# Asthmagenicity of coal mine roof-bolting resins: an assessment using inhalation provocation tests

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Inhalation provocation tests were used to assess whether the volatile products of an activated resin had caused occupational asthma in a non-random sample of six asthmatic coal miners. The resin system uses the polymerization of polyester and styrene under the influence of the cross-linking agent dibenzoyl peroxide to secure roof, wall and floor bolts in mine tunnels. The tests were conducted sequentially in a double-blind fashion over a 'dose' range which extended just beyond the maximum likely to have been experienced occupationally during a single day's work. The tests were monitored by symptoms, changes in the forced expiratory volume in 1 s ($FEV_1$) and changes in airway responsiveness. All subjects completed the series of tests without any significant decrements in $FEV_1$ or significant increases in airway responsiveness. We conclude that the use of this resin system is not likely to have been the cause of the asthma in the test subjects, nor in the larger group of miners of which they were a sample, but neither possibility is fully excluded and the participants may not have been adequately representative of other asthmatic coal miners.

Key words: Airway responsiveness; coal mining; dibenzoyl peroxide; occupational asthma; roof-bolting resins; styrene.

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## Introduction

In 1991, the conditions governing state compensation for occupational asthma in Britain were revised, thereby allowing an award if the causal agent is not a commonly recognized asthma inducer [1]. This assumes that there is convincing evidence of asthmatic sensitization. A cluster of 21 coal miners and ex-miners subsequently made claims. All had first reported symptoms after starting work underground (pre-employment screening should have excluded men with existing asthma); all had worked as roof-bolters; and several identified the polyester resin used to retain the roofing bolts as a possible cause of their symptoms.

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Although an association with chronic obstructive pulmonary disease is recognized, coal mining is not generally thought to pose a risk of asthma. However, the case of an underground miner with occupational asthma attributed to *Rhizopus* sensitization has been reported, and in a surface miner occupational asthma has been attributed to dimethylene diisocyanate exposure [2,3].

Roof-bolting represents a major advance in mining technology since the late 1960s. Tunnel roof, wall and even floor stability is achieved by the perpendicular insertion of long (2–5 m) steel bolts through the various layers of surrounding rock and sediment, rather than by traditional steel arches. These inhibit local movement of one layer on another, thus producing rigidity and strength. After bore holes are drilled, the bolts are fixed in position using resins of polyester dissolved in styrene and the cross-linking chemical dibenzoyl peroxide. The unpolymerized polyester has a two-dimensional lattice


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structure with a maleic side branch, and the dibenzoyl peroxide provides free radicals which 'catalyse' the polymerization of the polyester resin and styrene to form a three-dimensional solid gel of high tensile strength. The gel time (a matter of minutes) is controlled by the relative proportions of the chemical reactants and, in some formulations, by very small quantities of an amine accelerator. A number of different formulations are used according to the gel time that is required, and a mixture of various inert fillers adds further strength to the final solid gel. Many gaseous products are released during polymerization, and a distinctive odour (chiefly from the styrene, which has an odour threshold of only 0.3 p.p.m.) is easily recognized.

The resin components, separated in sealed capsules, are inserted into the bore holes first; capsule rupture, content mixing and resin activation follow when a rotating bolt is forced into position. The number of bolts required varies according to the nature of the local strata, but they are generally inserted at 3 m intervals over the exposed surface area. Once the bolts are secured, plates are attached at their free ends and brought tightly against the surface with retaining nuts. The tunnel space under this network is thus unencumbered by the need for other means of support, and the system (which is highly resistant to corrosion) has produced critical improvements in safety, speed and economy.

Fourteen of the initial 21 claimants were referred for evaluation, and in eight we found convincing evidence of asthma, for which the clinical histories suggested a probable or possible occupational cause. We considered styrene to be an improbable causal agent since it has only rarely been reported to induce occupational asthma despite widespread industrial use, often at high concentrations (≥100 p.p.m.) [4,5]. Measured levels in British coal mines have been substantially less (generally <1 p.p.m., and always <5 p.p.m.), the national maximum exposure limit averaged over 8 h being 100 p.p.m. and the short-term exposure limit averaged over 10 min being 250 p.p.m. Volatile cross-linking agents, such as diisocyanates, acid anhydrides and a further peroxide (dicumyl peroxide), by contrast, are known to be potent asthma inducers [6]. Volatile derivatives of dibenzoyl peroxide (dibenzoyl peroxide itself is not volatile) or the other components consequently seemed stronger candidates.

