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A survey of a small group of workers exposed to toluene di-isocyanate

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Abstract **All 20 workers exposed to toluene di-isocyanate (TDI) in a chemical processing and packing factory were tested for TDI-induced asthma. The assessment included a respiratory symptom questionnaire, spirometry, skin prick tests for common allergens and assessment of total and TDI-specific immunoglobulin E (IgE) levels by radio-allergosorbent tests. Six workers had symptoms suggestive of TDI-related asthma. Three of these 6 workers had a significant cross-shift decline in forced expiratory volume in 1 second (FEV_1) (10% or greater). Two of the 6 had high levels of TDI-specific IgE. Of the 14 workers without work-related symptoms, 1 had a significant cross-shift decline in FEV_1. There was no significant association between the levels of exposure to TDI and symptoms, lung function parameters or immunological findings. This study demonstrates the difficulties in correlating immunological status with clinical and lung function findings in workers exposed to TDI. Recommendations include a stepwise approach to diagnosing TDI-induced asthma in exposed workers.**

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Toluene di-isocyanate (TDI) exposure occurs widely in the manufacture and use of many plastics, foams, paints and resins. Although no figures are available, it is likely that many thousands of South African workers are exposed to TDI. In 1982, Butcher[1] estimated that there were 250 000 workers exposed to this chemical in the USA.

The health effects of TDI are well-documented, with occupational asthma the most common serious health risk. Longitudinal studies have shown that it occurs in between 5 - 25% of workers exposed to TDI.[1,2] A useful review on the health effects of isocyanates appeared in 1985.[3] To our knowledge, however, no work has been published in South Africa identifying affected workers and formulating a protocol for investigating them. It is likely that TDI-induced asthma will soon become a compensable occupational disease in South Africa; this increases the importance of drafting an approach to its investigation.

This article reports the results of a respiratory health survey conducted to: (*i*) describe the TDI exposure, respiratory history, clinical features, lung function test results and immunological status of a group of TDI-exposed workers so that cases of occupational asthma could be identified, and (*ii*) formulate tentative guidelines for the investigation of cases of TDI-induced asthma in South African workplaces.

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Methods

All 20 workers from a TDI processing plant on the East Rand were studied. Occupational history, past medical history and symptom history were obtained by a trained interviewer in a standardised manner. Workers were examined by one of the doctors at the National Centre for Occupational Health Occupational Medicine Clinic. The examinations were conducted during the course of a routine working week. Special attention was given to detecting signs of asthma and other conditions that could be attributed to TDI, such as rhinorrhoea, pharyngitis, or conjunctivitis.[4] Postero-anterior chest radiographs were taken of all subjects. Flow-volume loop lung function tests were performed using a Jaeger Masterlab lung function machine, and normal values used were those of the European Community for Coal and Steel.[5] Subjects were tested before and 15 minutes after administration of two metered doses of salbutamol bronchodilator aerosol. Pre- and post-shift lung function tests were performed at the workplace using a Vitalograph Model-S portable volume-time spirometer. Workers were tested before starting work on the first day of the working week and retested after finishing work on the same day or on developing respiratory symptoms. Lung function testing was performed according to American Thoracic Society recommendations.[6] Skin prick tests were performed using the Bayer-Miles Standard Test Kit for common inhaled allergens (allergens tested for are listed in Table I). A reaction $\geq$ 3 mm diameter was interpreted as positive. Total immunoglobulin E (IgE) was measured using the Pharmacia IgE Radio-Immunoassay ACT kit and TDI-specific IgE was assayed by radio-allergosorbent test using the Pharmacia Phadebas RAST kit, in both cases according to the manufacturer's instructions.

The factory concerned is housed in a single building and consists of production, packing, laboratory and office areas. The packing area leads directly off the production area, and the offices and laboratory have doors which open onto the production area. Air levels of TDI were measured during a period of normal production at 8 different sites in the factory. Three sites were in the production and packing area, 3 in the laboratory, and 2 in the offices. Sampling was performed for a minimum of 30 minutes at each site, using a Sieger Gasalarm model 7000 detector meter.

