

CHAPTER 7

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Human laboratory studies of the health effects of air pollutants

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Introduction

7.1. Laboratory-based exposure studies have the advantage that conditions such as concentration and dose of pollutant, the nature of the volunteer (i.e. asthmatic, normal subject, etc.) and temperature can be controlled leading to reproducible results. In addition further experiments can be carried out, such as fibre-optic bronchoscopy with BAL.

7.2. The disadvantage of this approach is that sample numbers tend to be small, only one or two pollutants can be investigated at any one time, exposure times are relatively short and it is difficult to study those most at risk, e.g. brittle asthmatics. Questions such as whether air pollutants increase sensitization cannot easily be answered using this approach. Generally it is difficult to mimic the pattern of natural exposure and this may be one reason for apparent differences between the findings of epidemiology and laboratory studies on the health effects of air pollutants.

7.3. A large number of laboratory exposure studies have been performed investigating both physiology and more recently immunotoxicology combining exposure with fibre-optic bronchoscopy. The findings of these studies are summarized below.

Sulphur dioxide (SO₂), acid aerosols and particulates

7.4. SO₂ causes bronchoconstriction. Asthmatics are more hyperresponsive to the effects of SO₂ than normal subjects. For example in a study of the effects of 1–5 ppm of SO₂ asthmatics developed bronchoconstriction severe enough to require bronchodilators at all concentrations tested whereas non-asthmatics developed only mild bronchoconstriction at 5 ppm [130].

7.5. A key feature of SO₂ is that it is very water soluble with potentially different effects in people who are nose breathing, where it would be largely absorbed in the upper airway, and people who are mouth breathing either because

of exercise or nasal obstruction. The extent to which this theoretical consideration is important in practice is not certain as one study demonstrated that in rabbits exposed to less than 1 ppm only 5% of SO₂ was removed in the upper airways [131]. When asthmatics exercised under conditions of mouth breathing they developed bronchoconstriction at 0.25 ppm and wheeze at 0.5 ppm within 10 minutes [132]. Changes were less marked when normal breathing was undertaken presumably because of absorption of SO₂ in the nose [133, 134].

7.6. In a similar study no difference in the effect of SO₂ (0.4–0.6 ppm) was observed between 5-minute and 1-hour exposure suggesting that it is the dose rate and concentration rather than total dose which is important [135].

7.7. Generally asthmatics are at risk of developing significant bronchoconstriction at concentrations in the region of 0.2–0.5 ppm. These are high concentrations by current U.K. standards. Bronchoconstriction appears transient and readily reversible by bronchodilators. There appears to be quite marked individual variation in the bronchoconstrictor response to SO₂ with some individuals becoming markedly wheezy after inhaling 1 ppm of SO₂ for 1 minute [136]. Most studies have included only mild asthmatics raising the possibility that severe, labile asthmatics might respond to lower concentrations. However Linn *et al.* did not observe any difference in the bronchoconstrictor response to SO₂ between mild asthmatics who were not requiring medication and symptomatic asthmatics requiring regular medication [137]. (They described this latter group as moderate to severe but defined them as requiring bronchodilator medication at least once a week.)

7.8. One study reported that 0.12 ppm of ozone sensitized a group of very mild asthmatics so that they developed bronchoconstriction at 0.1 ppm SO₂ although the effect was small and not accompanied by marked symptoms.

7.9. Normal volunteers were exposed to 120 hours of SO₂ continuously at a concentration of 0.3–8 ppm. No major adverse effects on symptoms were observed although some transient impairment of lung function was seen at the highest doses [138]. This study emphasizes the tolerance of normal sub-

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jects to even high doses of SO₂. However after exposure of normal volunteers to between 4 and 12 ppm of SO₂ for 20 minutes there was an increase in the number of mast cells, lymphocytes and macrophages in BAL fluid 24 hours after challenge which had resolved by 72 hours [139].

7.10. Ipratropium bromide was unable to block SO₂-induced bronchoconstriction [140].

7.11. SO₂ caused nasal obstruction in allergic subjects after 10 minutes of exposure. This was blocked by chlorpheniramine [141, 142].

