

Toluene di-isocyanate-induced asthma

II. Inhalation challenge tests and bronchial reactivity studies

I. M. O'BRIEN, A. J. NEWMAN-TAYLOR, P. S. BURGE,
M. G. HARRIES, I. W. FAWCETT and J. PEPYS

Department of Clinical Immunology, Cardiothoracic Institute, Brompton, London

(Received 10 August 1978; accepted 22 August 1978)

Summary

In sixty-three workers exposed to toluene di-isocyanate (TDI), no overall differences in bronchial reactivity to histamine inhalation and to exercise testing were found between the total groups of positive and negative TDI reactors to provocation tests. A subgroup of TDI highly sensitive subjects reacting to very low concentrations (≤ 0.001 p.p.m.) were more sensitive to both histamine and exercise than the group who were less sensitive to TDI, and who reacted to higher concentrations (0.002-0.02 p.p.m.) than the group of non-reactors. There were, however, in the last group a number of subjects with high degrees of histamine reactivity who did not react to the TDI. These findings suggest that, on the one hand, the asthmatic reactions to TDI cannot be attributed solely to non-specific mechanisms and, on the other, that in subjects with high degrees of specific sensitivity non-specific mechanisms may also be playing a part.

Introduction

Respiratory disease associated with the inhalation of TDI, a highly reactive chemical of low molecular weight used in the manufacture of polyurethane, was first reported by Fuchs & Valade (1951). At atmospheric concentrations in excess of 0.05 p.p.m. it is a potent mucosal irritant (Henschler, Assman & Meyer, 1962). The pathogenesis of asthmatic reactions provoked by exposure to low concentrations is uncertain. Reactions to low concentrations occur in a minority of those exposed, developing only after a period of asymptomatic exposure, and are then provoked by concentrations of TDI not affecting other exposed workers, suggesting an allergic basis. Evidence for the involvement of specific immunological mechanisms has not been consistently demonstrated (Taylor, 1970; Avery *et al.*, 1969; Butcher *et al.*, 1976), but progress is now being made in this respect (Karol, Ioset & Alarie, 1978).

Correspondence: Professor J. Pepys, Department of Clinical Immunology, Cardiothoracic Institute, Brompton, London SW3 6HP.

It has been suggested that TDI acts as a β -receptor-blocking agent, with an action similar to propranolol, provoking asthma only in those workers with bronchial hyper-reactivity (Butcher *et al.*, 1977; Davies *et al.*, 1977).

We have studied bronchial reactivity as determined by histamine inhalation and exercise testing in a group of workers in whom inhalation testing with TDI was carried out for diagnostic purposes.

Materials and methods

All sixty-three subjects had been occupationally exposed to TDI and were referred for investigation of possible work-related respiratory symptoms.

Atopic status was determined by prick testing with twenty-three common environmental allergens, the subjects being considered atopic if there was one or more positive reaction.

TDI inhalation challenge testing

This was carried out on all sixty-three subjects in a 6.0 m³ closed cubicle. The atmospheric concentration of TDI was measured by a Model 700 TDI monitor (Universal Environmental Instruments Ltd) and compared in twenty-three instances with readings from a personal monitor sampling air 10–15 cm from the subject's mouth.

On the control day a varnish (Wilkinson's Marine Varnish) not containing TDI was brushed onto a surface on a bench at waist height. On subsequent days graded amounts of TDI were added to the varnish until an asthmatic reaction was elicited, up to a maximum atmospheric concentration of 0.02 p.p.m. The challenge period was 30 min, except for one subject exposed for 120 min to 0.006 p.p.m. and another for 120 min at 0.01 p.p.m.

Measurements of FEV₁ and FVC using a dry wedge spirometer (Vitalograph) was made prior to and following challenge at 5 min intervals for the first 30 min, at 10 min intervals for the next 30 min, at 30 min intervals for the next 60 min and then hourly for a minimum of 8 hr. A positive reaction was taken as a fall in FEV₁ of 15% more than on the control day.