Data were analysed with the assistance of Epi-Info statistical software. The relationships between exposure and clinical and immunological data were analysed using multivariate linear regression and the Kruskal-Wallis test of variance as described in the software publisher's manual.[7]

Results

TDI levels exceeded the American Conference of Government Industrial Hygienists' threshold limit value (TLV)[9] of 0,005 ppm in all 8 factory areas measured and the ACGIH 10-minute ceiling level[8] of 0,02 ppm in 3 areas on the production floor (range 1,8xTLV - 10xTLV).

Table I shows the duration of TDI exposure, current and cumulative exposure, and the immunological status

TABLE I.
Subjects by TDI exposure and immunological status

Subject	Exposure duration (yrs)	Current exp. level*	CEI† TLV (yrs)	Total IgE (KU/l)	Skin prick test‡	RAST grade§
1	4	Med.	10,8	688	–ve	3
2	3	High	21,6	89	–ve	0
3	6	Med.	15,0	185	–ve	0
4	3	Med.	11,8	12	–ve	0
5	5	Med.	27,3	107	–ve	2
6	6	Med.	17,1	80	–ve	0
7	3	High	21,6	27	+ve	0
8	2	High	14,4	18	–ve	0
9	1	Med.	2,5	146	+ve	0
10	7	Med.	26,0	62	–ve	0
11	5	Med.	11,5	10	–ve	0
12	2	High	14,4	82	–ve	1
13	6	Med.	18,8	99	–ve	0
14	2	Med.	5,0	5	–ve	0
15	13	Med.	31,8	25	–ve	0
16	5	High	36,0	106	–ve	0
17	3	High	21,6	8	–ve	0
18	8	Med.	22,8	810	–ve	0
19	3	Med.	7,5	62	+ve	0
20	5	High	36,0	231	–ve	0

* High = TDI level > 4xTLV (i.e. > 0,02 ppm); Med. = TDI level from 1,8xTLV to 4xTLV (i.e. from 0,009 to 0,02 ppm).
† CEI = cumulative exposure index i.e. yrs worked in area multiplied by level in area as % of TLV; additive for each work area.
‡ +ve indicates reaction of 3 mm or more to one or more of: Bermuda grass, cat hair/dander, *D. pteronyssinus*, dog hair/dander, feather mix, 5 grass mix, tree mix.
§ RAST grading: 0 = no detectable TDI-specific IgE; 1 = TDI-specific IgE up to double reference serum count; 2 = TDI-specific IgE between 2 and 10 times the reference serum count; 3 = TDI-specific IgE between 10 and 50 times the reference serum count. A RAST grade of 2 or more was taken as positive.

TABLE II.
Subjects by respiratory symptoms, cigarette smoking history and lung function test results

Subject	Cigarettes smoked (pack yrs)	FEV_1 (1% pred.)	FEV_1/FVC (%)	FEV_1 increase with β_2 stimulant (%)	Cross shift FEV_1 change (%)
Subjects with work-related symptoms					
1*	12	1,8 (52)	51	+17	–55
2	6	3,4 (84)	73	+17	–11
3†	0	1,8 (84)	81	+9	–10
4	0	4,6 (118)	93	+5	–2
5*	5	3,6 (96)	80	–1	0
6	0	2,1 (81)	73	+13	+5
Subjects with non-work-related symptoms					
7	1	3,4 (89)	83	+6	–11
8	11	4,4 (111)	86	+2	–2
9	1	3,2 (85)	81	+5	0
10	4	4,2 (103)	74	+1	+1
11	3	3,7 (98)	86	–2	+3
Subjects without symptoms					
12	2	5,3 (126)	88	+2	–3
13	6	4,2 (107)	79	0	–2
14	0	3,2 (96)	83	+3	0
15	0	3,8 (122)	89	+2	0
16	4	3,5 (85)	83	–2	+3
17	4	3,9 (93)	80	+4	+3
18	0	3,1 (88)	73	+7	+4
19	11	3,6 (110)	82	+3	+5
20	15	2,8 (73)	69	+13	+11

* Subjects with positive RAST.
† Subject on regular inhaled β_2-stimulant and inhaled beclomethasone.

of the 20 workers. The cumulative exposure index shown is a product of time worked and TDI levels in the area. Two workers had a high level of TDI-specific IgE but there was no association between exposure, total IgE, positive skin prick test, or specific IgE ($P > 0,05$).

