altered their content of proteins, including allergens. However, pollen grains collected from roadsides with heavy traffic and from other areas with high levels of air pollution, are covered with large numbers of airborne microparticulates (usually less than 5 μm), and it has been suggested that the interaction between particulate components of air pollution and pollen alters the antigenicity of pollen allergens (22,23).

Despite shorter and less severe grass pollen seasons, confirmed by lower pollen counts, the prevalence of seasonal rhinitis and asthma has increased in some European cities in recent years. In England the London area have had a reduction in the length and severity of pollen seasons over the last 30 years coupled with more cases of pollen-related respiratory symptoms (26). A possible explanation of this apparent contradiction is that air pollutants have interacted with pollen grains to make them more allergenic, rather than inducing or increasing airway inflammation and reactivity in predisposed subjects. Pollinosis patients can experience symptoms even out of the pollen season, when there is no presence of a relevant quantity of pollen grains and symptoms can be induced by the same pollen allergens carried by airborne particles, much smaller than pollen grains, deriving from allergenic

plants (17–19). Some of these paucimicronic particles are plant debris, such as fragments of leaves and stems (20). However, during thunderstorms and after rupture by osmotic shock, pollen grains may release tiny starch granules of mean diameter less than 5 μm which can be responsible for epidemics of asthma attacks (21). Also aeroallergens released by pollen grains can be transferred to other small, non-biological particles of air pollution such as those of the diesel exhaust particulate (DEP) acting as biological aerocontaminants of the inhaled air, which can penetrate deep into the airways inducing allergic symptoms in sensitized subjects (27).

Air pollution-induced increase in IgE-mediated response in predisposed subjects

Of airborne particulate emissions, interest has focussed on DEP because experimental studies showed that DEP can modify the immune response in predisposed animals and humans. In fact, DEP seems to exert an adjuvant immunological effect on IgE synthesis in atopic subjects, thereby influencing sensitization to airborne allergens (28). The effects of DEP on IgE production have been studied both *in vivo* and *in vitro* (29). DEP exerts its effects by way of chemical agents, i.e. polyaromatic hydrocarbons, and it has been observed that combined exhaust particulate and ragweed allergen challenge markedly enhances human *in vivo* nasal ragweed-specific IgE and skews cytokine production to a T-helper cell 2-type pattern (30). A pollutant such as DEP can influence the way a pollen, once inhaled, is processed. In particular, T cell responses to aeroallergens may be skewed in a Th2 direction in the presence of pollutants such as DEP. In other words DEP increases *in vivo* IgE and cytokine production at the human respiratory mucosa, exacerbating allergic inflammation. We hope that the new diesel engines are able to reduce DEP emissions in atmosphere.

Air pollution-induced increase in airway reactivity and impaired respiratory health

Several studies have evaluated whether air pollution exposure reduces the threshold dose of aeroallergens able to induce airway responsiveness to the specific bronchial challenge in sensitized subjects. The effect of previous exposure to nitrogen dioxide or ozone on subsequent allergen-induced changes in the nasal mucosa of subjects affected by seasonal allergic rhinitis or perennial allergic asthma has been investigated (2,31). The results suggest that exposure to NO_2 and ozone may prime the eosinophils to subsequent activation by inhaled antigen in atopic subjects. Ozone induces inflammatory effects in upper and lower airways favouring the migration in nasal and bronchial mucosa of eosinophils, neutrophils, eosinophil peroxidase, myeloperoxidase, eosinophil cationic protein and other inflammatory mediators (2,31). Seltzer *et al.* (32) have shown increased numbers of neutrophils and levels of some prostaglandins in BAL fluids of subjects 3 h after termination of a 2-h exposure to 0·4 or 0·6 ppm O_3. These authors were also able to demonstrate an increase in airway responsiveness to methacholine aerosol in the O_3-exposed subjects. Koren *et al.* (33) have shown that a single O_3 exposure (0·4 ppm for 2 h) induces an acute lung inflammatory response in humans as evidenced in BAL fluids by increased levels of inflammatory cells and soluble factors potentially capable of producing damage in the lower airways.

