Comparison of soybean epidemic asthma and occupational asthma

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Asthma is an important public health problem because of its increasing prevalence and associated morbidity. It is a major research issue because its aetiology is not established and the reasons for its increasing occurrence are unknown. Occupational asthma is a valuable model of asthma caused by specific environmental exposures which could be useful for a better understanding of the disease.1 Retrospective and prospective studies have shown that, for most of its causes, occupational asthma occurs during the first two years of exposure. Both the intensity and timing of exposure have been found to be risk factors for occupational asthma. Prospective investigations in laboratory animal workers have found a higher prevalence of new work-related symptoms in those exposed to higher airborne concentrations of antigen. Factors such as atopy and smoking have been reported to increase the risk of some causes of occupational asthma. Long term follow up of patients with occupational asthma has shown persistent symptoms, airways hyper-responsiveness, and evidence of sensitisation many years after avoidance of exposure to the initiating cause.

A similar pattern of interrelationships has been observed in soybean epidemic asthma.2 In November 1979 soybean started to be unloaded in the harbour of Barcelona and, in 1981, the first asthma outbreak was described. Asthma outbreaks were repeatedly identified until 1987 when it was established that soybean unloaded at a particular silo was the causal agent. The unloading of soybean was stopped until appropriate filters had been installed in the responsible silo. This intervention prevented further outbreaks of asthma. Several studies have been conducted to assess the magnitude and characteristics of the epidemic as well as its aetiology. Current evidence suggests that soybean epidemic asthma is a useful model of community asthma which has many similarities to occupational asthma. In this review we have compared the characteristics of soybean epidemic asthma and occupational asthma, with special emphasis on the nature of the risk factors for both conditions.

Initial step: from the identification of outbreaks to the soybean hypothesis

In Barcelona asthma outbreaks were first identified in 1981 by a sudden and massive influx of patients with acute severe asthma seeking medical attention at the emergency room of a large teaching hospital. A retrospective analysis carried out in 1983 identified six outbreaks although evidence for the aetiology of the outbreaks was lacking. In 1984 a collaborative asthma group formed by epidemiologists and clinicians from the main hospitals of the city was established by the Department of Public Health. All available evidence was reviewed and a prospective monitoring system for respiratory emergency room admissions was developed, with the participation of the emergency departments of the four largest hospitals which accounted for 76% of all emergency room admissions for asthma in Barcelona. In all patients with asthma or chronic obstructive pulmonary disease admitted to the emergency room the following data were recorded: age, sex, address, date of admission, hour of arrival, and outcome (referral or discharge). A standardised questionnaire was developed for asthmatic patients affected on particular (possibly epidemic) days.

Between 1981 and 1986 a total of 12 outbreaks of asthma were identified. A study of these outbreaks revealed that most asthma attacks lasted for short periods – usually less than four hours – and occurred in the districts nearest to the harbour, adjacent to a large industrial area. The presence of a simultaneous time and geographical cluster suggested a point source epidemic,3 and the hypothesis was proposed that asthma outbreaks were due to inhalation of a biological or chemical substance intermittently emitted from a point source in the harbour or its vicinity. Repeated efforts, however, failed to identify the point source. Although an association between asthma outbreaks and peaks in nitrogen dioxide was suggested, no significant impairment of patients with epidemic asthma was observed during an air pollution episode in which maximum hourly means of nitrogen dioxide and sulphur dioxide of 846 and 810 µg/m³, respectively, were recorded.4

Despite systematic efforts to identify environmental events potentially related to the occurrence of asthma outbreaks, a plausible hypothesis was not developed until the first months of 1987 when the harbour administration recognised that at least three outbreaks had occurred on days when soybean...
was unloaded. The presence of specific IgE antibodies against 22 different commercial antigens including soybean was assessed in a panel of 18 serum samples from patients affected in at least two asthma epidemics. Measurable levels of IgE against soybean were detected in 13 of the 18 samples, whereas measurable levels to any of the remaining allergens were only documented in three samples.