Histamine inhalation testing

Fifty-two subjects were tested with an aerosol of histamine acid phosphate solution produced by passing oxygen at 8.0 l/min through a Wright's nebulizer. This was inhaled through a face mask from a re-breathing bag. Doubling concentrations from 0.125 to 32 mg/ml were inhaled for periods of 30 sec at 5 min intervals until a fall in FEV₁ of 20% occurred, or until the maximum concentration was reached.

Bronchial hyper-reactivity was considered to be present if a 20% fall in FEV₁ occurred at a concentration of 32 mg/ml or less.

Exercise testing

Forty-six subjects were tested by free running on a flat surface for up to 6 min, sufficient to increase their heart rate to at least 140 beats/min. Measurements of FEV₁ and FVC (thirty-five subjects) or PEFR (eleven subjects) were made prior to and immediately after exercise, and then at 5 min intervals for 30 min and at 10 min intervals for a further 30 min. A post-exercise fall in FEV₁ or PEFR exceeding 9% of the initial value was considered abnormal (Godfrey, Silverman & Anderson, 1973).

Table 1. Details of sixty-three subjects challenged with TDI

Details	TDI	
	Sensitive	Non-sensitive
Total number	37	26
Age range (years)	25-61	26-60
Mean	46	42
Positive prick test(s)	14 (38%)	9 (31%)
Asthma prior to exposure	1	5
Rhinitis prior to exposure	3	4
Atopic family history	5	11
Total histamine tests/smoking	31	21
Smokers	9	5
Ex-smokers	9	6
Non-smokers	13	10

Results

The age, atopic status and history of rhinitis were similar in the TDI-sensitive and TDI 'non-sensitive' groups. There was a higher incidence of asthma prior to TDI exposure in the TDI non-sensitive group (Table 1) and of a history of allergy in first degree relatives.

TDI inhalation tests

Asthmatic reactions were elicited by atmospheric concentrations of TDI ranging from

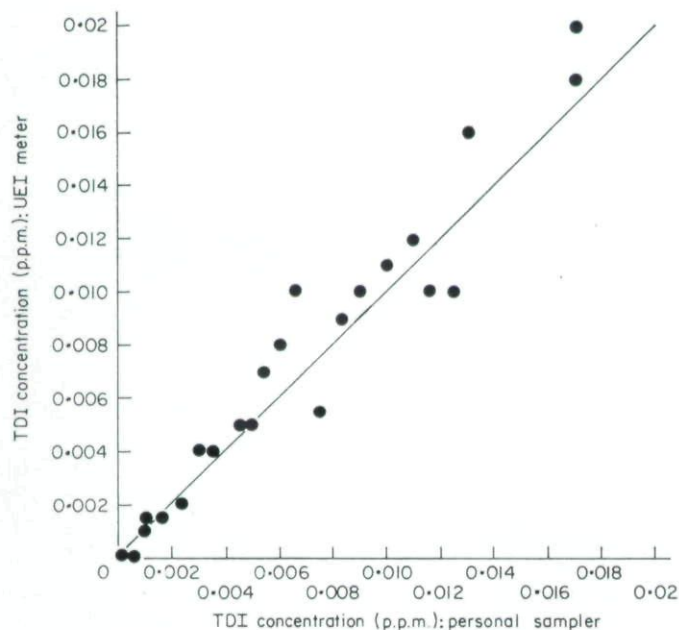


Fig. 1. TDI concentration (p.p.m.): UEI meter *vs* personal sampler. Correlation coefficient=0.9539.

<0.001 p.p.m. to 0.02 p.p.m. in thirty-seven subjects: two immediate, seventeen non-immediate (late) and eighteen combined (dual). The correlation coefficient of the TDI concentrations in the challenge cubicle as measured by the UEI meter and personal monitor was 0.9539 (Fig. 1). Of the 9 reacting to TDI concentrations of ≤ 0.001 p.p.m. one had atopic, and of the 22 with reactions to 0.002–0.02 p.p.m. 12 were atopic.

