Review Article

Air pollution and asthma

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Summary: The role of air pollution in the increased prevalence and morbidity of asthma has been widely debated, but results to date indicate that the normally encountered levels of air pollution are unlikely to contribute to a worsening of asthma. When the levels of sulphur dioxide (SO₂) are exceptionally high it is possible that asthmatic patients may have increased symptoms after exertion, since this irritant gas acts as a trigger to bronchoconstriction. There is also evidence that suspended particles may also act as an inciter of asthma symptoms when concentrations are high. Experimentally, ozone in high concentrations may increase airway responsiveness in both normal and asthmatic subjects by inducing airway inflammation, but asthmatic individuals show the same responses as normal subjects and there is little or no evidence to link increases in ambient ozone with an increase in asthma. There is little evidence that nitrogen dioxide (NO₂), even at the peak levels recorded, has any significant effect on airway function in normal or asthmatic individuals.

Other air pollutants which are present in lower concentrations have not been studied as extensively, but there is no convincing evidence that they cause significant respiratory symptoms in asthmatic patients. It is still possible that combinations of air pollutants may have greater effects on airway function than exposure to a single pollutant, although there is little evidence to support this. Epidemiological evidence provides little support for the idea that atmospheric pollution levels are related to the frequency of asthma symptoms or the frequency of attacks. More importantly, there is no evidence that asthma prevalence or aetiology is related to the level of air pollution.

A review of currently available information therefore provides little evidence for the widely expressed view that atmospheric pollution is related to increased prevalence or morbidity of asthma or is related to the causation of asthma.

Introduction

The role of air pollution in the pathophysiology of asthma has recently become an important area of debate in view of epidemiological evidence for a worldwide increase in asthma and other allergic diseases. Many studies have attempted to investigate the role of individual atmospheric pollutants either in a laboratory setting in the form of controlled exposure, or by association between levels of pollutants in the atmosphere and exacerbations of asthma symptoms. It has even been suggested that atmospheric pollutants may underlie the increased prevalence of allergic diseases. This review considers the recent evidence of the association between air pollution and asthma in relation to our current understanding of asthma as a chronic inflammatory disease of the airways.

Epidemiological trends

There is evidence that the prevalence of asthma is rising in adults and children^{1–3} and these trends have been reported from many different countries. A study in the UK showed that between 1971 and 1981 there was a doubling of patients diagnosed as asthma which could not be explained by a shift in the diagnosis from chronic bronchitis.⁴ Interestingly, a similar increase in the diagnosis of hay fever was also found in this population. Severity of asthma is difficult to quantify in epidemiological studies, but the increased admission rates to hospital for asthma might indicate that there has been an increase in asthma severity.⁵ In the USA hospital discharge rates for asthma increased nearly three-fold between 1970 and 1987.⁶

The increased morbidity of asthma has been reported in many different countries and is found in industrialized and developing countries.⁷ This makes it unlikely that air pollution is an important

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factor, particularly since countries with the greatest increases in asthma prevalence include Australia and New Zealand, which are usually considered to have low levels of air pollution.

Inducers and inciters

Our current understanding is that all asthmatic patients have an underlying chronic inflammatory process in the airways. This inflammation is characterized by the presence of activated CD4⁺ T lymphocytes, eosinophils and mast cells.^{8,9} In allergic ('extrinsic') asthmatic patients, this inflammatory state may be driven by exposure to inhaled allergens, such as house dust mite, pollens or mould spores. In non-allergic ('intrinsic') asthma, the nature of the driving mechanism is unknown, whereas in the case of some occupational asthmas a sensitizing chemical encountered in the workplace (such as toluene diisocyanate) is responsible. The chronic inflammatory state is associated with increased airway responsiveness and usually with symptoms. Exposure to various agents may increase asthma symptoms and it is important to distinguish between factors that increase airway inflammation leading to increased airway responsiveness (*inducers*) and factors which merely increase asthma symptoms by triggering airway narrowing (*inciters*). Exposure to allergens and chemical sensitizers results in increased airway inflammation and increased airway responsiveness to various challenges. By contrast, exposure to spasmogens (such as histamine and methacholine which constrict airway smooth muscle directly), exercise, hyperventilation and laughing (resulting in cooling and drying of the airway mucosa), fog (resulting in reduced osmolarity or airway lining fluid), metabisulphite, SO₂ and bradykinin (resulting in activation of airway sensory nerves) lead to transient airway narrowing and symptoms of wheezing, but do not increase inflammation or airway responsiveness. The natural triggers of asthma, such as exercise, fog and hyperventilation are indirect constrictors, implying that they release bronchoconstrictors from other cells in the airways (such as mast cells, sensory nerves or other inflammatory cells) and are only effective in the presence of asthmatic inflammation. In other words, inflammation is a necessary precondition for these triggers/inciters to produce symptoms.