Table II lists subjects according to symptoms, cigarette smoking history, and lung function test results. Subjects 1, 2 and 3 had fairly convincing evidence of TDI-induced asthma in terms of the criteria suggested in Fig. 1. Subject 6 showed mild airflow limitation, borderline response to a bronchodilator and complained of work-related symptoms, but did not show an across-shift decline in forced expiratory volume in 1 second (FEV_1). He warranted further testing especially to detect late asthmatic reactions. Subject 7 had an across-shift decline in FEV_1 of 11% and could be considered a possible case (this subject complained of variable shortness of breath unrelated to work, and showed sensitisation on skin prick test to common allergens, which suggested non-specific hyperresponsiveness). There was poor association between high levels of TDI-specific IgE and lung function parameters ($P > 0,05$).

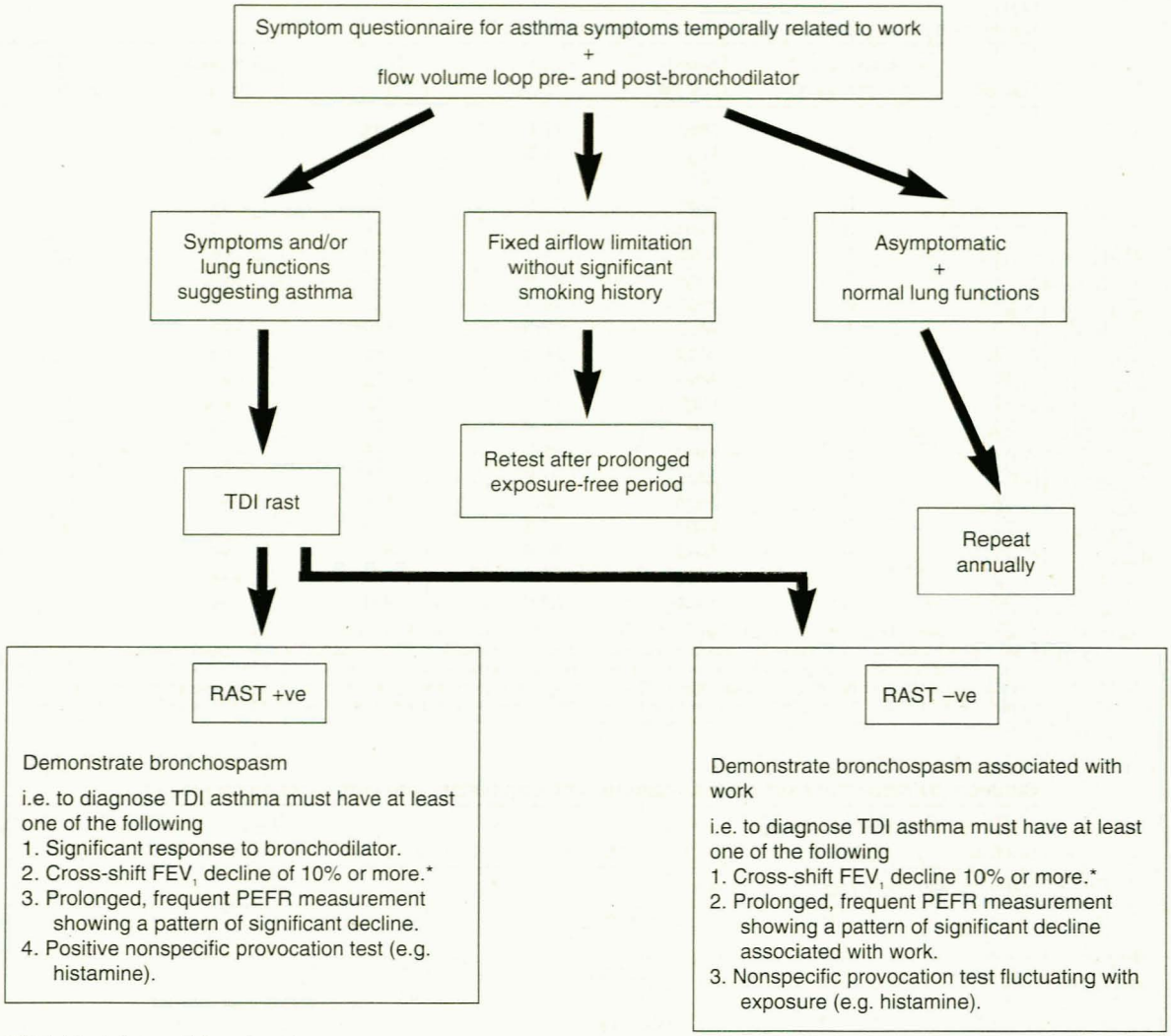

FIG. 1.
A stepwise approach to diagnosing TDI-induced asthma in exposed workers.

Discussion

The poor correlation between the immunological and pulmonary function variables studied demonstrates the difficulties in diagnosing TDI-induced asthma using these routine investigations. This finding is in keeping with the suspected dual causality of isocyanate-induced asthma. Baur[9] divides this asthma into two subgroups: an IgE-mediated subgroup and a non-allergic subgroup. Published studies have found the incidence of specific IgE antibodies to TDI in symptomatic workers who have had positive TDI provocation tests to be between 14% and 27%.[10-13] It is assumed that in the remainder a non-IgE-mediated mechanism is responsible. Possible mechanisms suggested include direct adrenergic antagonism, inhibition of the production of cyclic adenosine monophosphate and a direct irritant effect.[1,11]

The 2 symptomatic workers with significant cross-shift FEV_1 decline but negative RAST results (subjects 2 and 3) may fall into the non-immunological group. Because bronchospasm in TDI-associated asthma can present hours after first exposure (e.g. at night), it is also possible that subject 6 forms part of this non-allergic group. Subject 5 had chronic nasopharyngitis associated with work; this was verified on repeated examination as well as by a positive RAST, but no evidence of it appeared on lung function testing of airflow limitation. A similar case of a patient with TDI-induced allergic rhinitis who subsequently developed asthma has been described by Paggiaro *et al.*[4] Studies of larger workforces exposed to TDI have demonstrated a dose-related effect on airflow, and our failure to show this could be because of the small number of workers studied and the limited exposure data.