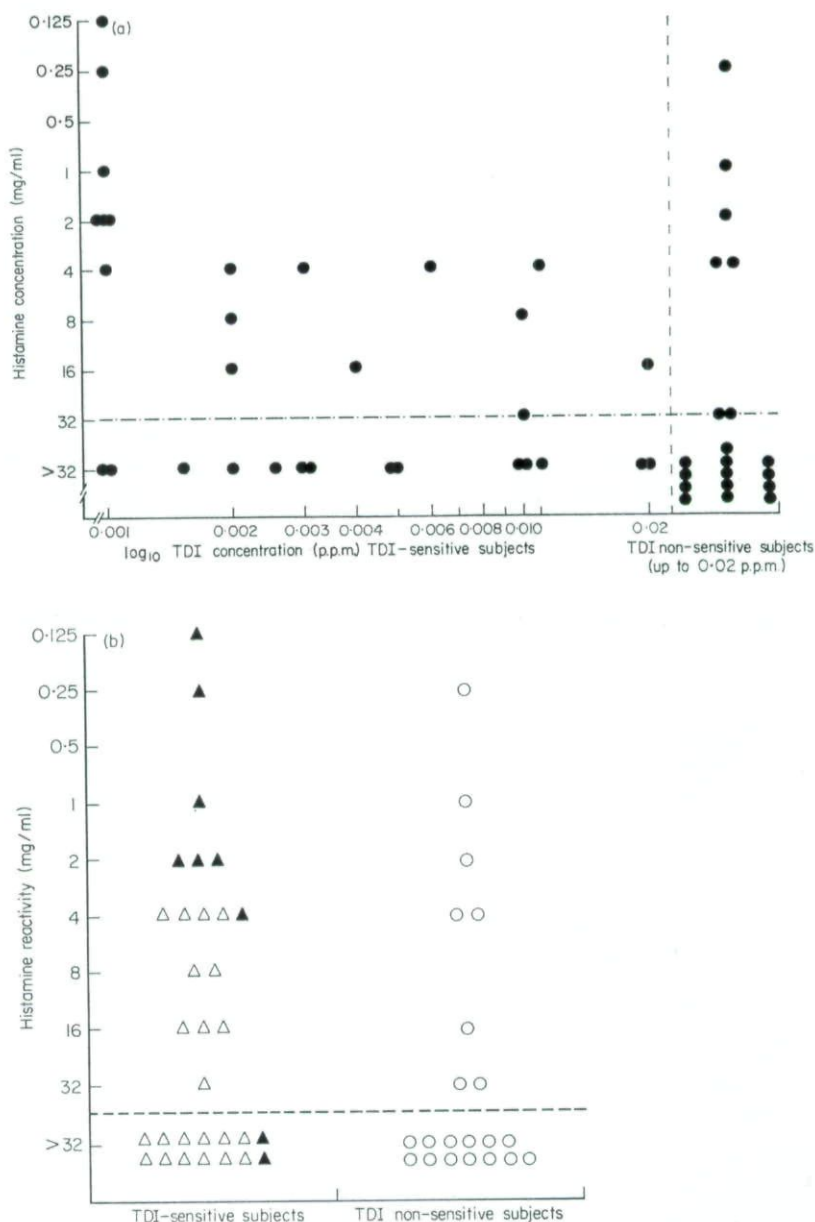


Fig. 2. (a) Histamine reactivity vs TDI reactivity in TDI-exposed workers ($n=52$; thirty-one TDI sensitive and twenty-one non-sensitive). (b) Histamine reactivity in fifty-two subjects challenged with TDI (same subjects as in 2a) ▲ Asthmatic reactions to ≤ 0.001 p.p.m. △ Asthmatic reactions to 0.002–0.02 p.p.m.