What is air pollution?

Air pollution has been implicated in the aetiology, the epidemiological changes and in the worsening of asthma. Although episodes of major air pollution have been associated with increased asthma

morbidity and mortality, at present there is little evidence to suggest that the normally encountered levels of air pollution play any significant role in the aetiology or symptomatology of asthma.¹⁰⁻¹³

There are several major pollutants in ambient air and their effects on the airways have been studied separately and in combination. Sulphur dioxide is an urban pollutant derived from the burning of coal and oils, the smelting of sulphur-containing ores and industrial processes, such as the manufacture of cement. Although the atmospheric levels have fallen in many countries with control of combustion, the upper recommended level of 0.04 parts per million (p.p.m.) may be temporarily exceeded and peak values of up to 0.2 p.p.m. may be reached. SO₂ in the ambient air may form an aerosol of sulphuric acid and mix with other acids, such as nitric, hydrochloric and hydroxy-methanesulphonic acid as acid fog.¹⁴

Particulate matter (smoke) is also an important component of air pollution and may be measured as total suspended particles, which the complex mixture of organic and inorganic dusts collected in a filter, or as PM₁₀, which measures only those particles of < 10 µm which are respirable.

Oxides of nitrogen (NO_x), of which nitrogen dioxide is the major component, are derived from car exhausts and fuel combustion. NO₂ may also occur inside houses and is derived from gas cookers, and gas and oil heaters. Ambient concentrations depend on the density of cars and annual mean concentrations in cities are approximately 0.06 p.p.m. but peak concentrations on busy roads may occasionally exceed 2 p.p.m. Hourly concentrations in Los Angeles, which has one of the highest average levels, may reach 0.5 p.p.m. on occasions. Nitric oxide is a much smaller component of pollution and is rapidly converted to NO₂.

Ozone (O₃) is a powerful oxidizing agent formed by the action of sunlight on NO₂ in the presence of hydrocarbons resulting from photochemical smog. There is a background O₃ concentration derived from the upper atmosphere of approximately 0.2 p.p.m. Ozone formation is favoured by high temperature, sunlight and low winds, and may be carried long distances by prevailing winds. Because O₃ is broken down in the presence of NO₂, its concentration in cities may be less than in rural areas. In the UK peaks of O₃ of > 0.2 p.p.m. may be reached in the summer months in the presence of sunlight and windless conditions.

There may be several other atmospheric pollutants in lower concentrations, such as carbon monoxide, formaldehyde, secondary aldehydes and mixtures of short-lived radicals, but there has been little research on their airway effects at relevant concentrations.

Studies in asthma

There are several ways in which an air pollutant may have effects on the airways of asthmatic patients.

1. The pollutants may act as inciters or triggers when the airways are hyper-responsive, resulting in transient airway narrowing.
2. The pollutant may act as an inducer to increase airway inflammation and therefore airway hyper-responsiveness, which may persist beyond the exposure time.
3. The pollutant may have a direct toxic effect on the airways, leading to asthma-like symptoms in normal individuals.
4. The pollutant may affect the immune system, resulting in sensitization or increased allergic responses in the airway.

Theoretically air pollutants may therefore cause exacerbation of pre-existing asthma or may increase the risk of developing asthma.

The link between air pollutants and asthma has been studied using two main approaches. Laboratory studies have been used to measure the airway response following exposure to a particular pollutant under carefully controlled conditions and at relevant concentrations. Although it is possible to make careful measurements it is not possible to examine long-term exposure and the effects of interacting pollutants is difficult to evaluate. In addition, the patients studied usually have mild asthma. The alternative approach is to undertake epidemiological studies, either in large populations, some of whom will be asthmatic, or in defined groups of asthmatic patients. These studies may be difficult to interpret because of confounding effects of aero-allergen exposure, infections and climatic changes. Furthermore, it is very difficult to estimate individual exposure.