After the claims of these miners had been adjudicated, we were invited to investigate the matter more conclusively using inhalation provocation tests in six volunteers.

## Materials and methods

### Subjects

Six volunteers were sought from among the men referred to us. All underwent airway responsiveness measurements using methacholine tests and a standardized protocol [7], providing the baseline forced expiratory volume in 1 s ($FEV_1$) was ≥60% of predicted. Short-acting β agonists were avoided for at least 12 h, and long-acting β agonists for at least 24 h. Only those with values associated unequivocally with active asthma were recruited. Attempts were then made over a closely supervised 2–4 week period to reduce (even withdraw) current asthmatic medication, after consultation with supervising general practitioners. All subjects gave written informed consent, performed satisfactory spirometric manoeuvres unsupervised using a Vitalograph spirometer (Buckingham, UK) and had a baseline $FEV_1$ ≥50% of predicted prior to each daily challenge.

### Airway responsiveness

Airway responsiveness was quantified by the cumulative dose of nebulizer-administered methacholine provoking a 20% decrement in $FEV_1$ ($PD_{20}$) over an available dose range of 3.125–6400 μg [7]. $PD_{20}$ levels <200 μg are associated with other unequivocal evidence of active asthma, while levels >1000 μg are generally unassociated with asthmatic symptoms. $PD_{20}$ values are repeatable within the range 0.5- to 2-fold under ideal conditions (±1 doubling), or 0.33- to 3-fold otherwise (±1.6 doublings). Thus, the coefficient of repeatability is of the order 2–3, and repeated values outside this range imply a significant change.

### Challenge exposure system

The resin and activator were weighed immediately before each challenge test to produce the manufacturer's recommended 25:1 ratio (Exchem Mining and Construction Ltd, Alfreton, UK). The components were then mixed and activated. The off-gassing styrene together with other volatile emissions were diluted with dry compressed air and directed into a 200-l inert Tedlar bag (polyvinyl fluoride). Each bag had dual stainless steel fittings, which allowed simultaneous sampling access to the atmosphere developing within it. Using styrene as a marker of overall concentration of the mixture of respirable products, the contents were assayed serially, though crudely, with GASTEC calorimetric indicator tubes (Milton Keynes, UK). Further dilution to achieve the desired value more precisely was carried out with a Bruel & Kjaer 1302 gas monitor (Naerum, Denmark).

A Tedlar bag containing the appropriate concentration of the challenge agents for each test was connected to the breathing circuit of the challenge system. The test subject breathed through the mouth, wore a nose clip until he left the laboratory, and initially inhaled room air through the system with the switch to the Tedlar bag closed. When he was comfortable, with a steady respiratory rate and

minute volume, the Tedlar bag was switched into the circuit as the sole breathing source for 5 min. The expired air was passed through a filter to be exhausted into the external environment. A sample of the challenge mixture remaining within the bag was collected on absorption tubes and sent to an independent laboratory for analysis, again using styrene as a marker of overall concentration.

## Study protocol

### *Challenge doses*

One 5 min challenge at 10:00 h was used per day, with a 3.2-fold ($\sqrt{10}$) dose increment for each successive test—a 1, 3.2, 10, 32, etc. dose sequence. Experience has shown this to be safe and practical [8]. The aim is to start with a relatively trivial and entirely safe dose (one that each worker can be expected to have encountered on many working days without obvious adverse effect), and end with a dose that exceeds the cumulative maximum ever likely to be experienced in the workplace in 1 day. The dose level that generates a clear asthmatic reaction and a significant increase in airway responsiveness identifies the approximate threshold for a positive reactor (the protocol would be discontinued at this point if these responses are shown to be repeatable), whereas a failure to react throughout the sequence defines a negative outcome and reasonably excludes the possibility of occupational asthma due to the test agent. We erred on the side of safety by using for the initial challenge a styrene 'marker' level of 0.01 p.p.m. for the first two participants, 0.1 p.p.m. for the next two participants, and 1 p.p.m. for the last pair. We concluded each sequence with a styrene 'marker' level of 320 p.p.m., implying a cumulative dose of 27 p.p.m.-h. Multiple monitoring measurements in British coal mines have shown that the maximum cumulative daily exposure in the workplace is not likely to have exceeded 8 p.p.m.-h. The threshold for styrene irritant effects is said to be 100–200 p.p.m. after 20 min [13].