Histamine inhalation tests

Increased bronchial reactivity to histamine was present in (a) seventeen out of thirty-one TDI sensitive subjects, consisting of seven out of nine with asthmatic reactions to TDI concentrations of <0.001 p.p.m. and ten out of twenty-two with reactions to 0.002–0.02 p.p.m.; and (b) eight out of twenty-one TDI non-sensitive subjects (Fig. 2a, b). Using Wilcoxon's non-parametric test for unpaired samples, there was no significant difference between the TDI-sensitive and TDI non-sensitive groups. There were, however, significant differences between the subgroup of TDI highly sensitive subjects, with asthmatic reactions to concentrations of 0.001 p.p.m., and the TDI-sensitive subgroup, with reactions to TDI concentrations of 0.002–0.02 p.p.m. ($P<0.005$) and the TDI non-sensitive group ($P<0.01$).

In terms of an atopic background, increased histamine reactivity in the TDI-sensitive group was found in seven out of thirteen atopics and ten out of eighteen non-atopics and in the TDI non-sensitive group in three out of nine atopics and five out of twelve non-atopics.

Exercise tests

The mean exercise times in the TDI-sensitive and non-sensitive groups were 5.2 min and 5 min respectively, and the mean pulse rate was 155 beats/min in both groups. Exercise-induced asthma occurred in eighteen out of twenty-nine TDI-sensitive subjects, seven out of nine of those with asthmatic reactions to TDI concentrations of 0.001 p.p.m. and eleven out of twenty of those with reactions to concentrations of 0.002–0.02 p.p.m.; and in nine out of seventeen TDI non-sensitive subjects (Fig. 3a, b). Using Wilcoxon's non-parametric test there was no significant difference between the TDI-sensitive and TDI non-sensitive groups. Again, however, there was a significant difference between the subgroup of TDI highly sensitive subjects with asthmatic reactions to concentrations of <0.001 p.p.m., the TDI-sensitive subgroup with reactions to concentrations of 0.002–0.02 p.p.m. ($P<0.01$) and the TDI non-sensitive group ($P<0.025$). In terms of an atopic background, exercise-induced asthma was present in the TDI-sensitive group in seven out of ten atopic and eleven out of

Table 2. Atopic status *vs* bronchial reactivity

Subjects	Histamine challenge		Exercise challenge	
	Total	Increased reactivity	Total	$>9\%$ fall in FEV ₁ or PEFR
TDI-sensitive subjects				
Atopic	13	7	10	7
Non-atopic	18	10	19	11
Total	31	17	29	18
TDI non-sensitive subjects				
Atopic	9	3	8	5
Non-atopic	12	5	9	5
Total	21	8	17	10

nineteen non-atopic subjects, and of the TDI 'non-sensitive' group in five out of eight atopic and five out of nine non-atopic subjects (Table 2).

Smoking history, sensitivity to TDI, exercise and histamine

No significant differences were shown (Fig. 4) between smokers, ex-smokers and non-smokers in terms of TDI sensitivity and responses to exercise and histamine tests.