Sulphur dioxide

Many studies have been performed with exposure of normal, atopic and asthmatic individuals to SO₂. SO₂ causes chest tightness and an immediate bronchoconstriction but the concentration required depends to some extent on the degree of airway hyperresponsiveness (AHR). For normal subjects concentrations of > 5 p.p.m. are usually required to provoke bronchoconstriction, whereas for asthmatics bronchoconstriction develops at concentrations > 1 p.p.m.^{15,16} With moderate exercise bronchoconstriction is found in asthmatic patients at concentrations of 0.25 p.p.m. when the subjects breathe through a mouthpiece, but concentrations of > 0.4 p.p.m. are needed when subjects breathe through the nose as some SO₂ is removed in the upper respiratory tract. The incremental effect of these low concentrations of SO₂ on exercise-

induced asthma appears to be similar, irrespective of the severity of asthma.¹⁶ Since the highest concentrations encountered in the atmosphere are likely to be in the order of 0.25 p.p.m., this suggests that SO₂ may induce symptoms in asthmatic individuals only with exercise. The bronchoconstrictor response to SO₂ in asthmatic subjects is rapid in onset and recovers rapidly once exposure ceases; there is no evidence that SO₂ increases AHR at these concentrations. The mechanism of action of SO₂ is probably as a bronchial irritant via activation of sensory nerves resulting in cough and wheeze.

Interactions with other pollutants have been examined. Prior exposure to ozone increased the sensitivity of SO₂ in a group of mild asthmatics, so that concentrations as low as 0.1 p.p.m. cause bronchoconstriction during moderate exercise.¹⁷ However, the effects on lung function are extremely small and of doubtful clinical significance. Prior inhalation of NO₂ had no effect on the airway response to SO₂ inhalation in asthmatic patients.¹⁸

Oxides of nitrogen

There has been great interest in the effects of NO₂ on airway function in normal and asthmatic individuals, since the concentrations of this pollutant have increased with traffic density, whereas concentrations of many other air pollutants have decreased. The effects of relevant concentrations of NO₂ in normal and asthmatic individuals have been studied extensively.¹⁹ In normal subjects exposure to high concentrations of NO₂ have caused small and inconsistent effects, but exposure to concentrations of less than 1 p.p.m. have not had any significant effects.¹⁹ A widely quoted study by Orehek *et al.* demonstrated an increased bronchoconstrictor response to carbachol in asthmatic patients exposed to 0.1 p.p.m. NO₂.²⁰ Some subsequent studies demonstrated a small effect on airway responsiveness after exposure of asthmatic patients to 0.1–0.3 p.p.m. for one hour,^{21–23} but most have failed to demonstrate any effect at concentrations up to 4 p.p.m. with exercise in either normal or asthmatic individuals.^{18,24–30} Long-term exposure of asthmatic patients (including patients with severe asthma) to NO₂ at concentrations of 0.3 and 0.6 p.p.m. and to ambient air in Los Angeles with an NO₂ content of 0.09 p.p.m. had no effect on airway function, even in the patients with most severe asthma.³¹ The majority of studies have also failed to demonstrate any effect on lung function. Thus NO₂, even at concentrations higher than those achieved in the atmosphere at peak periods, has little or no effect on airway function in patients with asthma. Nor is there any evidence that NO₂ effects are potentiated by other pollutants such as ozone³² or potentiate the bronchoconstrictor effects of SO₂.¹⁸ A recent study of cultured human

airway epithelial cells demonstrated that exposure to an NO₂ concentration of 0.4 p.p.m. for 6 hours caused increased expression of proinflammatory cytokines, such as interleukin-8 and tumor necrosis factor- α ,³³ but the relevance of these *in vitro* studies to exposure *in vivo* is not yet certain.

Nitric oxide is now recognized to have an important physiological role in the regulation of vascular tone and as a neurotransmitter.³⁴ It is present in high concentration in cigarette smoke,³⁵ but its concentration in the ambient air is low. High inhaled concentrations may cause bronchoconstriction in normal individuals,³⁶ although lower concentrations (300 p.p.m.) have no effect³⁷ and a recent study showed a small and variable bronchodilator effect in asthmatic patients at a concentration of 80 p.p.m.³⁸

