

infections.<sup>9</sup> Whether or not chest tube drainage in *L. monocytogenes* empyema is necessary remains unclear. However, a complete resolution of the empyema was obtained in both previously mentioned cases with medical treatment only.

We therefore believe that *L. monocytogenes* should be considered in the differential diagnosis of empyema in patients with HIV infection.

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*Thorax* 1997;52:746–748

## Occupational asthma in an isothiazolinone manufacturing plant

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### Abstract

**A chemical plant operator developed asthma five months after starting work in an isothiazolinone manufacturing plant. He described symptoms of late asthmatic reactions after work with isothiazolinone. Airway responsiveness to methacholine improved tenfold when he was removed from the plant for 18 days. A workplace challenge study then resulted in a deterioration in airway responsiveness to its earlier level and in progressive falls in forced expiratory volume in one second (FEV<sub>1</sub>) over three days at work compared with control days, indicating statistically significant late asthmatic reactions of increasing severity.**

(*Thorax* 1997;52:746–748)

Keywords: occupational asthma, biocides, isothiazolinone.

Isothiazolinones are being used increasingly as broad spectrum biocides in various water systems and in products such as paper, paints, and cosmetics.<sup>12</sup> In some circumstances they have been used as substitutes for formaldehyde and glutaraldehyde which are known to cause asthma.<sup>3</sup> There have been many reports of isothiazolinones causing occupational dermatitis but evidence of asthma due to isothiazolinones is lacking.<sup>4,5</sup> We describe the occurrence of asthma in an isothiazolinone manufacturing plant, and a workplace challenge study which suggested it was occupational in origin. We think it likely that this was the result of sensitisation to isothiazolinone.

### Case report

A 53 year old chemical plant operator developed asthma five months after starting work in an isothiazolinone manufacturing plant. He had no previous history of asthma or atopic disease and he was an ex-smoker. His job involved the filling of containers with various formulations of isothiazolinones in aqueous solution, including a combination of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one. This was performed in an enclosed booth fitted with an extractor, but as he frequently opened the door of the booth to replace containers there was potential exposure to low concentrations of airborne isothiazolinone, which is weakly volatile. He described symptoms of cough and wheeze, which occurred towards the end of his working shifts, persisted into the evenings after work, and often disturbed his sleep at night. He was diagnosed as having asthma by his general practitioner and was prescribed salbutamol and beclomethasone inhalers. He had noticed that his symptoms were related to his work and he had tried to reduce his exposure, but he remained at the same job over the next five years until he was referred for assessment. His forced expiratory volume in one second (FEV<sub>1</sub>) was 3.91 litres (109% predicted) and his forced vital capacity (FVC) was 5.69 litres (127% predicted) while taking salbutamol and beclomethasone, and he had moderate airway responsiveness to methacholine with a provoking dose responsible for a 20% fall in FEV<sub>1</sub> (PD<sub>20</sub>) of 230 µg. Skin tests for atopy gave negative results. His history was suggestive of occupationally provoked late asthmatic reactions and a workplace challenge study was undertaken.

### WORKPLACE CHALLENGE STUDY

His asthma treatment was stopped, he was withdrawn from the workplace for 18 days, and then re-exposed to his normal work environment. Spirometric tests were performed hourly from 07.00 hours to 17.00 hours on three control days away from work, and hourly from 07.00 hours to 23.00 hours on a fourth control day. He then returned to his normal job, working a 07.00 hours to 15.00 hours shift,

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Received 4 April 1996  
Returned to authors 18 July 1996  
Revised version received 22 August 1996  
Accepted for publication 26 September 1996