As is the case with other studies in this field, our data are difficult to interpret and apply clinically. The increasing awareness of occupational asthma among health professionals, management and workers necessitates that guidelines be formulated for the assessment of workers exposed to it. The implications of making a diagnosis of occupational asthma can be far-reaching, including loss of job and loss of future employability in a given occupation. These need to be weighed against the likelihood of acute severe asthma attacks and the development of nonspecific asthma or fixed airflow limitation if exposure continues.

Fig. 1 illustrates a possible stepwise approach to investigating cases of TDI-associated asthma. The authors have tried to emphasise the use of tests which are relatively accessible in South Africa, and cost-efficient, while retaining relatively stringent diagnostic criteria and thereby avoiding unnecessary job loss due to

overdiagnosis. Although some of the tests listed in Fig. 1 did not form part of this survey, our own experience of them, and that of other researchers, has shown them to be useful, cost-effective tools in diagnosing occupational asthma.[14,15] Some workers with a long symptomatic period may have airflow limitation which appears fixed. This subgroup will need a prolonged exposure-free period and possibly on-going monitoring to confirm the diagnosis. Low-dose TDI provocation testing remains the most specific testing procedure, but necessitates hospital admission and sophisticated isocyanate measuring equipment, and is both hazardous and uncomfortable for the patient. Isocyanate measuring equipment is available at the National Centre for Occupational Health, and TDI provocation tests have been performed,[16] but we agree with Zwi[3] that this should be reserved for exceptional cases only. These might include workers simultaneously exposed to multiple potential causes of occupational asthma including TDI, and cases where TDI asthma must be proven for medicolegal purposes (excluding Workmen's Compensation Act cases). We would hope that this protocol serves as a catalyst for further debate and practical testing.

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