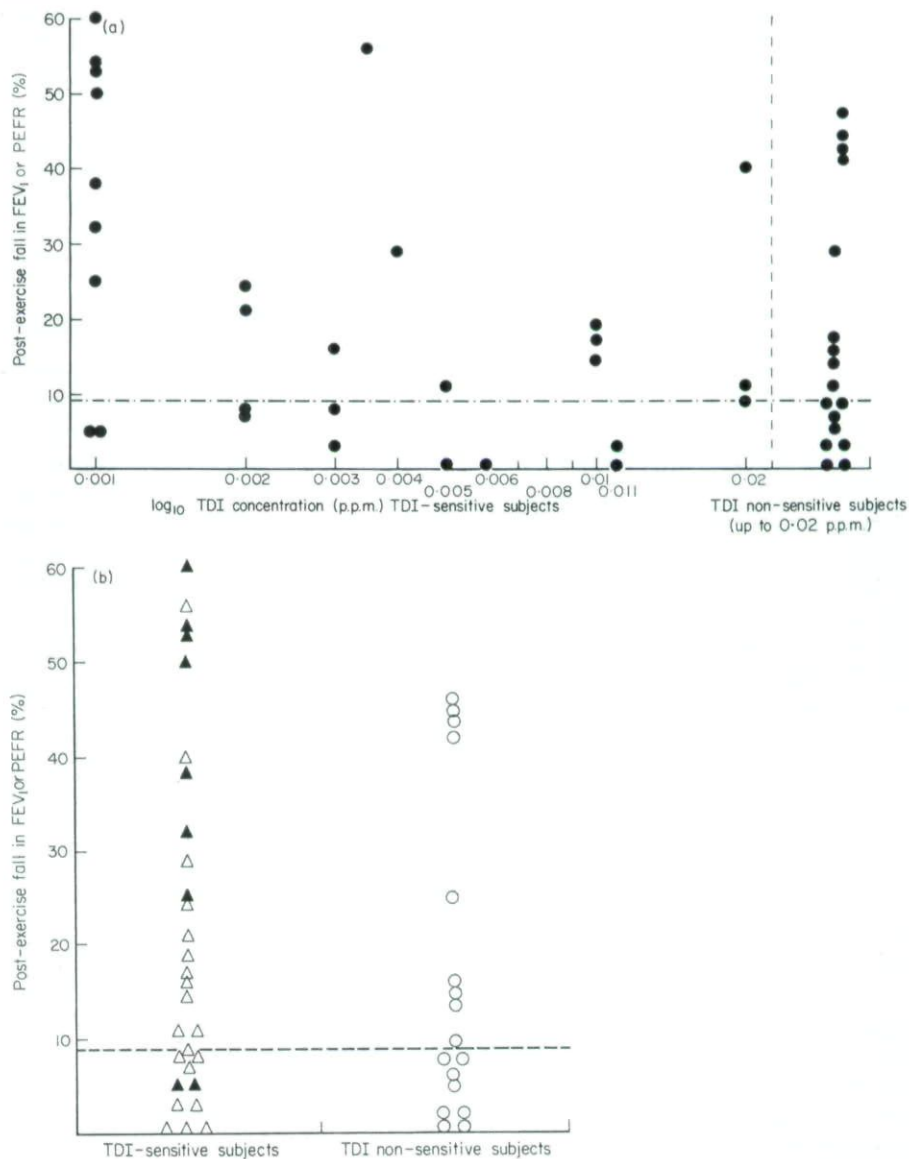


Fig. 3. (a) Post-exercise fall in $FEV_1/PEFR$ vs TDI concentration eliciting asthmatic reactions. ($n=46$; twenty-nine TDI-sensitive and seventeen non-sensitive). (b) Exercise testing in forty-six subjects challenged with TDI (same subjects as in 3a) $\blacktriangle$, Asthmatic reactions to ≤ 0.001 p.p.m.; $\triangle$, Asthmatic reactions to 0.002-0.02 p.p.m.