Ozone

The effects of ozone on respiratory function have been extensively investigated.³⁹ Early studies in animals and humans used high concentrations which had tissue damaging effects that are unlikely to be relevant to ambient exposure. Most studies have reported a small increase in airway responsiveness at concentrations of 0.1–0.3 p.p.m. and there do not appear to be any differences in the responses of normal and asthmatic subjects.^{26,40} With heavy exercise a concentration of 0.2 p.p.m. over one hour may increase responsiveness and cause tracheal irritation.⁴¹ With longer exposure effects at lower concentrations may be observed. Thus exposure to 0.08–0.12 p.p.m. for over 6 hours has been reported to increase AHR in normal individuals.⁴² The mechanism of increased reactivity has been investigated in humans, with an increase in neutrophils in bronchoalveolar lavage, suggesting that ozone provokes an inflammatory response.^{43,44} This inflammatory response is still present 18 hours after exposure to 0.08 p.p.m. ozone for 6 hours.⁴⁵ Ozone may also increase airway responsiveness to asthma triggers. Exposure to asthmatic subjects to 0.12 p.p.m. ozone for one hour caused a small increase in airway response to inhaled allergen,⁴⁶ although there was no increase in exercise-induced bronchoconstriction.⁴⁷ Ozone at a concentration of 0.4 p.p.m. for 4 hours increased the eosinophilic inflammatory response to intranasally applied allergen in atopic subjects.⁴⁸ These studies suggest that ozone, at concentrations which may be present during the summer months, may have a small effect on airway responsiveness, which may be associated with an increase in airway inflammation. However, there is no evidence that asthmatic patients are more susceptible to the effects of ozone than normal individuals. In the UK a recent government

sponsored survey assessed the available data on ozone and came to the conclusion that at levels of ozone which are the hourly average in the UK (0.1 p.p.m.) there was no convincing evidence for any effect on respiratory symptoms or function, apart from in occasional individuals during heavy exercise.⁴⁹ Symptoms become more common as concentrations increase with most subjects reporting some symptoms at levels of > 0.2 p.p.m.

Acid aerosols

Inhalation of sulphuric acid fog at relevant concentrations has little or no effect on airway function in either normal or asthmatic individuals.¹⁴ Similarly, another constituent of acid fog, hydroxymethanesulphonic acid has no effect on lung function in asthmatic subjects.⁵⁰

Epidemiological studies

There are three documented episodes of major air pollution associated with cold weather and little wind, so that polluted air became trapped as a result of temperature inversion, resulting in high concentrations of SO₂ (over 1 p.p.m.), sulphuric acid and particulate matter.¹⁰ These occurred in the Meuse Valley (Belgium) in 1930, in Dondora (USA) in 1948, and in London in 1952. In each episode there was evidence that asthmatic patients became more symptomatic with increased hospital admissions. Similarly in Yokohama there was evidence for increased asthma symptoms amongst US servicemen and their families which corresponded with periods of smog,⁵¹ although this was not seen to the same extent in resident Japanese asthmatic patients.⁵² In the famous London smog of 1952 Fry noted the absence of any problems amongst his younger asthmatic patients.⁵³ Similarly there was no increase in hospitalization for asthma during a severe episode of fog in Germany in 1985.⁵⁴

Large population studies of respiratory symptoms in relation to air pollution are difficult to interpret due to socio-economic factors, the effect of coexistent aero-allergens, the influence of cigarette smoking and the difficulty in diagnosing asthma. In a study of six US cities there was an association between the level of suspended particles and cough and bronchitis, but no association between levels of particulates, SO₂ or NO₂ was found in patients with persistent wheeze or asthma.^{55,56} In a large survey in Switzerland there was no relationship between the levels of air pollutants and respiratory symptoms in children, apart from an association with total suspended particles,⁵⁷ although there was no evidence for increased symptoms in asthmatic compared with

non-asthmatic children. In another study in children in the US there was an association between the PM₁₀ value and respiratory symptoms such as cough and wheeze, which was more marked in children with asthma,⁵⁸ suggesting that particulates may act as an irritant in the same way as SO₂. There are relatively few studies which have monitored the effects of air pollution on known asthmatic patients. In one study in Los Angeles there was a small effect of ozone concentrations of >0.3 p.p.m. on asthma symptoms in only a proportion of the 45 asthmatic patients studied⁵⁹ and some studies have demonstrated small effects of SO₂ levels on asthma symptoms.

In a study of schoolchildren in Austria there was evidence for a small increase in airway responsiveness in areas of high ozone (0.12 p.p.m.) compared with low ozone (<0.06 p.p.m.) but there was no difference in respiratory symptoms suggesting that these small changes in reactivity are unlikely to be clinically relevant.⁶⁰ A recent study in Dutch children found a small association between ambient ozone level and lung function, but no difference between asthmatic and non-asthmatic children.⁶¹

Studies linking admission to hospital with asthma and levels of air pollution have produced conflicting results, with some studies demonstrating a weak association with levels of SO₂, whereas others have shown no association with air pollution levels. It is possible that a combination of pollution and allergen may be relevant.