Although this preliminary association lacked strength and consistency, cessation of soybean unloadings was recommended during an asthma outbreak that occurred in September 1987.

Investigation of the soybean hypothesis and intervention

The soybean hypothesis was confirmed by the results of two different epidemiological studies: a time series study of asthma outbreaks and a case-control study of epidemic patients.

The first study assessed the association between unloading of 26 products from ships in the harbour and the occurrence of asthma outbreaks for the period 1985–6. All 13 asthma epidemic days during these two years coincided with the unloading of soybean; in contrast, no asthma epidemics occurred in the remaining 468 days on which soybean was not unloaded. Moreover, there were two silos in the harbour (silo A and silo B), and it was found that 12 of the 13 outbreaks occurred during unloading of soybean at silo A, whereas only one outbreak had occurred during unloading of soybean at silo B. Of the remaining 25 products, only wheat was associated with asthma epidemics — but concurrently with soybean unloading. It was appreciated that the lack of bag filters at the top of silo A permitted the release of soybean dust into the air.

In the case-control study serum samples were taken from 86 patients seen at the emergency room on a particular epidemic day. Controls were selected from emergency room admissions for asthma on non-epidemic days. A total of 86 controls were matched by age, sex, and area of residence. Specific IgE levels against soybean and other common allergens were measured by RAST, and 74-4% of cases were found to have increased binding to commercial soybean extract compared with 4-6% of controls (odds ratio (OR) = 61). Western blot and thin layer electrofocusing/blotted radioimmunoelectrofocusing showed that, on epidemic days, IgE of patients with asthma bound strongly to glycoprotein bands of molecular weight <14-4 kD and isoelectric point <6, which appeared to be the major allergens.

The unloading of soybean in silo A was temporarily interrupted in September 1987. Three months later, bag filters were installed at the top of the silo and soybean unloading resumed under controlled conditions. Following this intervention there was a mean 10-fold reduction in soybean Aeroallergen concentrations and 100-fold reduction in peak levels. The number of referrals from emergency rooms to intensive care units showed a 25-fold decrease. No asthma outbreaks have occurred since the intervention, whereas on epidemic days between 1981 and 1987 there had been 26 asthma outbreaks with 687 emergency room visits for asthma.

Risk factors for soybean epidemic asthma and occupational asthma

Although these studies allowed identification of the cause of the asthma outbreaks, they did not provide information about other individual risk factors. Current evidence of the role of risk factors other than soybean — that is, exposure, sex, age, atopy, and smoking — as well as the evidence on these factors from studies of occupational asthma, are reviewed in this section.

**INTENSITY OF EXPOSURE**

Direct assessment of the levels of soybean allergen on epidemic days was obtained from a case-control study and collected from air filters installed in Barcelona. Of a total of 38 days sampled, 22 corresponded to the period when the cause of outbreaks was still unknown and the remaining 16 occurred after the installation of bag filters at silo A. Air samples were processed by gas chromatography and combined gas chromatography/mass spectrometry. The mean concentration of soybean esterols was 5–15 times higher on epidemic days than on non-epidemic days. In addition, soybean allergens were eluted from 16 fiberglass filter sheets and assayed by RAST inhibition. Because it was not possible to express allergen concentration in mass units, an arbitrary value of 10⁶ units was assigned to the reference soybean husk extract, one unit containing approximately 1 ng of allergen. Epidemic days showed varying levels of soybean allergen from 1600 to 10 600 U/m³, whereas on non-epidemic days the range was 0-3–320 U/m³. The levels on epidemic days were below the maximum concentrations of Aeroallergens reported by Reed et al in various occupational work places (range <10 ng/m³ to 36 000 ng/m³).

**SEX**

No differences according to sex were observed in particular outbreaks. However, in a case-control study cases were more likely to be men than were controls, although the increased risk for men was not significant (OR = 1.3; 95% confidence interval (CI) 0.7 to 2.1) after adjustment for age and smoking. Attack rates on soybean epidemic asthma days reported in Cartagena, Spain did not show differences between men and women. Thus, there was no evidence that sex per se was associated with an increased risk of soybean epidemic asthma.