7.12. Acid aerosols appear to have a similar pattern of activity to SO₂ in that asthmatics are more susceptible responding to between 100 and 350 µg/m³ compared to more than 1000 µg/m³ for normal subjects [143, 144]. However, not all investigators have shown this with one study in asthmatics only showing an effect over 1000 µg/m³ [145] and in another study where 12 healthy non-asthmatic volunteers inhaled 1000 µg/m³ of SA for 2 hours with intermittent exercise there was no effect on symptoms, lung function, BAL cell populations or AM function between saline and SA exposure [146]. Even concentrations of 100 µg/m³ are high relative to current U.K. concentrations and effects when seen were mild and transient.

7.13. Inhalation of SA by asymptomatic asthmatics caused slowing of tracheobronchial mucociliary clearance [147, 148].

7.14. One study showed that SA exposure increased BHR in asthmatics [149].

7.15. Exposure of 10 healthy volunteers to high concentrations of nitric acid (HNO₃) (500 µg/m³) with and without ozone for 4 hours during moderate exercise resulted in no effects on lung function and no evidence of airway inflammation. In addition there was no synergistic effect with ozone [150].

7.16. Few studies have investigated the effects of diesel particulates, smoke or exhaust fumes in humans.

Nitrogen dioxide

7.17. Studies with NO₂ have been contradictory, with some studies showing increased bronchial hyperresponsiveness and airway resistance in asthmatics at concentrations in the region of 0.1–0.3 ppm [151–154] whereas other studies have shown no effect at concentrations up to 4 ppm [155, 156]. These data are hard to reconcile as there are no major differences in methodology between the studies. In addition prior inhalation of NO₂ did not effect the subsequent response to SO₂ [157].

7.18. Eighteen healthy male non-smokers were exposed for 24 hours to NO₂ with 20 minutes' light exercise at concentra-

tions between 2.25–5.5 ppm. There was an increase in BAL lymphocytes and mast cells although total cells stayed the same. This could be explained by epithelial damage leading to release of inter-epithelial leucocytes into the airway lumen. From the same group 4 ppm for 20 minutes increased mast cells and lymphocytes between 4–24 hours but numbers had returned to normal by 72 hours [158, 159].

7.19. In 14 healthy non-smoking adults exposed to 2.3 ppm for 5 hours there was no change in lung function, but decreased alveolar permeability (DTPA clearance) and decreased serum (but not whole blood) glutathione peroxidase activity was observed although changes were small, not seen in all subjects and only at one time point in any one individual (11 and 24 hours, respectively) [160].

7.20. There is little work investigating the role of traditional air-pollution gasses in occupational asthma. Nitrogen oxide exposures are also a problem in workers exposed to diesel exhausts, particularly in bus garages. One study found an increased incidence of wheeze with NO₂ levels around 500 ppb [161]. Higher exposures have been reported in silo filters [162], ice-hockey players (from faulty diesel engines on ice preparation machines) [163], and astronauts accidentally exposed to nitrogen dioxide with exposures around 250,000 ppb [164], who have developed pulmonary oedema. Survivors may subsequently develop obliterative bronchiolitis. Studies of coal miners, exposed to nitrogen oxides from diesel exhaust and shot blasting, with mean levels of about 50 ppb have shown no increase in bronchitic symptoms or reduced lung function when smoking and dust exposure are controlled for [165]. Wheeze was not examined in this study.

7.21. One hundred and fifty-two normal volunteers were exposed to 1–3 ppm of NO₂ for 2 hours a day for 3 days. No effect was observed on BHR, lung function tests or infection rate with influenza virus [166].

7.22. *In vitro* exposure of human bronchial epithelial cells to 400–800 ppb of NO₂ increased epithelial permeability, decreased ciliary beat frequency and caused the release of leukotriene C₄, GM-CSF, TNFα and IL-8 [167, 168].

Ozone

7.23. Inhalation of O₃ causes a restrictive defect with falls in both FEV₁ and FVC and increased bronchial hyperresponsiveness to non-specific irritant, such as methacholine. Approximately 10% falls in lung function are seen with exposure to O₃ in the region of 80–120 ppb for 6 hours with exercise and 20% falls for exposure in the region of 0.3 ppm [169]. There is however marked individual variation. In the study by Hortzmann *et al.* the response for a 0.12 ppm challenge ranged between a subject who had a 37% fall and individuals who showed very little change in lung function. The basis

for this variation is unclear although animal studies have suggested there may be a genetic component [170]. Exposure of normal subjects to 0.12 ppm of ozone for 6 hours caused a 120% increase in bronchial hyperresponsiveness to methacholine. Effects of O_3 are dose-dependent and therefore increase in severity with exercise.

