J Microbiol Immunol Infect.
2008;41:337-341

Original Article

Asthma-like syndrome in school children after accidental exposure to xylene and methylene diphenyl diisocyanate

Ren-Long Jan[1,2], Shin-Hong Chen[1,3], Ho-Yuan Chang[4], Hui-Jung Yeh[4,5], Chi-Chang Shieh[1,5], Jiu-Yao Wang[1,5]

[1]Department of Pediatrics, College of Medicine, National Cheng Kung University, Tainan; [2]Department of Pediatrics, Chi Mei Medical Center, Liou Ying Campus, Tainan; [3]Department of Pediatrics, Ma-Do Shin-Lau Hospital, Tainan; and [4]Department of Environmental and Occupational Health and [5]Institute of Basic Medical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Received: October 3, 2007 Revised: December 4, 2007 Accepted: January 26, 2008

Background and Purpose: We assessed the signs and symptoms, pulmonary function changes and residual chemical body burden of school children in the vicinity of an accidental exposure to volatile xylene and methylene diphenyl diisocyanate (MDI).
Methods: After the exposure episode, children with significant symptoms after MDI exposure (e.g., dizziness, nausea, sore throat, and breathing difficulties) were sent to nearby emergency medical units for evaluation and admission if necessary. Clinical work-up included pulmonary function tests and measurement of residual MDI in the body by high-performance liquid chromatography analysis of urine.
Results: 203 students appeared to develop symptoms associated with contaminant exposure, and 173 affected students were sent to nearby emergency units. In the subsequent surveillance, 22 of 203 affected students (10.8%) revealed a positive history of asthma, which was strongly correlated with the incidence of dyspnea arising from the incident. For children with no previous history of asthma, 60.8% (110 of 181) complained of dyspnea during the episode, and 16.2% required inhaled bronchodilator therapy at the emergency medical units for relief of wheezing symptoms. In a simulation, we found the raw material used for tract surfacing, primarily MDI dissolved in xylene, to be present at a concentration (870 ppm w/w) more than 8000-fold the level defined as safe for a working environment.
Conclusions: We have detected a direct cause-effect relationship between the accidental spillage of MDI and the appearance of an acute asthma-like syndrome among previously unexposed school children.

Key words: Adhesives, adverse effects; Air pollutants, occupational; Asthma; Isocyanates; Xylenes

Introduction

Outbreaks of asthma, characterized by short-term increasing emergency admissions for severe asthma in one particular area, have been reported in various parts of the world [1-3]. We report a situation of accidental discharge of methylene diphenyl diisocyanate (MDI) during the construction of an athletic track, leading to the development of acute asthma-like condition among affected children in adjacent schools. Isocyanate homologues, including MDI, are often used as major components of adhesive materials, and have been occasionally reported to cause occupational sensitization of airways and bronchoconstriction-derived asthma in work places [4]. Although some previous studies have investigated the rather detailed immunological and clinical aspects of MDI-induced occupation asthma during chronic exposure [4,5], to the best of our knowledge, the acute and adverse health events associated with the inhalation of MDI among previously unexposed individuals have not yet been reported on.

*Corresponding author: Dr. Jiu-Yao Wang, Division of Allergy and Clinical Immunology, Department of Pediatrics, National Cheng Kung University Medical College, 138 Sheng-Li Road, Tainan 70248, Taiwan.
E- mail: a122@mail.ncku.edu.tw*

Methods

Report of accident

The MDI exposure incident occurred on October 21, 2005, at a time when construction workers were paving a school polyurethane artificial surface athletics track using a mixture of MDI and xylene (functioning as the solvent). Within a short period of time (about 20 min) following a change of wind direction, students in several classrooms of an adjacent junior high school and elementary (primary) school started complaining of dizziness, nausea, sore throat and breathing difficulties. Affected students were sent to nearby emergency medical units. Children with apparent chest discomfort and wheezing were admitted for further observation.

Data collection

On the date of the episode, samples of exhaled air were collected in specialized gas-collecting plastic bags for each of the admitted patients, and subsequently underwent analysis for volatile organic acids by gas chromatography. One day after the episode, an ad hoc team comprised of industrial hygienists and chemical analysts was authorized to investigate the underlying causes of this incident. The geographical location of classrooms in which students were affected by MDI exposure is shown in Fig. 1. In addition, the relationship between classroom incidence and distance from the emission source was calculated. The classroom incidence was defined as the number of affected children divided by the total student number in the class. To investigate the dosage effect of toxic inhalation, a simulation of the track-spraying process was also performed according to the protocol used at that time of the incident.