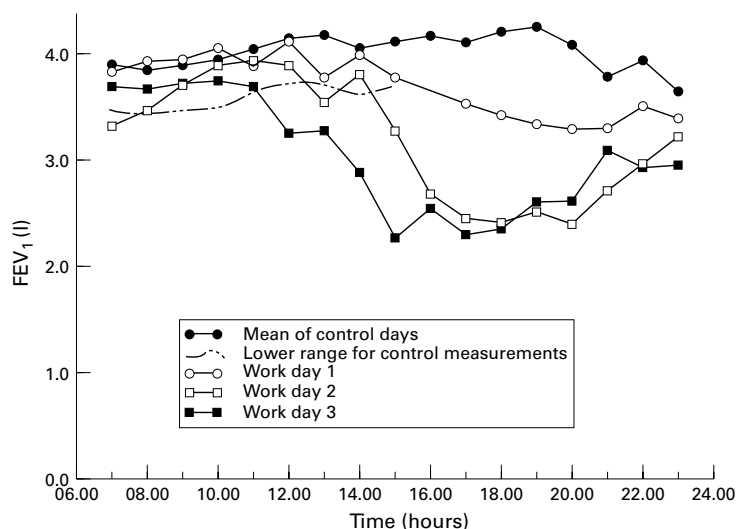


Figure 1 Serial measurements of FEV<sub>1</sub> during workplace challenge study.

and spirometric testing was performed hourly from 07.00 hours to 23.00 hours on three consecutive work days. He spent each shift as usual filling containers with isothiazolinone formulations containing a mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one. This was performed as an enclosed process within the booth but he opened the door of the booth frequently throughout the shift, as usual, putting containers in place and screwing on their lids.

On each of the three study days at work he developed nasal irritation, cough, wheeze and chest tightness starting 4–6 hours into the shift and persisting into the evening with sleep disturbance at night. Figure 1 shows the mean FEV<sub>1</sub> values for the control days 1–3 (07.00–17.00 hours), a “lower boundary” equivalent to a 95% confidence limit, and evening values (18.00–23.00 hours) for control day 4. Superimposed are the plots for the three days at work. Each crosses the “lower boundary” at a progressively earlier time and with progressively greater strength, indicating statistically significant late asthmatic reactions of increasing severity.<sup>6</sup> Airway responsiveness to methacholine was measured on four occasions. On his last day at work before the study the PD<sub>20</sub> was 115 µg; on days 10 and 18 away from work it improved sequentially to 267 µg and 1107 µg, but three days after his return to work it had deteriorated to 110 µg.

Air monitoring in the manufacturing plant had shown low but measurable levels of isothiazolinone of 0.01–0.3 mg/m<sup>3</sup>. These were well within the control limits set internally by the manufacturer in order to avoid possible irritant effects. Out of a total of 20 workers in the plant two others developed symptoms of asthma after beginning employment. Both then changed the nature of their work so that the possibility of ongoing exposure to isothiazolinone was much reduced. One recovered fully and the other, a maintenance technician, improved. However, the maintenance technician was subsequently involved in an accident which resulted in facial and eye contact with

dissolved isothiazolinone. This caused a brief period of conjunctival inflammation but not worsening asthma.

## Discussion

The clinical history of the chemical plant operator was strongly suggestive of occupational asthma in that he had developed asthma de novo after a short latent interval of employment, with a close relationship between symptoms and periods at work. The workplace challenge study provided objective evidence of statistically significant late asthmatic reactions occurring at progressively earlier times and with progressively greater magnitude on each of the three successive days during which he worked with isothiazolinone.<sup>7</sup> This suggests increasing levels of airway responsiveness during the study period.

Changes in airway responsiveness associated with emergent or resolving occupational asthma (or with inhalation provocation tests) may be rapid and dramatic, though such changes in asthmatic activity are rarely seen in other circumstances.<sup>7</sup> The significance of changes of PD<sub>20</sub> can be assessed when population samples undergo two methacholine tests and the coefficient of repeatability (CR) is calculated. Estimates for CR using our dosimeter method for methacholine tests have given values in the range of 2–3, indicating that an increase in PD<sub>20</sub> to threefold or a decrease to one third identifies a statistically significant change.<sup>8</sup> During the period of investigation in this case the PD<sub>20</sub> values increased approximately tenfold over the 18 day period away from work and then fell to almost exactly the initial value on re-exposure to the work environment for three days. The importance of being able to identify significant changes in airway responsiveness in association with inhalation provocation tests is that the test agent or environment can be shown to be a potential inducer of asthma, not merely a provoker of asthmatic attacks.