'Dummy' control challenges with air alone in the Tedlar bag were interspersed irregularly during the sequence so that neither test subject nor physician directly supervising the day's investigation knew the identity of the challenge agent. The higher doses could, however, be recognized by taste or odour, and styrene sometimes escaped into the laboratory. Throat lozenges and anaesthetic pastilles were consequently sucked immediately before each challenge, and low concentrations of styrene (<1 p.p.m.) were released with the test subject's knowledge into the laboratory during the second half of the challenge sequence, irrespective of the nature of the challenge agent.

### *Test monitoring*

Each challenge test was monitored over the following 24 h by symptoms and $FEV_1$. The $FEV_1$ was taken as the mean of three measurements at each time point, the forced expiratory manoeuvre being discontinued after 1 s to avoid the discomfort of expiring to residual volume. Measurements were taken at 10 min intervals from 30 min before to 90 min after challenge onset to detect an immediate reaction, then at hourly intervals from 2 to 12 h, and (as practical) from 22 to 24 h to detect a late reaction. The measurements from 30 min before to 2 h after challenge onset were undertaken under our supervision, but if there was then no clear evidence of a reaction the subject returned home. Subsequent measurements were unsupervised unless there was a decrement in $FEV_1$ to a predetermined level (80% of the day's baseline) or the subject experienced worsening symptoms. In such circumstances, a telephone surveillance arrangement required the subject to contact the duty physician so that symptoms and $FEV_1$ measurements could be reviewed. Whenever a late reaction appeared likely, the two were to meet so that such a reaction could be verified.

Airway responsiveness was measured before and within 3 days after each sequence of challenge tests. A positive methacholine test is followed by refractoriness for up to 24 h, and so it is not practical to monitor airway responsiveness more frequently [9].

### *Control data*

Before any double-blind challenge tests were carried out, $FEV_1$ was measured at the same times over 3 days to provide control data.

### *Statistical evaluation*

The $FEV_1$ data for each challenge test were plotted against time over the 24 h surveillance period, and compared against mean control values for the identification of late asthmatic reactions. Two statistical techniques, described fully elsewhere, were used [10]. Briefly, a pooled variance was calculated from the control data obtained from all time points, thereby defining a parallel lower boundary equivalent to a 95% confidence limit. This assumed that the variance for each individual did not change from hour to hour, and we use the term 'lower 95% band' to distinguish this from the true confidence limit. An excursion of the serial $FEV_1$ measurements below this band on a challenge day indicates a significant decrement in ventilatory function; and a significant decrement persisting for at least 1 h (a minimum of two consecutive hourly measurements) implies a late asthmatic reaction. A late asthmatic reaction was recognized secondly from an increase in the $FEV_1$ 2–12 h area decrement (the area from the daily $FEV_1$ versus time plot 2–12 h after challenge onset, which is bounded above by the extrapolated $FEV_1$ mean baseline and below by the $FEV_1$ plot) beyond its 95% confidence limit from the

three control days. A late asthmatic reaction is confirmed when both the serial $FEV_1$ and area decrement methods give positive results, but is considered equivocal if only one is positive.

*Analysis of volatile emanations from activated resin*

Conventional gas chromatographic and mass spectrometric techniques were used to identify the various volatile substances released following activation of the resin mixture against a computer library of organic compounds.

*Safety and ethical approval*

All participants understood that they were free to use inhaled bronchodilator medication at any time if they perceived the need, and to phone the supervising duty physician if concern arose. They knew that the use of additional medication without the physician first supervising the relevant spirometric measurements might invalidate the particular day's investigation. The study protocol was approved by the local ethics committee.