Experimental studies on allergic asthmatics, using ozone exposure or non-polluted air exposure before allergen challenge showed an increased sensitivity to inhaled allergens in subjects pre-esposed to ozone and not in pre-exposed to non polluted air (34–36). In other words less inhaled allergen was required to cause a decrease in forced expiratory volume in 1 s (FEV_1) after ozone exposure.

As for the health effects of air pollution in subjects living in polluted urban areas, both in U.S. (11–12) and in Europe (37) an association of daily concentrations of particulates and other components of urban air pollution (NO_2 and SO_2) and daily mortality has been found. However, the mechanism through wich PM_{10} is related to respiratory health is unclear (38). In this context Seaton *et al.* (39) hypothesized that fine particulate of urban areas, penetrating deep into airways, is able to induce alveolar inflammation which is responsible for variation in blood coagulability and release of mediators which induce acute episodes of respiratory and cardiovascular diseases. To explain the acute respiratory effects associated with PM_{10} the same authors (39) hypothesize that some elements such as transition metals in the particles damage airways generating free radicals and that PM_{10} mass concentration serve as a proxy for these elements. In particular responsibility for the adverse respiratory effects seems to be iron, which is able to generate hydroxyl radicals (40–41). Other transition metals (chromium, cobalt, copper, manganese, nickel, titanium, vanadium and zinc) derived from various urban or combustion source samples were also correlated to radical activation and lung injury in animal experiments (41–45).

Air pollution, climate changes and pollen-related respiratory allergy

The quality and quantity of recent publications relating to the cause and to the meteorological and ecological effects of global warming (the greenhouse effect) are worthy testimony to the scale of the problem which now faces the world community. Estimates of the scale of the temperature rise vary. Although it seems likely that a mean rise in the order of 1–2°C have occurred in the world in the last 20 years, with consequences on the vegetation. Predictions regarding rainfall are less certain and it is virtually impossible to predict changes relating to wind speed and direction. Moreover, anticipating the ecological and agricultural

consequences of climatic change is highly problematic. There is also the thorny question as to how increasing levels of greenhouse gases and concomitant climate changes will influence the frequency and severity of pollen-induced respiratory allergy. A variety of direct and indirect evidence suggests that climate changes may affect pollen release and consequently pollen-related asthma. In fact, climate variations are likely to influence vegetation with consequent changes in growth, reproductive cycle, and in the production of allergenic pollen (seasonal period and intensity) with greater proliferation of weed species.

Evidence has emerged that the flowering times of birch trees in the U.K. (46) and of Parietaria in Southern Italy (13,16) are getting notably earlier in response to the warmer springs of recent years. Climate changes vary region to region. Some areas will be subject to increases in ultraviolet radiation and/or rainfall frequency and other areas to reductions.

However, the role of climatic factors such as barometric pressure, temperature and humidity in the triggering and/or exacerbation of respiratory allergic symptoms is still poorly understood. For example, while the relationship between thunderstorms and exacerbation of pollen allergy during the pollen season has been demonstrated for some plant species such as grasses, the relationship between respiratory allergy and barometric pressure is not clear. Indeed, asthma crisis have been linked not only with low atmospheric pressure (47) but also with high pressure (48). Therefore, more studies are required to clarify this issue.

We still have much to learn about the effects of other climate factors which seem to be of major importance to asthma crisis, e.g. wind speed and passage of cold fronts. It is well known that the inhalation of cold air may induce bronchoconstriction in asthmatics. Moreover, exercise in polluted areas results in greater deposition in lower airways of air pollutants such as particulate matter, including particles carrying allergens. In fact, exercise increases oral breathing, total ventilation and inertial impaction of inhaled particles in the airways.