There is no evidence that air pollution is related to the prevalence of asthma, as evidenced by the fact that asthma is no more common in urban communities in industrialized countries where levels of air pollution would be expected to be higher. For example, there is no evidence that the prevalence of asthma in Los Angeles which has high levels of air pollution, is higher than in other areas of the USA. In a recent detailed study there was no evidence for an increase in the prevalence of asthma in polluted areas of Sydney compared with non-polluted areas.⁶²

The reunification of Germany has provided data on two populations exposed to very different levels of air pollutants.¹² Each German industrialized towns, such as Leipzig and Erfurt, have high concentrations of SO₂ and particulates, whereas West German cities, such as Munich and Hamburg, have low levels of SO₂ and particulates, but higher levels of NO₂. The prevalence of asthma and allergic diseases was reported to be higher in Munich than in Leipzig, but the prevalence of bronchitis was higher in Leipzig.⁶³ Similar differences have been reported based on questionnaires, with a much higher frequency of reported asthma attacks in Hamburg (West Germany) than in Erfurt (East Germany).⁶⁴ There is also a higher

prevalence of sensitization to the indoor allergens house dust mite and cats in schoolchildren from Leuna (East Germany) compared with Duisberg (West Germany), although there was no difference in sensitivity to outdoor allergens such as grass pollens.⁶⁵ This evidence suggests that indoor exposure to allergens is a more important determinant of asthma than exposure to outdoor air pollutants, such as SO₂ and particulates.

It has been argued that air pollution may increase the risk of developing allergic disease. A report from Japan suggested that there was an increase in pollen-induced rhinitis in districts polluted with diesel exhaust,⁶⁶ but other studies are needed to address this possibility. There is no evidence that air pollution increases either total serum IgE or the skin sensitivity to aero-allergens.⁶⁰

Summary and conclusions

There has been much debate about the role of air pollution in the increased prevalence and morbidity of asthma, but results to date indicate that the normally encountered levels of air pollution are unlikely to contribute to a worsening of asthma. When exceptionally high levels of SO₂ are encountered, it is possible that asthmatic patients may have increased symptoms, since this irritant gas acts as a trigger to bronchoconstriction. There are similar data to suggest that high levels of suspended particles may act as an inciter of asthma symptoms. There is evidence that, experimentally, ozone in high concentrations may increase airway responsiveness in both normal and asthmatic subjects by an increase in airway inflammation, but there is little evidence to link increases in ambient ozone with an increase in asthma. NO₂ concentrations are associated with car exhausts and there is evidence that its levels are rising in urban areas. However, there is little evidence that even peak levels cause significant effects on airway function. Other air pollutants which are present in lower concentrations have not been studied as extensively, but there is no convincing evidence that they cause significant respiratory symptoms in asthmatic patients. It is possible that a combination of air pollutants may have more effect on airway function than exposure to a single pollutant, and that there is an interaction between the effects of air pollution and allergen exposure. Few studies have explored these possibilities and further work is needed in this area.

Epidemiological evidence provides little support for the idea that atmospheric pollution levels are related to the frequency of asthma symptoms or the frequency of attacks. More importantly, there is no evidence that asthma prevalence or aetiology is related to the level of air pollution.