## Results

### Subjects

Demographic data for the six volunteers are given in Table 1. Initially there were six ex-coal miners, but when it became evident that the unsupervised measurements of $FEV_1$ in one were unreliable, we substituted a man who had used the same resin system to repair the bodywork of buses/coaches and was also suspected to have developed occupational asthma.

In one subject we were able to withdraw medication completely, but it proved to be impractical to reduce the medication level in the other five apart from omitting the use of short-acting β agonist bronchodilators 'as required'.

### Challenge tests

*Symptoms*

Four subjects experienced minor discomfort immediately following challenge with the higher doses, but none reported worsening asthmatic symptoms during the remaining hour of the surveillance period. However, Subjects 1, 2 and 5 subsequently admitted to having taken sporadic doses of inhaled bronchodilator medication during the challenge series, without consulting the on-call physician. No significant decrements in $FEV_1$ were documented by their spirometric measurements before any of these treatment doses, but each subject ultimately underwent repeated double-blind challenges at the styrene 0 p.p.m. (i.e. air) and styrene 320 p.p.m. levels in case these bronchodilator doses had inhibited or masked a subsequent late reaction. All refrained from the use of such medication during these 'Series 2' challenges. Subject 5 again reported immediate chest tightness following the final 320 p.p.m. challenge, but there were no other reported symptoms.

**Table 1.** Demographic data (numbers and %, or means and ranges) and changes in $PD_{20}$

| | *Subject 1* | *Subject 2* | *Subject 3* | *Subject 4* | *Subject 5* | *Subject 6* |
|---|---|---|---|---|---|---|
| Age (years) | 51 | 49 | 34 | 54 | 52 | 50 |
| Underground work (years) | 33 | 31 | 13 | 32 | 30 | 0[a] |
| Roof-bolting work (years) | 8 | 15 | 5 | 15 | 15 | 10[a] |
| Time since last exposure (years) | 2 | 2 | <1 | 3 | 3 | 3 |
| Medication during study[b] | Beclo 2000 Salm 200 | Budes 800 Salm 100 | Beclo 1000 | Beclo 1000 | Nil | Beclo 400 |
| Smoker status | Former | Former | Never | Never | Former | Never |
| Pack-years | 4 | 4.5 | 0 | 0 | 1 | 0 |
| Baseline $FEV_1$ (litres)[c] | 1.99 | 1.85 | 2.92 | 2.55 | 3.12 | 3.16 |
| % predicted | 59 | 51 | 73 | 75 | 90 | 84 |
| $PD_{20}$ Series 1 | | | | | | |
| Before (μg)[d] | 100 | 16 | 4.0 | 261 | 128 | 36 |
| After (μg) | 119 | 44 | 3.0 | 338 | 65[e] | 53 |
| $PD_{20}$ Series 2 | | | | | | |
| Before (μg)[d] | 338 | 57 | | | 65[e] | |
| After (μg) | 151 | 271 | | | 306 | |

[a]Not a coal miner, but had worked with the same resin system.

[b]μg per day; Beclo = beclomethasone, Budes = budesonide, Salm = salmeterol.

[c]Mean 10:00 h value from the three control days.

[d]Where >1 $PD_{20}$ measurements were obtained during the recruitment and medication stabilization period, the last before the challenge series is given.

[e]The values refer to the same methacholine test.

*FEV1 measurements*

Figure 1 shows graphs of serial $FEV_1$ measurements for all participants for the final (styrene 320 p.p.m.) challenge test, together with the respective control means and the lower 95% confidence bands. Those from the second series are illustrated for Subjects 1, 2 and 5. There were no convincing immediate asthmatic reactions in any subject, and none of the lower 95% confidence bands were breached during the period 2–24 h after challenge.

The corresponding $FEV_1$ 2–12 h area decrement values are given in Table 2. Again, no hint of a late asthmatic reaction was observed.

