Occupational asthma after exposure to azodicarbonamide: report of four cases

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ABSTRACT Azodicarbonamide (Chemical Abstract Service Registry No 123.77.3) is an organic low molecular weight agent used for blowing and foaming plastics. Finely ground azodicarbonamide can be a pulmonary and sometimes a cutaneous acute sensitiser. Four cases of work related asthma are reported.

Azodicarbonamide or 1,1' azobisformamide (chemical formula: $\text{H}_2\text{N}-\text{OC}-\text{N}=\text{N}-\text{CO}-\text{NH}_2$ is a low molecular weight amide widely used in industry as an expanding and blowing agent for resins and rubbers¹; it releases a large volume of gas when heated. Generally, azodicarbonamide is a fine yellow powder but it may also have an orange crystalline appearance.

Its acute oral or inhalation² toxicity is low in animals and no chronic toxicity has been reported.³ It is considered as a non-toxic product for man,⁴⁻⁶ although it has a low potential for causing allergic sensitisation.

It is allowed for use in some European countries and since 1962 in the United States to mature and bleach cereal flours. In France it is only allowed as a component of food packaging material.

We here report four cases of lung disease associated with exposure to azodicarbonamide in the plastic industry.

Case 1

A 50 year old man, a former smoker and a chronic alcoholic, first experienced breathlessness when at work in 1975 and in 1978 presented with an eczematous dermatitis of the face.

Since the end of 1972 he had worked at a small plastic processing factory and been employed as a pigment grinder since the beginning of 1982. This job consists of preparing pigments and blowing agents in mixing and grinding machines.

He was seen for the first time at the beginning of 1983, with complaints of acute episodes of shortness of breath for three months. His dyspnoea gradually developed five or six hours after he had started work and often appeared in the middle of the night. The

symptoms became worse at the end of the week and disappeared during the holidays. They disappeared completely in July 1983, when he was transferred because of his symptoms to the dispatching store.

As he handled over 30 different products, inhalation tests were performed—several months after he had changed jobs—with the following selected agents: prepolymerised polyurethane resin in April 1984 and formaldehyde and melamine formaldehyde resins in May 1984. The test results all proved negative and the causative agent of his asthma remained unknown. His baseline spirometric values showed a mild obstructive syndrome in April 1984 and were thereafter within normal limits (table).

After we had seen the second patient, we performed in June 1984, a provocation test with azodicarbonamide. No immediate reaction occurred but the patient reported having had an attack of asthma in the middle of the following night (figure). When we saw him in February 1985 he had had no further attacks of asthma.

Case 2

This healthy non-smoking man aged 45 had worked in

Selected pulmonary function data (with % predicted values in parentheses)

	<i>FVC (l) % pred</i>	<i>FEV₁ (l) % pred</i>	<i>FEV₁/FVC (%)</i>
Case 1			
April 84	4.3 (89.8)	2.56 (73.6)	59.5
May 84	4.36 (91)	2.78 (79.9)	63.8
June 84	4.4 (91.9)	2.92 (83.9)	66.4
Case 2			
February 84	3.6 (96)	2.52 (91.6)	70.0

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Inhalation challenge to azodicarbonamide in cases 1 and 2.

the same firm as the first patient since 1971. Initially he had been employed at the calender, where in 1973 he developed eczema of the hands and forearms, a condition that he had previously had as a baker in 1959. He later prepared raw material but had to change job because of a recurrence of eczema (1979). In November 1983 he replaced the first patient as a pigment grinder.

We saw him in January 1984 when he complained of shortness of breath at the end of the day's work or a few hours later; the symptoms had started two months before and the patient blamed the blowing agents.

An inhalation test with azodicarbonamide powder was performed in February 1984. All his baseline spirometric values were within normal limits (table). After 40 minutes exposure, the patient developed an asthmatic reaction (22% fall in FEV₁), reaching a maximum three hours and 40 minutes after the exposure (fig); recovery occurred gradually after five hours.

The patient remained at his job but with improved working conditions. In February 1985 he complained only of vague respiratory symptoms but an accidental re-exposure to azodicarbonamide powder had induced an asthmatic reaction a few months before.

Case 3

This 50 year old man, an ex-smoker, had worked since 1969 in another small plastic processing factory in which azodicarbonamide was used during one fortnight a year only.