In occupational asthma sex has been considered a less important risk factor since work forces often consist predominantly of either men or women; furthermore, both are likely to be involved in different jobs within the same factory with the possibility of confounding by exposure. In a study of laboratory animal workers in a pharmaceutical company 60% of the symptomatic group were women compared...
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with 31% in the group without symptoms. Respiratory symptoms related to work with animals were reported by 16% of women and 7.3% of men. Given that the association between sex and the risk of occupational asthma was not formally assessed, differences could have been due to the fact that 41% of women were in the exposure category with most frequent and intense exposure to animals. In a survey of workers exposed to tetra-chlorophthalic anhydride (TCPA) the prevalence of sensitisation to TCPA was similar in both sexes. Studies on occupational asthma do not usually provide sufficient information to exclude a differential risk of either sensitisation or work-related respiratory symptoms by sex. Nonetheless, studies of soybean epidemic asthma and occupational asthma studies do not suggest that sex is an independent risk factor for asthma.

AGE

The risk of suffering soybean epidemic asthma increased with age. In a descriptive study of an asthma outbreak, the ratio of attack rates on epidemic days to control periods showed an increasing magnitude with increasing age (2.42, 2.88, 6.58, 8.70, for those aged <14, 15-44, 45-64, and >65 years, respectively). A similar trend was also observed in other outbreaks. In a case-control study, after adjustment for skin reactivity, total IgE, sex, smoking, and exposure, there was a consistent association between age and epidemic asthma (OR 1.9 (95% CI 1.1 to 3.6) and 2.8 (95% CI 1.4 to 6.0)) for patients aged 45-64 years and those >64 years, with subjects of <45 years serving as a reference category. After the installation of bag filters at the harbour silo the reduction in the mean number of emergency room admissions for asthma was higher in the older groups. The proportional reduction in the daily mean of emergency room admissions for asthma after the intervention was 26% for men aged 15-44 years, 60% for those aged 45-64 years, and 62% for those >64 years. Figures for women in the same groups were 20%, 31%, and 33%, respectively.

These observations, however, contrast with the current understanding that the incidence of asthma is higher during childhood and that it is more likely to be non-allergic in those who develop it after 40 years of age. Given an homogeneous attack rate and severity, it is possible that, in our studies, older patients with epidemic asthma would have been more likely to attend the emergency room on epidemic days than younger patients. Unfortunately, based on the data available, this possibility cannot be excluded. On the other hand, it has been suggested that the elderly might be less able to tolerate exposure to novel allergens, either because of reduced immunological tolerance or accumulated exposure to modifying factors such as cigarette smoking which increase the risk of sensitisation.

As pointed out by Becklake, age has rarely been considered an important risk factor for occupational asthma, with age ranges within working populations restricted to adulthood and from which elderly people are excluded. Using the SWORD voluntary reporting scheme in the UK, Meredith has shown an increasing incidence of occupational asthma with increasing age. The standardised rate ratio in men increased from 0.80 in those aged 16-29 years to 1.24 in those >44 years. The corresponding ratios in women were 0.64 and 1.40. This age pattern was more pronounced after adjusting for occupation. Although the age pattern was consistent for all occupational categories, the author suggested that older cases might be more likely to report asthma or to be notified, but could not exclude the possibility of risk increasing with increasing age. In two recent prospective studies of occupational asthma in laboratory animal and bakery workers, we have assessed whether or not the risk for asthma is increased with increasing age (unpublished results). In both studies, after adjusting for intensity of exposure and smoking, the risk of developing respiratory symptoms after employment was slightly higher in the younger workers, contrary to this hypothesis.

In summary, although there is no consistent evidence of an increased risk of occupational asthma with increasing age, the possibility needs further assessment in studies of both epidemic asthma and occupational asthma.