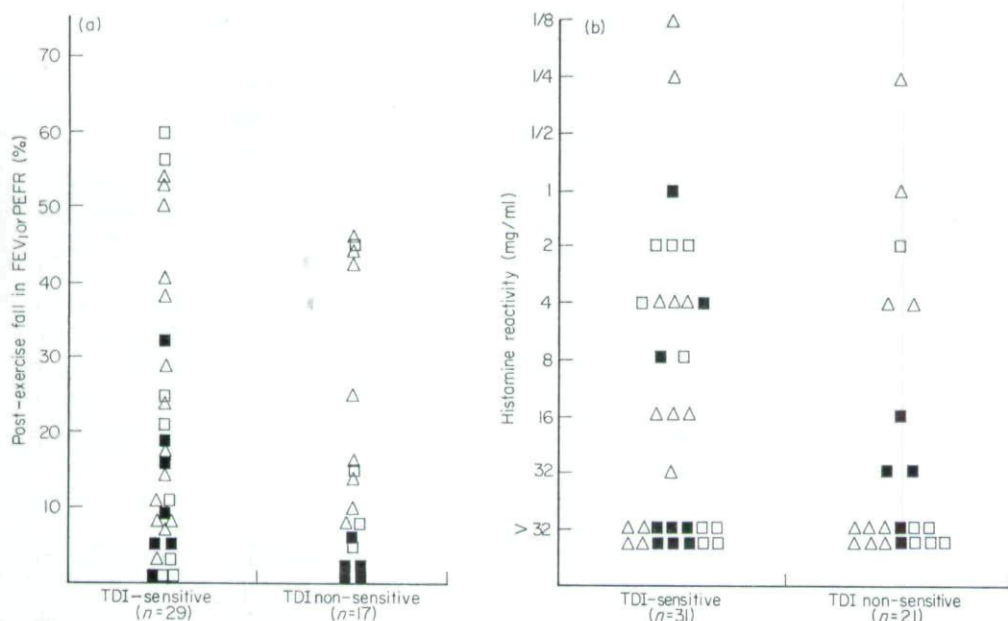


Fig. 4. Bronchial reactivity *vs* smoking history in subjects challenged with TDI. (a) Exercise fall in FEV₁/PEFR *vs* smoking; (b) histamine reactivity *vs* smoking. (■) Smoker; (□) ex-smoker; (Δ) non-smoker.

Discussion

This study shows that of subjects giving asthmatic reactions to TDI tests, seventeen out of thirty-one (55%) had increased histamine reactivity and eighteen out of twenty-nine (62%) had exercise-induced asthma. Although non-specific bronchial hyper-reactivity is regarded as an almost universal feature of asthma (Makino, 1966; Laitinen, 1974; Fish *et al.*, 1976; Cockcroft *et al.*, 1977), it was not demonstrated in a significant minority of the subjects who, as shown by TDI inhalation testing, fulfilled the defining characteristic of asthma: that is, variability of airflow obstruction over short periods of time.

In subjects working with TDI but not reacting to it on inhalation testing, increased bronchial reactivity to histamine and exercise was present in eight out of twenty-one (38%) and nine out of seventeen (53%) respectively. Although there was no significant difference between the groups of TDI-sensitive and non-sensitive subjects on either histamine or exercise testing, the subgroup of TDI highly sensitive subjects with asthmatic reactions to concentrations of 0.001 p.p.m. showed a significantly greater increase in bronchial reactivity to both histamine and exercise than the TDI-sensitive subgroup, with asthmatic reactions to TDI concentrations of 0.002–0.02 p.p.m., and the TDI non-sensitive group. There was no significant relationship between histamine reactivity in the atopic and non-atopic subjects in both positive and negative TDI reactors. In the fifty-two subjects tested by inhalation of histamine, of whom forty-six also had exercise tests, there were no significant differences in smoking habits in relation to these two tests or to the TDI inhalation test. Of the thirty-one reacting to the TDI test, nine were smokers, nine ex-smokers and thirteen non-smokers.

compared with the twenty-one negative reactors in whom the numbers were 5, 6 and 10 subjects respectively. These results arising from provocation testing contrast with the report (Gandevia, 1963) of an additive effect of smoking on bronchial reactivity to histamine of subjects not assessed by provocation tests but with actual factory exposures to concentrations of 0.1 to 0.9 p.p.m. TDI. The possibility that other potential irritants could have been present under the working conditions cannot be excluded, in contrast to our own findings under controlled conditions with tests to atmospheric concentrations of 0.001 to 0.02 p.p.m. TDI.

It has been postulated that TDI acts as a β -adrenergic receptor-blocking agent, because it has an inhibitory effect on the isoprenaline-induced increase in 3',5'-cyclic AMP in peripheral blood lymphocytes in subjects occupationally exposed to TDI with or without evidence of sensitivity (Butcher *et al.*, 1977; Davies *et al.*, 1977). Bronchial hyper-reactivity to methacholine was found in seven out of ten of these TDI-sensitive but in only one out of ten of the non-sensitive subjects. It was therefore suggested that TDI at subirritant concentrations might provoke asthma in terms of cholinergic stimuli because of the effects of β -receptor blockade and hyper-reactive airways.