He had reported attacks of asthma or of asthmatic bronchitis requiring the use of antiasthma drugs as soon as he started work during this period every year since 1979. He had no symptoms outside this period.

During the 1974 episode the patient concurrently suffered from eczema of the hands and forearms. This did not appear in the following years as he then wore gloves.

Case 4

This 54 year old man had worked in the same plastic firm as case 3 since 1977. During an apprenticeship in a bakery he had had chronic eczema and attacks of asthma. As a result he had to change jobs and he had had no further skin or respiratory complaints. Attacks of asthma appeared, however, during the first period of using azodicarbonamide. The symptoms were minimised by preventive medical treatment. The rest of the year he had no asthma and took no treatment.

Discussion

On the basis of their strong relation to work both with regard to time and location, we are confident that the four cases of asthma described were due to exposures at work. We cannot totally exclude the possibility that substances other than azodicarbonamide were implicated in the cases described; however, the inhalation challenges performed with the azodicarbonamide used by two workers and the clear association with the use of azodicarbonamide in the other two subjects strongly point to this (or possibly a contaminant) as the causative agent.

The causative agent remained unknown until we saw the second patient, who worked on the same job as the first and who associated his complaints with the use of azodicarbonamide. This led us to attempt specific inhalation tests which proved to be positive. In the first case the test, though performed a year after withdrawal of the exposure, was positive, showing a late reaction occurring at home (in France it is current practice not to admit to hospital subjects undergoing inhalation challenge testing). Patients 3 and 4 were not tested because we thought the relation between exposure to azodicarbonamide and asthma was sufficiently established on clinical grounds.

In all cases the attacks of asthma disappeared after exclusion of the agent or changes in working conditions. They have reappeared only after an accidental or controlled medical re-exposure.

Asthma and asthmatic dyspnoea resulting from inhalation of azodicarbonamide powder have been previously described. They were mentioned for the first time in the United States in 1971, after ten cases appeared in a grinding factory⁷; 28 cases were

identified in the United Kingdom in 1980 on the basis of a questionnaire study in the plastics industry,⁸ and two cases were described in Canada.⁹ In France azodicarbonamide has been considered as a possible respiratory allergen in the rubber industry.¹⁰

The characteristics of our four cases of asthma are similar to those described elsewhere. After the first contact and a short period with no signs, the attacks appear suddenly, generally within six months of exposure,^{7,9} and in 75% of the cases before the end of the first year.⁸ The attacks happen with delay at the end of the day's work (more than half of them)⁸ or late in the night.^{7,9} The occurrence of symptoms in case 4 on his first industrial exposure to this agent suggests that he had previously been exposed—for instance, as a baker even though the use of azodicarbonamide is not allowed as a food additive in France, or that other substances may cross react with azodicarbonamide.

Our patients have also noticed that their attacks of asthma occur both sooner and last longer as exposure persists for prolonged periods.⁸

We have not been able to assess the prevalence of respiratory complaints in the firms involved, but estimates have varied between 18.5% (151 workers),⁸ 16.4–47.3% (110 workers),¹¹ and 90% (11 workers)⁷ of those exposed. Not all these subjects, however, had asthma.

Only two patients have had a specific inhalation test with results similar to the second case.⁹

Two of our patients (cases 1 and 4) had had occupational asthma previously, though no increased incidence of azodicarbonamide induced asthma has been reported among atopic people.⁸

Three of our patients (1, 2, and 4) had had eczematous dermatitis, two when working in a bakery. Two cases of allergic contact dermatitis to azodicarbonamide have been reported, one in Italy¹² (a man working in an industrial bakery had eczema of the face and arms) and the other in the United Kingdom¹³ (a worker in a plastic transforming factory had eczema of the body but not on face or arms). The skin tests have, in both cases, shown a delayed hypersensitivity to azodicarbonamide. The insolubility of azodicarbonamide in the usual solvents, however, renders testing difficult and is thus rarely performed.

The mechanism for the sensitisation, whether immunological or otherwise, has not yet been identified. It may be speculated, however, that as with other diazo compounds, the high reactivity of the diazo bond of azodicarbonamide may be the basis for its allergenic potential.

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