Whereas most of the studies carried out in the Western world have shown that the incidence of asthma peaks before the teenage years, data from tropical countries appear to differ. Ross reported both men and women, the peak of asthma incidence was in the fourth decade with men showing a second peak between the ages of 50 and 60. This age pattern is consistent with the report by Woolcock from New Guinea which showed that the prevalence of asthma was 7.3% in adults and only 0.6% in children. It has been suggested that a low prevalence of asthma in childhood in developing countries may be due to a high prevalence of viral infections in early life with a selective enhancement on the development of Th1-type cells, subsequent inhibition of both Th2-like clones, and allergic sensitisation. However, the true explanation for the different age of onset of asthma in different latitudes and its relationship with the age pattern of the Barcelona soybean asthma epidemic remains obscure.

ATOPY (SERUM OR SKIN REACTIVITY TO COMMON INHALANT ALLERGENS)

Atopy, defined as a positive reaction to skin tests or the presence of circulating IgE antibodies to common aeroallergens, was a risk factor for soybean epidemic asthma. In a case-control study specific IgE was measured against Dermatophagoides, Parietaria, and Aspergillus. Patients with epidemic asthma were four times more likely than controls to react to any of these allergens (OR 4.1; 95% CI 1.7 to 10.7); Parietaria showed the strongest association with epidemic asthma (OR 9.1; 95% CI 1.7 to 111.6). Serum levels of specific IgE against legumes were also measured in a subset of patients who had been admitted to hospital on more than
Relationship between epidemic asthma and airborne exposure to soybean (measured as the area of residence of daily walking expressed in km), according to atopy (number of positive skin reactions) and smoking

<table>
<thead>
<tr>
<th>Airborne soybean exposure</th>
<th>Skin test</th>
<th>Non-smokers</th>
<th>Smokers</th>
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<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
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<tr>
<td>&gt;4</td>
<td>0</td>
<td>1-0</td>
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<tr>
<td>≤4</td>
<td>1-4</td>
<td>0-3 to 6-5</td>
<td>2-9</td>
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<td>&gt;4</td>
<td>≥1</td>
<td>0-6 to 5-2</td>
<td>3-2</td>
</tr>
<tr>
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<td>≥1</td>
<td>0-7 to 12-2</td>
<td>7-9</td>
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Adapted from Sunyer et al.11

one epidemic asthma day. IgE antibodies to pea, peanut, and white bean were observed in 10%, 15%, and 10% of cases and in 11%, 5%, and 5% of controls.

Atopy and epidemic asthma were also studied in a case-control study with 18 individually matched pairs in Cartagena (Spain) where soybean asthma outbreaks have also been reported.12 When skin test reactions to common inhalant allergens were considered, cases reacted slightly more frequently to other allergens although the differences did not reach significance, possibly because of the small number of subjects.

It has been shown that atopy is a risk factor for sensitisation and work-related respiratory symptoms in bakery workers,24 and for those working with platinum salts,25 laboratory animals,26 and detergent enzymes.27 In a study of 279 bakery workers a high prevalence (33%) of sensitisation to storage mites was found. Among those who were atopic, 37–52% had a positive skin prick test to storage mites compared with only 6–7% of non-atopic workers, a similar difference being observed for wheat and flour allergens.24 In a study of individuals working with laboratory animals asthma developed in 34.3% of atopic and 2.7% of non-atopic workers.27 In platinum refinery workers the risk of occupational asthma for atopic subjects, after adjusting for smoking, was more than twice that for non-atopic subjects, although statistically significant differences were not found, probably because the sample size was too small.25 In general, both high and low molecular weight agents causing occupational asthma which are associated with specific IgE antibody cause sensitisation more frequently in atopic than in non-atopic workers. In contrast, atopy is not a predisposing factor for low molecular weight chemicals not associated with specific IgE which cause asthma such as isocyanates and Western red cedar.28