References

- Gergen, P.J., Mullally, D.I. & Evans, R. National survey of prevalence of asthma among children in the United States 1976 to 1980. *Pediatrics*, 1988, **81**: 1–7.
- Burney, P.G.J., Chinn, S. & Rona, R.J. Has the prevalence of asthma changed? Evidence from the national study of health and growth 1973–86. *Br Med J* 1990, **300**: 1306–1310.
- Weitzman, M., Gortmaker, S.L., Sobol, A.M. & Perrin, J.M. Recent trends in the prevalence and severity of childhood asthma. *JAMA* 1992, **268**: 2673–2677.
- Fleming, D.M. & Crombie, D.L. Prevalence of asthma and hay fever in England and Wales. *Br Med J* 1987, **294**: 279–283.
- Sears, M. Epidemiological trends in bronchial asthma. In: Kaliner, M.A., Barnes, P.J. & Persson, C.G.A. (eds) *Asthma. Its Pathology and Treatment*. Marcel Dekker, New York, 1991, pp. 1–49.
- Evans, R., Mullally, D.I. & Wilson, R.W. Natural trends in the morbidity and mortality of asthma in the United States; prevalence, hospitalization, and death from asthma over two decades. *Chest* 1987, **91** (Suppl): 65S–74S.
- Burney, P.G.J. Epidemiology. *Br Med Bull* 1992, **48**: 10–22.
- Djukanovic, R., Roche, U.R., Wilson, J.W. *et al.* Mucosal inflammation in asthma. *Am Rev Respir Dis* 1990, **142**: 434–457.
- Barnes, P.J. & Lee, T.H. Recent advances in asthma. *Postgrad Med J* 1992, **68**: 942–953.
- Wardlaw, A.J. The role of air pollution in asthma. *Clin Exp Allergy* 1993, **23**: 81–96.
- Pierson, W.E. & Koenig, J.Q. Respiratory effects of air pollution on allergic disease. *J Allergy Clin Immunol* 1992, **90**: 557–566.
- Magnussen, H., Jörres, R. & Nowak, D. Effect of air pollution on the prevalence of asthma and allergy: lessons from the German reunification. *Thorax* 1993, **48**: 879–881.
- Cameron, K. & Maynard, R. A new look at the health effects of air pollution. *Health Trends* 1992, **24**: 82–85.
- Hackney, J.D., Linn, W.S. & Avol, E.L. Acid fog: effects on respiratory function and symptoms in healthy and asthmatic volunteers. *Environ Health Perspect* 1989, **79**: 159–162.
- Sheppard, D., Wong, W.S., Uehara, C.F., Nadel, J.A. & Boushey, H.A. Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. *Am Rev Respir Dis* 1980, **122**: 873–876.
- Linn, W.S., Avol, E.L., Peng, R., Shamoo, D.A. & Hackney, J.D. Replicated dose-response study of sulfur dioxide effects in normal, atopic and asthmatic volunteers. *Am Rev Respir Dis* 1987, **136**: 1127–1134.
- Koenig, J.Q., Covert, D.S., Hanley, G.B. & Pierson, W.E. Prior exposure to ozone potentiates subsequent responses to sulfur dioxide in adolescent asthmatic subjects. *Am Rev Respir Dis* 1990, **141**: 377–380.
- Rubenstein, I., Bidby, B.G., Reiss, T.F. & Boushey, H.A. Short term exposure to 0.3 ppm nitrogen dioxide does not potentiate airway-responsiveness to sulfur dioxide in asthmatic subjects. *Am Rev Respir Dis* 1990, **141**: 381–385.
- Samet, J.M. & Utell, M.J. The risk of nitrogen dioxide: what have we learned from epidemiological and clinical studies? *Toxicol Ind Health* 1990, **6**: 247–262.
- Orehek, J., Massair, J.P., Gayard, P., Grimaud, C. & Charpin, J. Effect of short-term, low-level nitrogen-dioxide exposure on bronchial sensitivity of asthmatic patients. *J Clin Invest* 1976, **57**: 301–307.
- Kleinman, M.T., Bailey, R.M. & Linn, W.S. Effects of 0.2 ppm nitrogen dioxide on pulmonary function and response to bronchoprovocation in asthmatics. *J Toxicol Environ Health* 1983, **12**: 815–826.
- Mohensin, V. Airway responses to nitrogen dioxide in asthmatic subjects. *J Toxicol Environ Health* 1983, **22**: 371–380.