Three days after the episode, with the aid of pediatricians and respiratory therapists, students retrospectively recorded their characteristics, past medical histories, and symptoms during the episode and after a follow-up period. Complete physical examinations were performed to assess their general condition. Pulmonary function tests were peformed to evaluate the residual adverse effects of the toxic inhalation episode. Pulmonary function testing was performed by trained technicians using simple spirometry, and an abnormal result was defined as forced expiratory volume in 1 second below 80% of the predicted value for age and body height. To assess the residual body

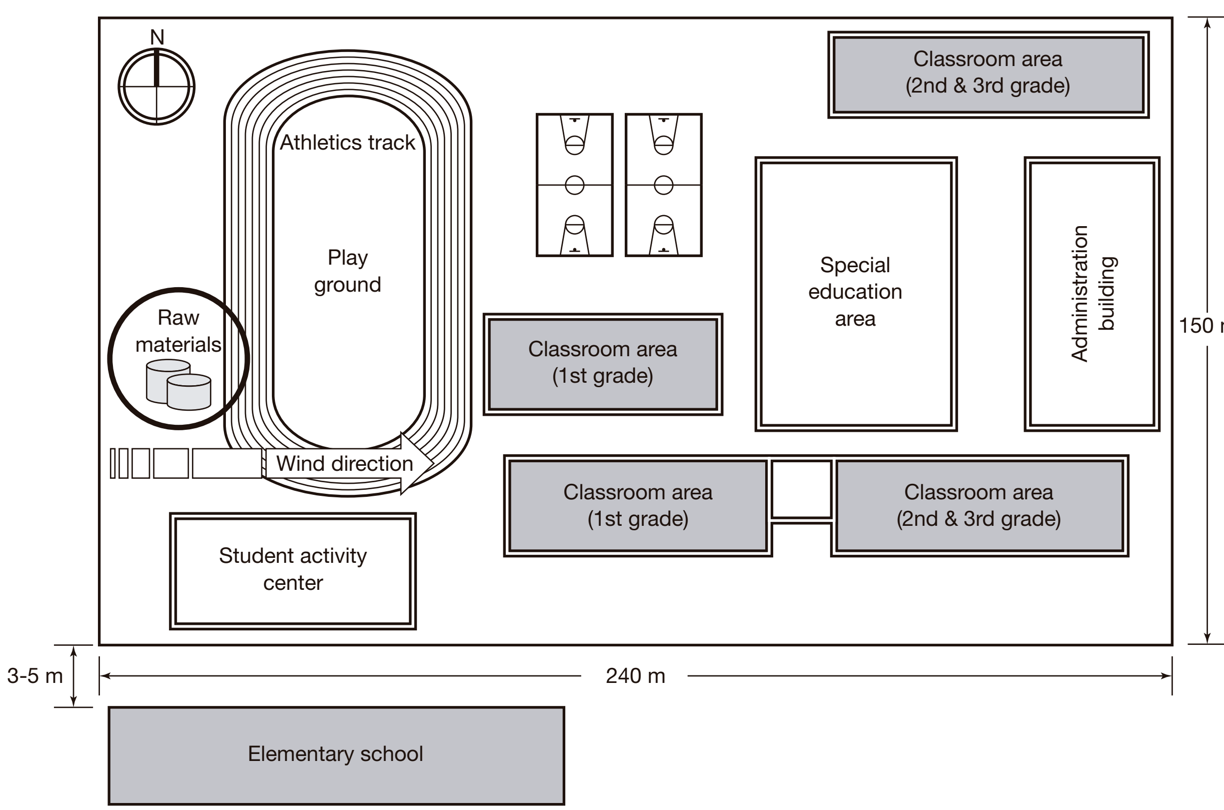

Fig. 1. Geographical distribution of affected classrooms (shaded) and location of the suspected methylene diphenyl diisocyanate emission source (circle).

burden of MDI, sequential spot urine specimens were collected initially after exposure and two weeks later, and analyzed using high-performance liquid chromatography, for the detection of 4,4'-methylenediphenyl diamine, a metabolite of MDI.