SMOKING

Following reports which suggested that smoking was a risk factor for occupational asthma,28 the hypothesis was tested in soybean epidemic asthma.11 Smokers were more likely to suffer from epidemic asthma than non-smokers regardless of the degree of exposure or atopy to soybean. The smoking-related risk was highest among those patients who lived near to the point source and had positive skin test responses to common aeroallergens. There was an interaction between exposure, atopy, and smoking (OR 7-9 compared with the reference category after adjusting for age and sex; table). When the smoking status was considered in relation to the period of time when the asthma outbreaks occurred, those who were smokers, lived in the proximity of the point source, and were atopic showed an OR of 9-6 (95% CI 0-9 to 169) compared with 2-5 (95% CI 0-2 to 50-6) in those who had stopped smoking before the start of the epidemics. When the previous analysis was restricted to atopic subjects with exposure to airborne soybean there was an association between the number of pack years smoked and risk of epidemic asthma (OR 12-6; 95% CI 1-3 to 114-5 for those who had smoked more than 33 pack years).

Occupational studies have shown that smoking is a risk factor for sensitisation in workers exposed to platinum salts,25 tetrachlorophthalic anhydride,29 and in ispaghula and green coffee workers.26 Smoking has also been reported to increase the risk of respiratory symptoms in laboratory animal workers14 and in workers who process snow crab.30 In the study of platinum refinery workers the risk of developing a positive skin test to platinum salts was 5–6 times greater among smokers than non-smokers, and the risk for respiratory symptoms doubled per 10 cigarettes/day.25 In contrast, smoking has not been found to be a risk factor for occupational asthma not associated with specific IgE such as Western red cedar.26 Our finding that ex-smokers were at lower risk of soybean epidemic asthma may be due to chance, although a similar result was reported in subjects who developed specific IgE when exposed to humidifier antigens.28 Smoking is a risk factor for both soybean epidemic asthma and occupational asthma; the implications of these findings in relation to the development of preventive strategies are important.

Natural history of epidemic and occupational asthma

LATENCY PERIOD

Soybean was initially unloaded in November 1979 and the first asthma outbreak was identified about 20 months later in August 1981. This 20 month period should be considered as the upper limit of the latency period as no systematic investigation of outbreaks was carried out before 1985. This is a latency period for the whole population as individual information on the period which had elapsed between the first exposure to soybean dust and the first epidemic attack is not available. This 20 month period, however, is consistent with an average interval of 1–3 years in the onset of occupational asthma after initial exposure.13 In a study of workers exposed to laboratory rats the median duration of employment before the onset of new work-related symptoms was one year, with a range from less than one month to 11 years.20 In a historical cohort study of 92 platinum refinery workers the incidence of respiratory symptoms and sensitisation to platinum salts was highest during the first year of employment, with no symptoms or positive skin tests being recorded after four years of exposure.25
FATAL AND NEAR-FATAL ASTHMA EPISODES
All deaths due to asthma or other causes that occurred in patients with epidemic asthma on epidemic days were monitored, and at least 26 such deaths were identified. In addition, more than 50 admissions to intensive care units occurred on epidemic days. A total of 687 cases were recorded at emergency room departments on all epidemic days, so this represents a high case fatality rate. The clinical course of near-fatal soybean epidemic asthma has been reported elsewhere.32 A recent immunohistochemical study has suggested that a lack of CD3 and CD8 in the mucosa and submucosa of lung specimens in patients who died from soybean asthma could be a specific marker of this condition.33 In contrast to soybean epidemic asthma, deaths among cases of occupational asthma have been reported only rarely. The low rate of mortality in occupational asthma was noted by Fabbri et al34 in a report of a 43 year old car painter who died within one hour of exposure to a polyurethane paint in the work place.