Moreover, ultraviolet radiations in the urban polluted atmosphere favour the formation of ozone levels which are highest in relation to elevated daytime temperatures, low wind speeds and clear skies. This association is characteristic of the Mediterranean area, California, and Central (Mexico City) (49) and South America. All these regions are plagued by high levels of car traffic, but there is also observed an association between ozone and fatal asthma in New York City (50). Ozone is the most important component of the so-called 'summer smog' and is produced by photochemical reactions induced by ultraviolet action on atmospheric mixtures of NO_2 and hydrocarbons.

Exposure to increased atmospheric levels of ozone causes decrements in lung function, increased airway reactivity to non-specific and specific bronchoconstrictor agents and is related to increased risk of asthma exacerbation in susceptible asthmatic patients. It has been also observed that ozone exposure has both a priming effect on allergen induced responses as well as an intrinsic inflammatory action in the nasal airways of allergic asthmatics (51).

Weather may affect levels of other pollutants commonly related with asthma exacerbation (SO_2, NO_2 and particulate matter). In particular inversions of temperature are usually associated with higher levels of particulate matter, SO_2 and NO_2.

Weather also exerts an indirect influence on allergic respiratory responses by acting on plants producing allergenic pollen (16,23). The influence of weather and air pollution on vegetation occurs over a wide range of environmental conditions and pollutant concentrations, and various factors are involved: plant species, plant age, soil conditions, nutrient balance, temperature, humidity and sunlight. Some susceptible plant species will probably not survive under great changes ecosystems.

Plants can absorb pollutants through the leaves or through the root system. In the latter case, deposition of air pollutants on soils can alter the nutrient content of soil in the proximity of the plant thus leading to indirect or secondary effects of air pollutants on vegetation. Metabolic variations, which probably involve also photosynthesis, affect the plant's structural integrity and there are probably changes in the pollen proteins, including those acting as allergens.

Due to heavy urban traffic with a high production of photochemical smog and sunny days for most of the year, the city of Naples provides an area to study the interrelationship between components of air pollution and pollen-derived allergens. The climate also favours the pollination of Parietaria, which grows in abundance throughout the city (16,52,53); indeed, about 30% of Neapolitans are allergic to this plant and more than 50% of these Parietaria pollen-allergic subjects experience bronchial asthma or its equivalent symptoms. We have observed that cases of pollen-induced respiratory disorders tend to increase when there is a parallel increase in the atmosphere of ozone, PM_{10} and Parietaria pollens. This parallel increase usually starts in February and reaches its peak in June or July, after which the production and release of Parietaria pollen usually decreases while ozone and PM remain high into the autumn. In addition, Parietaria pollen and ozone reach their highest levels in morning. Parietaria peaks earlier than ozone because of the time required for the photochemical reaction to develop.

In an attempt to test the hypothesis regarding the interaction between air pollution and pollen grains, we examined the effect of various polluting agents (gas from car powered by normal and catalized petrol, diesel car and motorcycle) on the pollen of Parietaria, placing 150 mg of this pollen in different tubes each filled with different exhaust gas. After seven days the Parietaria pollen samples at 5% weight/volume were extracted overnight. The solutions were centrifuged and the surnatants collected and filtered. The allergenic potency was determined by RAST inhibition test. We found that exhaust emissions from noncatalytic cars increased the allergenic potency of Parietaria pollen as compared with exhaust emissions from non-catalytic cars (16).

Conclusions

Over the past two decades there has been increasing interest in studies of air pollution and its effects on human health.

Although the role played by outdoor pollutants in allergic sensitization of airways has yet to be clarified, a body of evidence suggests that urbanization, with its high levels of vehicle emissions and a westernized lifestyle are linked to the rising frequency of respiratory allergic diseases seen in most industrialized countries. In particular three studies (11,54,55) have shown that people living in places with higher pollution levels have a reduced life expectancy. Pollinosis is a frequent disorder used to study the interrelationship between air pollution and respiratory allergy. Climatic factors (wind speed, temperature, humidity) can affect biological and chemical components of this interaction.