- Bauer, M.A., Utell, M.J., Morrow, P.E., Speers, D.M. & Gibb, F.R. Inhalation of 0.3 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics. *Am Rev Respir Dis* 1986, **134**: 1203–1208.
- Hazucha, M.J., Ginsberg, J.F., McDonnell, W.F. *et al.* Effects of 0.1 ppm nitrogen dioxide on airways of normal and asthmatic subjects. *J Appl Physiol* 1988, **54**: 730–739.
- Linn, I.V.S., Shampoo, D.A., Avol, E.L. *et al.* Dose-response study of asthmatic volunteers exposed to nitrogen dioxide during intermittent exercise. *Arch Environ Health* 1986, **41**: 292–296.
- Koenig, J.Q., Covert, D.S., Marshall, S.G., van Belle, G. & Pierson, V.E. The effects of ozone and nitrogen dioxide on pulmonary function in healthy and in asthmatic adolescents. *Am Rev Respir Dis* 1987, **136**: 1152–1157.
- Jörres, R. & Magnussen, H. Effect of 0.25 ppm nitrogen dioxide on the airway response to methacholine in asymptomatic asthmatic patients. *Lung* 1991, **169**: 77–85.
- Ahmed, T., Marchette, B., Danta, I. *et al.* Effect of 0.1 ppm NO₂ on bronchial reactivity in normals and subjects with bronchial asthma. *Am Rev Respir Dis* 1982, **125**: 152.
- Frampton, M.W., Morrow, P.E., Cox, C., Gibb, F.R., Speers, D.M. & Utell, M.J. Effects of nitrogen dioxide exposure on pulmonary function and airway reactivity in normal humans. *Am Rev Respir Dis* 1991, **143**: 522–527.
- Hackney, J.D., Linn, W.S., Avol, E.L. *et al.* Exposure of older adults with chronic respiratory illness to nitrogen dioxide. *Am Rev Respir Dis* 1992, **146**: 1480–1486.
- Avol, E.L., Linn, W.S., Peng, R.C., Valencia, G., Little, G. & Hackney, J.D. Laboratory study of asthmatic volunteers exposed to nitrogen dioxide and to ambient air pollution. *Am Ind Hyg Assoc* 1988, **49**: 143–149.
- Adams, W.C., Brookes, K.A. & Schelegle, E.S. Effects of NO₂ alone and in combination with O₃ on young men and women. *J Appl Physiol* 1984, **62**: 1698–1704.
- Devalia, J.L., Campbell, A.M., Sapsford, R.J. *et al.* Effect of nitrogen dioxide on synthesis of inflammatory cytokines expressed by human bronchial epithelial cells. *Am J Resp Cell Mol Biol* 1993, **9**: 271–278.
- Barnes, P.J. & Belvisi, M.G. Nitric oxide and lung disease. *Thorax* 1993, **48**: 1034–1043.
- Norman, V. & Keith, C.M. Nitrogen oxides in tobacco smoke. *Nature* 1965, **205**: 915–916.
- von Nieding, G., Wagner, H.M. & Krekeler, H. Investigation of the acute effects of nitrogen monoxide on lung function in man. In: *Proceedings of the 3rd International Clean Air Congress, Dusseldorf, Germany*. Verin Dautuber Ingenieur, Dusseldorf, 1973, pp. A14–16.
- Hulks, G., Warren, P.M. & Douglas, N.J. The effect of inhaled nitric oxide on bronchomotor tone in the normal human airway. *Am Rev Respir Dis* 1993, **147**: A287.
- Högman, M., Frostell, C.G., Hedenström, H. & Hedenstierna, G. Inhalation of nitric oxide modulates adult human bronchial tone. *Am Rev Respir Dis* 1993, **148**: 1474–1478.
- Lippman, M. Health effects of ozone. A critical review. *JAPCA* 1993, **39**: 672–695.
- Holtzman, M.J., Cunningham, J.H., Sheller, J.R., Irsigler, G.B., Nadel, J.A. & Boushey, H.A. Effects of ozone on bronchial reactivity in atopic and non-atopic subjects. *Am Rev Respir Dis* 1979, **120**: 1059–1067.
- Folinsbee, L.J., Bedi, J.F. & Horvata, S.M. Pulmonary function changes after 1 hour continuous hearing exercise in 0.21 p.p.m. ozone. *J Appl Physiol* 1984, **57**: 984–988.
- Folinsbee, L.J., McDonnell, W. & Horstman, D.H. Pulmonary function and symptom responses after 6.6 hour ozone exposure to 0.12 ppm will moderate exercise. *JAPCA* 1988, **38**: 28.