The contrast between the reported mortality from soybean and occupational asthma is striking, and several explanations can be proposed. Firstly, death from occupational asthma may not be recognised - for example, a sudden death may be attributed to a different condition from asthma such as myocardial infarction or, because of its legal or economic implications, it may not be reported. Secondly, the higher fatality rate in epidemic asthma could be related to exposure since the airborne concentrations of soybean may have been substantially higher than are usual in occupational asthma. However, indirect estimation of exposure levels during the asthma epidemics showed that the levels of soybean allergen were similar to those reported in occupational settings. The pattern of exposure could be more important than intensity alone; intermittent high exposure to toluene diisocyanate was associated with a higher risk of developing work-related asthma than continuous exposure to a lower concentration.35 Short term high exposures after an exposure-free window may have occurred in Barcelona during the unloading of soybean and could have been associated with a higher case fatality rate in epidemic asthma. It is possible that soybean allergen is a more potent allergen than those usually present in occupational settings. It is also possible that patients with soybean epidemic asthma, who are predominantly older and often with a previous history of asthma, were at a higher risk of death when exposed to soybean than relatively younger and healthier working populations.

Evolution of epidemic asthma after an intervention
IMPROVEMENT OF ASTHMA SYMPTOMS
A relevant question is the extent to which epidemic patients might be expected to improve after an intervention that reduced exposure levels sufficiently to prevent further asthma outbreaks. Unfortunately, information on patients with epidemic asthma is not available from before the soybean asthma outbreaks, so only a post-intervention assessment is possible.

The case-control study described earlier11 was used for this purpose.36 The cases comprised a random sample of asthmatic patients (n = 213) affected in one or more of the 26 asthma epidemics, and controls were a random sample of asthmatic patients admitted to the emergency room with attacks of asthma on non-epidemic days (n = 170). The study was carried out two years after the last epidemic.

Patients with epidemic asthma showed consistently fewer asthma symptoms during the preceding 12 months, although statistically significant differences were only found for "tightness in the chest", and had been admitted to the emergency room during the previous year with acute attacks of asthma less frequently (20-4%) than non-epidemic asthma patients (36-7%) (p<0-001).

Baseline spirometric tests in cases and controls showed airways limitation of moderate intensity and no statistically significant differences were found in ventilatory capacity. No differences were found between the two groups in baseline forced expiratory volume in one second (FEV1) when stratified by age, sex, and smoking habit. The proportion who showed a fall in FEV1 of >20% of baseline at each dose of methacholine was similar in both groups.

With regard to treatment taken at the time of the study, no differences were found in the types of drugs taken, except for inhaled corticosteroids which were used by fewer patients with epidemic asthma than controls (34-3% versus 49%; p<0-01).

In a separate study27 we found that two years after the last epidemic 52% of 142 patients admitted to an emergency room during a soybean asthma outbreak had measurable levels of IgE against soybean. In 38 patients it was possible to match serum samples obtained before and two years after the intervention. The mean serum concentration of specific IgE had decreased from 2 PRU/ml before the intervention to 1 PRU/ml after the intervention (p<0-001). A logistic regression analysis identified no relationship between the rate of decrease in the serum concentration of specific IgE and age, sex, total IgE, and proximity of the patient’s residence to the soybean point source.

Persistence of airway symptoms, hyper-responsiveness, and evidence of sensitisation for years after avoidance of exposure has been reported in studies of the outcome of occupational asthma. In a four year follow up of TCPA-induced asthma37 persistence of both specific IgE and symptoms after TCPA avoidance was observed. Specific IgE decreased exponentially with a half life of one year. All workers had a positive skin test to TCPA, showing a decrease in the weal size on each occasion that they were tested. All seven patients reported that their asthma had improved since leaving the factory, but they still reported symptoms which required treatment in five cases. Malo et al38 reported a follow up of 31 snow crab workers who showed a similar
to test whether older workers are at a higher risk of occupational asthma as was the case in the soybean epidemic asthma because of the limited age range of working populations and their possible assignment to lower exposures. Secondly, the healthy worker effect may reduce the risk of developing occupational asthma, whereas in epidemic asthma those with previous asthma may well have been more susceptible to soybean allergy. Finally, allergens are not inhaled as isolated particles but as complex aerosols which may differ both between occupational and epidemic asthma and between different occupational exposures.

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