By attaching to the surface of pollen grains and of plant-derived paucimicronic particles, pollutants can modify the morphology of these antigen-carrying agents and alter their allergenic potential. In addition, by inducing airway inflammation, pollutants may overcome the mucosal barrier and so 'prime' allergen-induced responses.

Fortunately, there is a considerable research activity and interest from national governments and international organizations to set new health-based air quality standards to protect the public. It is of great importance to investigate to what extent the use of alternative fuels or engine types can reduce the formation of tropospheric ozone and the production of other components of air pollution such as respirable particulate. However, important decisions need to be taken urgently by governments worldwide concerning motor vehicle induced air pollution to reduce the future costs of effects on health and on the environments.

References

1. United Nations Environment Programme. Air pollution in the world's megacities. *Environ* 1994; **36:** 5–37.
2. American Thoracic Society. Health effects of outdoor air pollution. Part I. *Am J Respir Crit Care Med* 1996; **153:** 3–50.
3. Lebowitz M D. Epidemiological studies of the respiratory effects of air pollution. *Eur Respir J* 1996; **9:** 1029–1054.
4. Gielen MH, Van der Zee SC,Van Eijenen JH,Van Steen CJ, Brunekreef B. Acute effects of summer air pollution on respiratory health of asthmatic children. *Am J Respir Crit Care Med* 1997; **155:** 2105–2108.
5. Viegi G, Enarson DA. Human health effects of air pollution from mobile sources in Europe. *Int J Tuberc Lung Dis* 1998; **2:** 947–967.
6. Burney P. Air pollution and asthma: the dog that doesn't always bark. *Lancet* 1999; **353:** 859–860.
7. Boezen HM, van der Zee S C, Postma D S, *et al*. Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children. *Lancet* 1999; **353:** 874–878.
8. Koenig JQ. Air pollution and asthma. *J Allergy Clin Immunol* 1999; **104:** 717–722.
9. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks and the use of asthma medications in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996; **9**: 687–695.
10. Burney PGJ. Evidence for an increase in atopic diseases and possible causes. *Clin Exp Allergy* 1993; 23: 484–492.
11. Dockery DW, Pope CA, Xu X, Spengler JD, *et al*. An association between air pollution and mortality in six US cities. *New Engl J Med* 1993; **329:** 1753–1759.
12. Schenker M. Air pollution and mortality. *New Engl J Med* 1993; **329:** 1807–1808.
13. D'Amato G, Liccardi G. Environmental injury of airways and allergic respiratory diseases. *Pulm Pharmacol Ther* 1998; **11:** 369–374.
14. Devalia J L, Rusznak C, Davies RJ. Allergen/irritant interaction-its role in sensitization and allergic disease. *Allergy* 1998; **53:** 335–345.
15. D'Amato G, Spieksma FTM, Liccardi G, *et al*. Pollen-related allergy in Europe. Position paper of the European Academy of Allergology and Clinical Immunology. *Allergy* 1998; **53:** 567–578.
16. D'Amato G. Urban air pollution and plant-derived respiratory allergy. *Clin Exp Allergy* 2000; **30:** 628–636.
17. Busse W W, Reed C E, Hoehne J H. Where is the allergic reaction in ragweed asthma? II. Demonstration of ragweed antigen in airborne particles smaller than pollen. *J Allergy Clin Immunol* 1972; **50:** 289–293.
18. Solomon WR, Burge HA, Muilenberg M L. Allergen carriage by atmospheric aerosol. I. Ragweed pollen determinants in smaller micronic fraction. *J Allergy Clin Immunol* 1983; **72:** 443–447.
19. Spieksma FThM, Nikkels BH, Dijkman JH. Seasonal appearance of grass pollen allergen in natural, paucimicronic aerosol of various size fractions. Relationship with airborne grass-pollen concentration. *Clin Exp Allergy* 1995; **25:** 234–239.
20. D'Amato G, De Palma R,Verga A, *et al*. Antigenic activity of non pollen parts (leaves and stems) of allergenic plants. *Ann Allergy* 1991; **67:** 421–424.
21. Knox RB. Grass pollen, thunderstorms and asthma. *Clin Exp Allergy* 1993; **23:** 354–359.
22. Behrendt H, Becker WM, Friedrichs KH, Darson V, Tomingas R. Interaction between aeroallergens and airborne particulate matter. *Int Arch Allergy Immunol* 1992; **99:** 425–428.
23. D'Amato G. Outdoor air pollution, climatic changes and pollenosis. In: D'Amato G, Bonini S, Bousquet J, Durham SR, Platts-Mills TAE, Eds. Pollenosis 2000: (Global Approach). *Naples, Italy: JGC Editions,* 2001; 91–96.
24. Emberlin J. The effects of air pollution on allergenic plants. *Eur Respir Rev* 1998; **53**: 164–167.
25. Hjelmeroos M, Schumacker M, van Hage-Hamster V. Variations in birch pollen (*Betula verrucosa*) allergens between different trees in view of both the provenance and air pollution. Proceedings of the 5th International Conference on Aerobiology, Bangalore, India, 1994.