*Measurements of airway responsiveness*

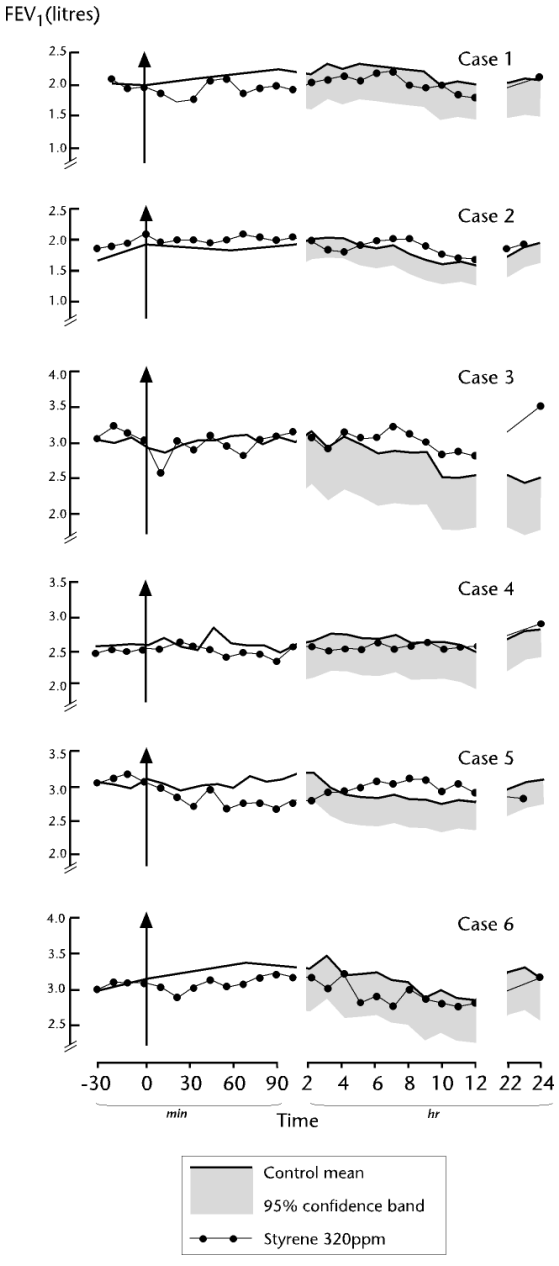
No significant increases in airway responsiveness occurred (Table 1). In Subject 1, for Series 2 the $PD_{20}$ decreased to just below half of the pre-series value, but this did not occur for Series 1, and the value before Series 2 was unusually high (an outlier) compared with all other values. In Subject 5, for Series 1 the $PD_{20}$ decreased almost to half of the pre-series value, but this did not occur for Series 2.

*Analysis of volatile emissions from the challenge procedure*

Styrene was readily identified as the most prominent constituent among the vapour products of resin activation (>98%), the principal trace constituents being xylene, ethyl benzene, toluene and benzaldehyde. Other trace constituents included benzenamine, a number of long-chain hydrocarbons, diethyl methyl phenol, dimethyl dioxane and dioxolane.

The independent estimates of styrene concentration were similar to those recorded by the gas monitor. For the target concentrations of 320 p.p.m. illustrated in Figure 1, the mean concentration measured later in the analytical laboratory was 346 p.p.m. (range 288–373 p.p.m.).

**Figure 1.** $FEV_1$ plots for each participant: control means, lower 95% band, styrene 320 p.p.m. challenge.




## Discussion

We would have considered an unequivocally positive outcome in any one of the subjects to comprise: worsening asthmatic symptoms, a significant decrease in $FEV_1$ over the 24 h plot, a significant increase in the 2–12 h area decrement and a significant increase in airway responsiveness, each being repeatable with a second double-blind challenge at the same dose level. We look particularly for evidence of late asthmatic reactions, since these are generally associated with increases in airway responsiveness and so provide persuasive evidence that the challenge agent under investigation is indeed asthmagenic. When isolated immediate asthmatic reactions occur, there is generally no change in airway responsiveness, and the reaction may simply be a consequence of non-specific irritancy.

The completed series of challenge tests demonstrated no evidence of late asthmatic reactions in any subject, nor were there significant increases in airway responsiveness as a result of the completed challenge series. The investigation did not, therefore, confirm that these men had developed occupational asthma as a consequence of using this resin system. Despite the high (and potentially irritant) concentrations of styrene, there were no convincing early asthmatic reactions either.