Our findings and the above come from different studies, in neither of which were the subjects tested with both histamine and methacholine. Asthmatics in general give comparable reactions to bronchial tests with histamine and methacholine, but it is possible that cholinergic mechanisms may be involved in these particularly sensitive subjects. The very low concentrations of TDI which suffice to elicit asthmatic reactions in sensitive subjects suggest that allergy plays an important, although not necessarily exclusive, role, and this is supported by the demonstration of tolyl-specific IgE antibodies in sensitive subjects (Karol *et al.*, 1978).

We wish to acknowledge the generous support of the International Isocyanate Institute Inc. (Dr I. O'Brien) and that of Mardon Flexible Packaging Ltd, Colodense Ltd and D.R.G. Flexible Packaging Ltd for the provision of funds, equipment and co-operation in our investigations.

References

- AVERY, S.B., STETSON, D.M., PAN, P.M. & MATHEWS, K.P. (1969) Immunological investigation of individuals with toluene di-isocyanate asthma. *Clinical and Experimental Immunology*, **4**, 685.
- BUTCHER, B.T., SALVAGGIO, J.E., O'NEIL, C.E., WEILL, H. & CARG, O. (1977) Toluene di-isocyanate (TDI) pulmonary disease: immunopharmacologic and methylcholy challenge studies. *Journal of Allergy and Clinical Immunology*, **59**, 223.
- BUTCHER, B.T., SALVAGGIO, J.E., WEILL, H. & ZISKIND, M.M. (1976) Toluene di-isocyanate pulmonary disease: immunological and inhalation challenge studies. *Journal of Allergy and Clinical Immunology*, **58**, 89.
- COCKCROFT, D.W., KILLIAN, D.N., MELLON, J.J.A. & HARGRAVE, F.E. (1977) Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clinical Allergy*, **7**, 235.
- DAVIES, R.J., BUTCHER, B.T., O'NEIL, C.E. & SALVAGGIO, J.E. (1977) The *in vitro* effect of toluene di-isocyanate on lymphocyte cyclic adenosine monophosphate production by isoproterenol, prostaglandin and histamine—a possible mode of action. *Journal of Allergy and Clinical Immunology*, **60**, 223.
- FISH, J.E., ROSENTHAL, R.R., BUTRA, G., MENKES, H., SUMMER, W., PERMUTT, S. & NORMAN, P. (1976) Airways responses to methacholine in allergic and non-allergic subjects. *American Review of Respiratory Disease*, **113**, 579.
- FUCHS, S. & VALADE, P. (1951) Etude clinique et expérimentale sur quelques cas d'intoxication par

- le Desmodur T (di-isocyanate de toluène 1-2-4 et 1-2-6). *Archives Maladies Professionnelles*, **12**, 191.
- GANDEVIA, B. (1963) Studies of ventilatory capacity and histamine response during exposure to isocyanate vapour in polyurethane foam manufacture. *British Journal of Industrial Medicine*, **20**, 204.
- GODFREY, S., SILVERMAN, M. & ANDERSON, S.D. (1973) Problems of interpreting exercise-induced asthma. *Journal of Allergy and Clinical Immunology*, **52**, 199.
- HENSCHLER, D., ASSMAN, W. & MEYER, K.O. (1962) The toxicology of the toluene diisocyanates. *Archives of Toxicology (Berlin)*, **19**, 364.
- KAROL, M.H., IOSET, H.H. & ALARIE, Y.C. (1978) Toluyl-specific IgE antibodies in workers with hypersensitivity to toluene di-isocyanate Abstract. *American Industrial Hygiene Conference*, May 1978.
- LAITINEN, L.A.I. (1974) Histamine and methacholine challenges in the testing of bronchial reactivity. *Scandinavian Journal of Respiratory Disease*, Suppl. **86**, 1.
- MAKINO, S. (1966) Clinical significance of bronchial sensitivity to acetyl choline and histamine in bronchial asthma. *Journal of Allergy*, **38**, 127.
- TAYLOR, G. (1970) Immune responses to toluene diisocyanate (TDI) exposure in man. *Proceedings of the Royal Society of Medicine*, **63**, 379.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.