26. Emberlin J, Savage M, Jones S. Annual variations in grass pollen seasons in London 1961–1990, trends and forecast models. *Clin Exp Allergy* 1993; **23**: 911–918.
27. Knox RB, Suphioglu C, Taylor P, *et al*. Major grass pollen allergen Lol p1 binds to diesel exhaust particles: implications of asthma and air pollution. *Clin Exp Allergy* 1997; **27:** 246–251.
28. Takafuji S., Suzuki S, Koizumi K, *et al*. Diesel exhaust particulates inoculated by the nasal route have an adjuvant activity for IgE production in mice. *J Allergy Clin Immunol* 1987; **79**: 639–645.
29. Nel AE, Diaz-Sanchez D, Ng D, Hiura T, Saxon A. Enhancement of allergic inflammation by the interaction between diesel exhaust particles and the immune system. *J Allergy Clin Immunol* 1998; **102**: 539–554.
30. Diaz-Sanchez D, Tsien A, Fleming J, Saxon A. Combined diesel exhaust particulate and ragweed allergen challenge markedly enhances human *in vivo* nasal ragweed-specific IgE and skews cytokine production to a T helper cell 2-type pattern. *J Immunol* 1997; **158:** 2406–2413.
31. Graham DE, Koren HS. Biomarkers of inflammation in ozone-exposed humans. Comparison of the nasal and bronchoalveolar lavage. *Am Rev Respir Dis* 1990; **142:** 152–156.
32. Seltzer J, Bigby BG, Stulborg M, *et al*. O_3 induced change in bronchial reactivity in methacholine and airway inflammation in humans. *J Appl Physiol* 1986; **60:** 1321–1326.
33. Koren HS, Devlin RB, Graham DE, *et al*. Ozone-induced inflammation in the lower airways of human subjects. *Am Rev Respir Dis* 1989; **139:** 407–415.
34. Molfino NA, Wright SC, Katz I, *et al*. Effect of low concentration of ozone on inhaled allergen responses in asthmatic subjects. *Lancet* 1991; **338:** 199–203.
35. Jorres R, Nowak D, Magnussen H. Effect of ozone exposure on allergen responsiveness in subjects with asthma or rhinitis. *Am J Resp Crit Care Med* 1996; **153:** 56–64.
36. Kehrl HR, Peden DB, Ball B, Folinsbee LJ, Horstrom D. Increased specific airway reactivity of persons with mild allergic asthma after 76 hours of exposure to 0.16 ppm ozone. *J Allergy Clin Immunol* 1999; **104:** 1198–1204.
37. European Commission. Environmental Research Programme. The APHEA Project. Short term effects of air pollution on health: a European approach using epidemiological time series date. *J Epidemiol Comm Health* 1996; **50**(Suppl.1): S2–S80.
38. Roemer W, Hoek G, Brunekreef B, *et al*. PM10 elemental composition and acute respiratory health effects in European children (PEACE project). *Eur Respir J* 2000; **15:** 553–559.
39. Seaton, MacNee W, Donaldson K, Godden K. Particulate air pollution and acute health effects. *Lancet* 1995; **345:** 176–178.
40. Smith KR, Aust AE. Mobilization of iron from urban particulates leads to generation of reactive oxygen species *in vitro* abd induction of ferritin synthesis in human lung epithelial cells. *Chem Res Toxicol* 1997; **10:** 828–834.