7.24. There appears to be no marked difference in the responsiveness of asthmatics and normal subjects to ozone in terms of the degree of bronchial hyperresponsiveness and decrements in lung function [171].

7.25. Symptoms of cough and substernal irritation occur in both asthmatics and normals on exposure to concentrations of ozone in the region of 0.2 ppm for up to 2 hours with associated falls in lung function [172–174].

7.26. Decrements in lung function and increased bronchial hyperresponsiveness were seen when normal subjects were exposed to concentrations in the region of 0.12–0.08 ppm for longer periods [175].

7.27. Effects with ozone tend to be slower to develop and longer lasting than effects with SO_2 . In one study the decrement in lung function was noticeable for 70 hours after a 70-minute exposure.

7.28. There is evidence that the response to ozone in terms of lung function becomes weaker with repeated exposure, i.e. there is an adaptive response [176–178].

7.29. A number of studies have investigated the inflammatory effects of O_3 using fibre-optic bronchoscopy with BAL mainly on normal volunteers. Normal volunteers exposed to 0.4 ppm for 2 hours had increased concentrations of BAL prostaglandins at 3 hours and neutrophils at 18 hours [179]. Healthy non-smoking male volunteers exposed to 0.08 and 0.1 ppm of O_3 for 6.6 hours with moderate exercise (40 litres/min) had a significant increase in neutrophils, PGE_2 , LDH, IL-6 and α_1 antitrypsin and decreased AM phagocytosis at both concentrations and increased BAL protein and fibronectin at 0.1 ppm [180]. Eleven healthy non-smoking volunteers were exposed to 0.4 ppm O_3 for 2 hours, with intermittent exercise. BAL was performed 18 hours later. There was an 8.2-fold increase in percentage of BAL neutrophils. Increased neutrophil elastase, protein, albumin IgG, prostaglandin E and fibronectin [181].

7.30. Some studies have also investigated the effects of ozone exposure on airway inflammation in atopic subjects. For example allergic rhinitis exposed to 0.5 ppm O_3 for 4 hours had a 20-fold increase in eosinophils and 7-fold increase in neutrophils in nasal lavage [182].

Summary

7.31. SO_2 causes bronchoconstriction in both asthmatic and normal subjects with asthmatics being responsive at markedly (in the region of 10x) lower concentrations. Bronchoconstriction in asthmatics is clinically significant although transient and readily reversible in the subjects tested. The threshold response is in the region of 0.1–0.2 ppm, concentrations which are encountered, although not often, in the U.K. It might be expected that the mechanism of SO_2 hyperresponsiveness is similar to other non-specific irritants in which case the more severe, brittle asthmatics may be more at risk. Few studies have investigated this possibility. Establishing whether this is indeed the case is an important gap in the literature.

7.32. The effect of SO_2 on symptoms of allergic rhinitis has not been well studied.

7.33. Asthmatics also appear to be hyperresponsive to the bronchoconstricting effect of acid aerosols, however, the data is less conclusive in this area and quite high concentrations appear to have limited adverse consequences in both normal and allergic subjects.

7.34. Particulates have not been well studied.

7.35. Studies of the effects of NO_2 are conflicting but both asthmatics and normal subjects appear to be able to tolerate high concentrations without major adverse events with limited evidence that NO_2 causes significant airway inflammation.

7.36. Ozone appears to have marked capacity to cause airway inflammation in humans and a threshold dose has not been established. This could lead to a number of health effects such as increased sensitization which would be difficult to detect with short-term exposure studies.

Future research

7.37. Establish the threshold effect for SO_2 in brittle asthmatics and asthmatics who have required hospital admission.

7.38. Establish whether symptoms of rhinitis are made worse by exposure to SO_2 .

7.39. Investigate the effects of particulates on allergic and asthmatic subjects.

7.40. Further studies to investigate the immunopathology of the effects of ozone on human airways in both normal and allergic subjects.

7.41. Further studies to investigate the basis for the individual variability in response to ozone to identify those at high risk.