43. Aris, R.M., Christian, D., Hearne, B.Q. *et al.* Ozone-induced airway inflammation in human subjects as determined by airway lavage and biopsy. *Am Rev Respir Dis* 1993, **148**: 1363–1372.
44. Koren, H.S., Devlin, R.B., Graham, D.E. *et al.* Ozone and induced inflammation in the lower airways of human subjects. *Am Rev Respir Dis* 1989, **139**: 407–415.
45. Devlin, R.B., McDonnell, W.I.F., Mann, R. *et al.* Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. *Am J Respir Cell Mol Biol* 1991, **4**: 72–81.
46. Molino, N.A., Wright, S.C., Katz, I. *et al.* Effect of low concentration of ozone on inhaled allergen responses in asthmatic subjects. *Lancet* 1991, **338**: 199–203.
47. Fernandez, A.L.G., Molino, N., Hoffstein, V. *et al.* The effect of preexposure to 0.12 ppm of ozone on exercise-induced asthma. *Am Rev Respir Dis* 1993, **147**: A642.
48. Bascom, R., Nacleirio, R.M., Fitzgerald, T.K., Kagey-Sobotka, A. & Proud, D. Effect of ozone inhalation on the response to nasal challenge with antigen in allergic subjects. *Am Rev Respir Dis* 1990, **142**: 594–601.
49. Department of Health. *First Report of Advisory Group on the Medical Aspects of Air Pollution Episodes: Ozone*. HMSO, London, 1991.
50. Aris, R., Christian, D., Sheppard, D. & Barnes, J.R. Acid fog induced bronchoconstriction: the role of hydroxymethane-sulfuric acid. *Am Rev Respir Dis* 1990, **141**: 546–551.
51. Huber, T.E., Joseph, S.W., Knoblocke, E., Redfearn, P.L. & Karakana, J.A. New environmental respiratory disease (Yokohama Asthma). *Arch Ind Hyg Occ Med* 1954, **10**: 399–408.
52. Ostima, Y., Ishizaka, T., Miyamoto, T., Kabe, J. & Makino, S. A study of Tokyo-Yokohama asthma among Japanese. *Am Rev Respir Dis* 1964, **90**: 632–634.
53. Fry, J. Effects of a severe fog on a general practice. *Lancet* 1953, **i**: 235–236.
54. Wichmann, H.E., Mueller, W. & Allhof, P. Health effects during a smog episode in West Germany in 1985. *Environ Health Perspect* 1989, **79**: 89–99.
55. Ware, J.W., Ferris, B.G., Dockery, D.W., Spengler, D., Stram, D.O. & Speizer, F.E. Effects of ambient sulfur oxides and suspended particles on respiratory health of pre-adolescent children. *Am Rev Respir Dis* 1986, **133**: 834–842.
56. Dockery, D.W., Speizer, F.E., Stram, D.O., Ware, J.H., Spengler, J.D. & Ferris, B.G. Effects of inhalable particulates on respiratory health of children. *Am Rev Respir Dis* 1989, **139**: 587–594.
57. Braun-Fahrlander, C., Ackermann-Lieblich, U., Schwartz, J., Gnehm, H.P., Rutishauser, M. & Wanner, H.U. Air pollution and respiratory symptoms in preschool children. *Am Rev Respir Dis* 1992, **145**: 42–47.
58. Pope, C.A. & Dockery, D.W. Acute effects of PM10 pollution on symptomatic and asymptomatic children. *Am Rev Respir Dis* 1992, **145**: 1123–1128.
59. Kurata, J.H., Grovsky, M.M., Newcomb, R.L. & Easton, J.C. Multifactorial study of patients with asthma. 2: Air pollution, animal dander and asthma symptoms. *Ann Allergy* 1976, **37**: 398–409.
60. Zwick, H., Popp, U., Wagner, C. *et al.* Effects of ozone on the respiratory health, allergen sensitization and cellular immune system in children. *Am Rev Respir Dis* 1991, **144**: 1075–1079.
61. Hoek, G., Fischer, P., Brunekreef, B., Lebret, E., Hofschreuder, P. & Mennen, M.R. Acute effects of ambient ozone on pulmonary function of children in the Netherlands. *Am Rev Respir Dis* 1993, **147**: 111–117.
62. Peat, J.K., Salome, C.M. & Woolcock, A.J. Factors associated with bronchial hyperresponsiveness in Australian adults and children. *Eur Resp J* 1992, **5**: 921–929.
63. von Mutius, E., Fritzsch, C., Weiland, S.K., Roll, G. & Magnussen, H. Prevalence of asthma and allergic disorders among children in united Germany: a descriptive comparison. *Br Med J* 1992, **305**: 1395–1399.
64. Nowak, D., Heinrich, J., Beck, E. *et al.* Differences in respiratory symptoms between two cities in Western and Eastern Germany: the first report in adults (abstract). *Am Rev Respir Dis* 1993, **147**: A378.
65. Klein, K., Oathe, R., Göllnitz, S. & Jäger, L. Allergies—a comparison between two vocational schools in East and West Germany. *Allergy* 1992, **47** (Suppl 12): 259.
66. Ishizaki, T., Koizumi, K., Ikemori, R., Ishiyura, Y. & Kushibiki, E. Studies of prevalence of Japanese cedar pollinosis among the residents of a densely cultured area. *Ann Allergy* 1987, **58**: 265–270.