Statistical analysis

The correlation of classroom incidence and the distance from classroom to emission source was calculated. Correlations involving asthma history, symptoms, and pulmonary function test were analyzed by Fisher's exact or Pearson chi-squared tests. Risk estimates with 95% confidence interval (CI) were also determined. All statistical hypothesis tests were two tailed and a p value <0.05 was considered to be significant.

Results

There were 2700 students in the vicinity of the accident. 203 students (182 from the junior high school and 21 from the elementary school) appeared to have suffered from some sort of contaminant exposure (Table 1), and 173 affected students were sent to nearby emergency medical units. The most common complaint was headache (70.9%), followed in order by persistent cough (67.5%), dyspnea (63.5%) and nausea (62.6%). In emergency medical units, most of the affected individuals (89.0%, 154 of 173) were treated with oxygen inhalation. Chest X-rays were taken for 48 students (23.6%) who had complained of chest discomfort; however, none of the corresponding radiographs demonstrated any significant abnormal findings. Additional bronchodilator inhalation was given to 32 students (15.8%) who had complained of difficult breathing and wheezing. Thirty three students (16.3%) were admitted to a hospital for further observation (Table 1). Spot urine and exhaled breathing air data from the hospitalized children revealed no evidence of previous exposure to MDI, or the retention of any metabolites of isocyanates. These lines of evidence were consistent with this exposure being a brief phenomenon. All admitted students were discharged the next day without any evidence of remaining symptoms of major discomfort.

In a simulation of the track spraying process, it was found that the raw surfacing materials were sprayed at an approximate speed of 800 m/h and the average consumption rate for the raw material was 84 mL/h. The raw material used for track surfacing was found to be primarily MDI dissolved in xylene at a concentration of 870 ppm w/w, by use of the reference Occupational Safety and Health Administration analytical method 42 [6], more than 8000-fold the recommended safe minimum inhalation concentration for a working environment [7]. The direct cause-effect relationship for MDI exposure and health effects on the students was confirmed by an inverse linear relationship between the incidence of students in various school classrooms and the distance from the site of MDI spillage ($r = -0.48$, $p<0.05$) [Fig. 2].

All affected students (n = 203) received respiratory health surveillance three days after the incident. Residual symptoms that might have been related to this incident included cough (30.0%), headache (19.7%), dyspnea (15.3%), sore throat (10.3%) and nausea (3.9%) [Table 2]. Twenty two of 203 affected

Table 1. Characteristics of the study population (n = 203)

Variable	Number of patients (%)
Male gender	86 (42.4)
Age (years; mean ± SD)	12.3 ± 1.21
Patient with positive asthma history	22 (10.8)
Chief symptoms during episode	
Eye irritation	32 (15.8)
Sore throat	89 (43.8)
Nausea	127 (62.6)
Vomiting	23 (11.3)
Headache	144 (70.9)
Cough	137 (67.5)
Dyspnea	129 (63.5)
Complaints ≥4 items	93 (45.8)
Visited emergency department	173 (85.2)
Hospitalized	33 (16.3)

Abbreviation: SD = standard deviation

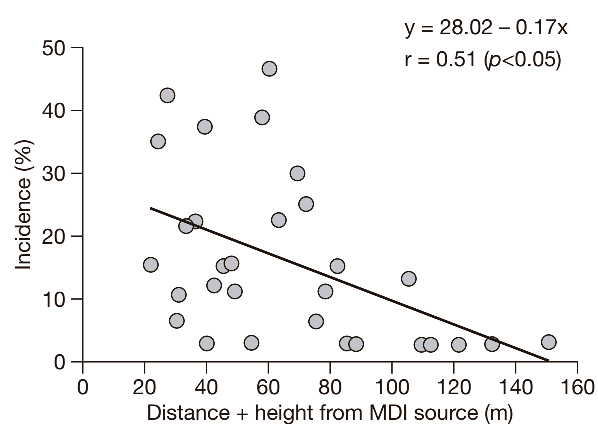

Fig. 2. Linear relationship between the incidence of affected students in various school classrooms and distance/height combinations from the suspected methylene diphenyl diisocyanate (MDI) emission source.