While an unequivocally positive outcome in any one of

**Table 2.** 2–12 h area decrement (AD) values in litre-hours for control challenges and challenges characterized by styrene 1–320 p.p.m.

| *Subject* | *95% CI for the three control challenges* | *Styrene 1.0 p.p.m.* | *Styrene 3.2 p.p.m.* | *Styrene 10 p.p.m.* | *Styrene 32 p.p.m.* | *Styrene 100 p.p.m.* | *Styrene 320 p.p.m.* |
|---|---|---|---|---|---|---|---|
| 1 | –1.21, +3.89 | +0.25 | +0.51 | –0.34 | –0.14 | –1.20 | –0.48 |
| 2 | –0.71, +3.02 | +0.03 | +0.35 | +0.53 | –0.35 | +0.15 | –1.30 |
| 3 | –2.71, +6.72 | +0.51 | –0.56 | –0.98 | +1.70 | +6.95 | +0.72 |
| 4 | –5.10, +3.27 | –1.65 | –1.39 | –0.77 | –0.68 | –0.62 | –0.65 |
| 5 | +0.89, +1.91 | +0.12 | –1.64 | –0.76 | –0.72 | +0.61 | +0.20 |
| 6 | –4.16, +1.84 | –0.20 | –2.00 | +1.20 | 0.00 | –0.60 | 1.00 |

A negative value for AD indicates a mean improvement in $FEV_1$ following the day's pre-challenge baseline measurement. No significant changes in AD were observed for those subjects undergoing challenges characterized by lower concentrations of styrene (0.01–0.32 p.p.m.). For Subjects 1, 2 and 5, the styrene 320 p.p.m. challenge refers to the second series.

the six subjects would have provided persuasive evidence to implicate the resin system, the negative outcome of the investigation does not fully exonerate it. A 'negative' is always more difficult to prove, and in five of these particular subjects the interval between investigation and last occupational exposure (2–3 years) may have been sufficient for the level of any 'hypersensitivity' to have lessened. In this respect, an earlier evaluation may have been more definitive, and ideally referrals for investigation should be made at a time when work and exposure are continuing.

A further problem was that five of the participants required the ongoing use of potent medication. This might additionally have diminished our ability to demonstrate asthmatic reactivity, particularly as there was a trend towards a decrease in airway responsiveness over the course of the investigation. This was possibly a consequence of improved medication compliance stimulated by the medical attention that was encountered. Neither factor has, however, prevented a positive outcome in other studies where we encountered similar difficulties. Furthermore, other investigators have shown that with serial challenge test exposures (such as were achieved with this protocol), asthmatic reactions and increases in airway responsiveness are to be expected in truly sensitized subjects even after intervals of several years without exposure [11,12].

It might be argued that trace (but asthmagenic) components of the volatile products from resin activation became disproportionately adherent to the Tedlar bag compared with styrene, and hence unavailable within the challenge system at the appropriate dose level. We think this is unlikely because the bags were chosen especially for their inert properties, and challenge mixtures were prepared immediately before each test. It might also be argued that our 5 min challenge system did not adequately simulate the natural occupational circumstances of exposure over a working day, but peak exposures probably offer a greater asthmatic stimulus than average exposures if the cumulative levels are standardized. More importantly, inhalation challenge tests for the investigation of occupational asthma generally provide satisfactory outcomes using the techniques we followed. Nevertheless, the exposure mixtures generated within the laboratory might not have simulated precisely those occurring in the workplace, and we cannot be certain that the negative results fully exclude the possibility that the roof-bolting resin system poses some risk for the development of occupational asthma.

We conclude that this resin system is not likely to have been the primary cause of asthma in these men, although this is not fully excluded. The fact that dibenzoyl peroxide itself is not volatile, and is not aerosolized by the roof-bolting procedure, is perhaps a critical point. The investigation additionally provided useful supporting evidence that styrene is not likely to be a common cause of occupational asthma, despite its noxious irritant nature and despite its very widespread use in industry.

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