41. Ghio AJ, Hatch GE. Lavage phospholipid concentration after silica instillation in the rat is associated with complexed (Fe^{3+}) on the dust surface. *Am J Respir Cell Mol Biol* 1993; **8:** 403–407.
42. Donaldson K, Brown DM, Mitchell C, *et al*. Free radical activity of PM10: iron mediated generation of hydroxyl radicals. *Environ Health Perspect* 1997; **105** (Suppl. 5): 1285–1289.
43. Costa DL,Dreher KL. Bioavailable transition metals in particulate matter mediate cardiopulmonary injury in healthy and compromised animal models. *Environ Health Perspect* 1997; **105**(Suppl 5): 1053–1060.
44. Dreher KL, Jaskot RH, Lehmann JR, *et al*. Soluble transition metals mediate residual oil fly ash induced acute lung injury. *J Toxicol Environ Health* 1997; **50:** 285–305.
45. Costa DL, Lehmann JR, Winsett D, McGee J, Ghio A. Pulmonary toxicity of Utah valley PM: are empirical indices of adverse health effects coherent with the epidemiology? *Am J Respir Crit Care Med* 1998; **152:** A880.
46. Emberlin J, Mullins J, Corden J, *et al*. The trend to earlier birch pollen seasons in the UK: a biotic response to changes in weather conditions? *Grana* 1997; **36:** 29–33.
47. Celenza A, Fothergill J, Kupek E, Shaw R J. Thunderstorms associated asthma: A detailed analysis of environmental factors. *BMJ* 1996; **312:** 604–607.
48. Garty BZ, Kosman E, Ganor E, *et al*. Emergency room visits of asthmatic children, relation to air pollution, weather, and airborne allergens. *Ann Allergy Asthma Immunol* 1998; **81:** 563–570.
49. Romieu I, Meneses F, Ruiz S, *et al*. Effect of air pollution on the respiratory health of asthmatic children living in Mexico City. *Am J Respir Crit Care Med* 1996; **154:** 300–307.
50. Thurston GD, Gwynn RC. Ozone and asthma mortality/hospital admissions in New York City. *Am J Respir Crit Care Med* 1997; **155:** A426.
51. Peden DB, Setzer RW, Devlin RB. Ozone exposure has both a priming effect on allergen induced responses as well as an intrinsic inflammatory action in the nasal airways of perennial allergic asthmatics. *Am J Respir Crit Care Med* 1995; **151:** 1336–1345.
52. D'Amato G, Ruffilli A, Ortolani C. Allergenic significance of Parietaria (pellitory-of-the-wall) pollen. In: D'Amato G, Spieksma F, Bonini S, eds. *Allergenic pollen and pollinosis in Europe*. Oxford: Blackwell Scientific Publications, 1991; 113–118.
53. D'Amato G, Liccardi G. Pollen-related allergy in the European Mediterranean area. *Clin Exp Allergy* 1994; **24:** 210–219.
54. Pope CA, Thun MJ, Namboodiri MM, *et al*. Particulate air pollution as a predictor of mortality in a prospective study of US-adults. *Am J Respir Crit Care Med* 1995; **151:** 669–674.
55. Abbey DE, Nishino N, McDonnel WF, *et al*. Long-term inhalable particles and other air pollutants related to mortality in nonsmokers. *Am J Respir Crit Care Med* 1999; **159:** 373–382.