The workplace challenge study in this case consequently provided strong evidence for a diagnosis of occupational asthma, and the suspicion that two of 20 fellow workers had similarly developed asthma provides additional support. The nature of the operator's work, the known sensitising properties of isothiazolinone in the skin, and the confirmed presence of respirable isothiazolinone (albeit in low concentrations) in the work environment suggest that isothiazolinone was the cause. We think this is likely, and we assume that isothiazolinone, like many reactive chemicals of low molecular weight, acts as a hapten through immunological mechanisms. This is thought to explain its effect in causing dermatitis.<sup>9</sup> Our investigations do not prove a causal relationship, however, and there is a need for specific inhalation provocation tests to provide definitive conclusions.

Sodium metabisulphite is used in the plant to inactivate isothiazolinone following accidental spillages, and this substance has been reported to cause immediate asthmatic reactions fol-

lowing inhalation.<sup>10</sup> It has consequently been implicated as a cause of occupational asthma, but it has not been shown to cause late asthmatic reactions nor to cause increases in airway responsiveness, and it is unclear whether the operator we describe could have been exposed to airborne metabisulphite during the three days of the workplace challenge study. We would consequently regard this as a much less plausible cause for his occupational asthma.

Isothiazolinone biocides are being used increasingly in a number of industries – for example, the manufacture of cosmetics, shampoos, synthetic fibre, and paper products. Their sterilising properties are used also in humidifier and air conditioning systems. Dermatitis has been reported in consumers as a result of topical contact in both occupational and domestic settings,<sup>4,5,9</sup> so the potential risk for the development of asthma may be widespread. The opportunity for respirable exposure may, however, be limited. Furthermore, isothiazolinones are generally encountered in

much greater dilution by consumers than by workers engaged in their manufacture.

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*Thorax* 1997; **52**:748–749

## Regression of polyvinylchloride polymer pneumoconiosis

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### Abstract

**A 35 year old man heavily exposed to polyvinylchloride (PVC) polymer dust developed dyspnoea and a mild restrictive lung disorder consistent with PVC pneumoconiosis. Clinical and radiological abnormalities cleared on removal from exposure, suggesting that in its early stages PVC pneumoconiosis is reversible.**

(*Thorax* 1997; **52**:748–749)

Keywords: polyvinylchloride, pneumoconiosis, lung disease.

### Case report

In November 1991 a 35 year old plastics factory employee presented with sore throat, blocked nose, chest tightness, and pleuritic chest pains. Physical examination and chest radiography were normal. Pulmonary function test values were at the lower limit of normal (table 1).<sup>1</sup> Serial peak flows recorded over two weeks showed no variability, and no diagnosis was made.

In July 1993 he returned with persistent sore throat, nasal and eye irritation, occasional dyspnoea, and a non-productive cough which had been present for several months. His effort tolerance had declined and he was no longer

able to play soccer. A detailed occupational history established that he had worked since 1985 primarily with a fine polyvinylchloride (PVC) powder, manually loading hoppers under very dusty conditions using only a simple mask as respiratory protection. A visit to the factory confirmed his description; there was no local exhaust ventilation and general ventilation was inadequate. Various pigments and other chemicals were added to the PVC, but he was not involved in this later part of the process.

He had never smoked, had no domestic bird exposure, no tuberculosis contact, nor any history suggestive of allergy or atopy. Examination showed sparse fine crackles over the left lower zone. Full blood count, differential count, international normalised ratio, and serum levels of angiotensin converting enzyme (ACE) were normal.

Pulmonary function testing showed a reduction of more than 600 ml in volumes and a slight decline in gas transfer, indicating mild restriction (table 1). The chest radiograph was unchanged. A high resolution computed tomographic (HRCT) scan of the chest showed a fine nodular pattern in both lower lobes, more extensive on the left, with no pleural or other pathology seen (fig 1). There was no lymphadenopathy nor other signs to suggest sarcoidosis such as nodularity along the bronchovascular markings.

Transbronchial biopsy specimens obtained by fiberoptic bronchoscopy from the left lower lobe showed focal areas of interstitial fibrosis. Conspicuous fibrin deposition was noted within the interstitium. There was a general paucity of inflammatory cells, but the bronchial wall showed a moderate infiltrate of chronic inflammatory cells. The basement membrane was mildly thickened. No granulomatous changes were seen. No exogenous material was

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Received 7 October 1994  
Returned to authors  
13 December 1994  
Revised version received  
29 August 1996  
Accepted for publication  
25 September 1996