Table 2. Follow-up physical examination of the affected students (n = 203)

Variable	Number of patients (%)
Residual symptoms	
Eye irritation	4 (2.0)
Sore throat	21 (10.3)
Nausea	8 (3.9)
Vomiting	0 (0.0)
Headache	40 (19.7)
Cough	61 (30.0)
Dyspnea	31 (15.3)
Complaints ≥4 items	5 (2.5)
Rhonchi with or without wheezing	32 (15.8)
Lung function test, abnormal	21 (10.3)

students (10.8%) revealed a positive history of asthma, which was strongly correlated with the incidence of dyspnea arising from the incident (odds ratio, 4.09; 95% CI, 1.17-14.32; $p<0.05$) [Table 3] and with an abnormal pulmonary function test result (odds ratio, 3.84; 95% CI, 1.09-13.5; $p<0.05$) [Table 4]. However, no other symptom during the episode was correlated with positive asthma history or abnormal pulmonary function test, and none of the residual symptoms was related to both of them. For children without a history of asthma, 60.8% (110 of 181) also complained of dyspnea during the episode, and 16.2% (23 of 142) required inhaled bronchodilator therapy in the emergency medical units to relieve their wheezing symptoms. Eighteen of these 181 individuals (9.9%) had an abnormal pulmonary function test result at the subsequent health check-up.

Table 3. Association between asthma history and symptoms during and after the episode

Variable	Odds ratio (95% CI)
Chief complaints during episode	
Eye irritation	1.21 (0.38-3.86)
Sore throat	0.87 (0.36-2.15)
Nausea	1.05 (0.42-2.64)
Vomiting	0.76 (0.17-3.49)
Headache	0.69 (0.27-1.74)
Cough	2.35 (0.76-7.23)
Dyspnea	4.09 (1.17-14.32)[a]
Residual symptoms	
Eye irritation	2.82 (0.28-28.4)
Sore throat	2.14 (0.65-7.07)
Nausea	1.18 (0.14-10.1)
Vomiting	-
Headache	1.15 (0.40-3.31)
Cough	0.86 (0.32-2.31)
Dyspnea	0.86 (0.24-3.11)

Abbreviation: CI = confidence interval
[a]$p<0.05$.

Table 4. Association between abnormal pulmonary function test and symptom characteristics during and after the episode

Variable	Odds ratio (95% CI)
Chief complaints during episode	
Eye irritation	0.24 (0.03-1.88)
Sore throat	0.61 (0.24-1.58)
Nausea	0.97 (0.38-2.46)
Vomiting	0.81 (0.18-3.71)
Headache	1.84 (0.59-5.72)
Cough	2.20 (0.71-6.81)
Dyspnea	3.84 (1.09-13.5)[a]
Residual symptoms	
Eye irritation	0.98 (0.96-1.0)
Sore throat	0.90 (0.2-4.18)
Nausea	0.96 (0.93-0.99)
Vomiting	-
Headache	1.62 (0.59-4.47)
Cough	0.92 (0.34-2.51)
Dyspnea	0.56 (0.12-2.51)

Abbreviation: CI = confidence interval
[a]$p<0.05$.

Discussion

Chronic exposure to diisocyanate homologues, such as MDI, toluene diisocyanate and hexamethylene diisocyanate has a known propensity to cause occupational asthma (OA) in the polyurethane industry [4,5]. Two different types of OA are distinguishable: immunological (OA with sensitization) and non-immunological, i.e., irritant-induced asthma or so-called reactive airways dysfunction syndrome, which typically occurs after a single exposure to high levels of certain irritants [8]. Immunological OA appears to be the common finding in diisocyanate exposure. Only a few cases of reactive airways dysfunction syndrome related to acute, high level exposure to MDI have been reported [8,9]. We have detected a direct cause-effect relationship between the accidental spillage of MDI and the appearance of an acute asthma-like syndrome, i.e., reactive airways dysfunction syndrome. Inhaled bronchodilators were needed to relieve symptoms of the condition among previously unexposed school children, regardless of their previous asthma history. Importantly, the irritant effect of MDI was dose (proximity of the source)-dependent. This has been documented in only one previous study [10].

Boulet [8] and Leroyer et al [9] suggested that there were risks for the appearance of immunological

OA one year after MDI exposure. Thus, the affected children in this study might have become sensitized to MDI and at increased risk for asthma in the future, given that the application of polyurethane products is diverse and ubiquitous in modern society [5]. We previously showed that polyurethane athletic tracks continue to release certain isocyanates and volatile solvents during the paving process and beyond. Adjacent to such tracks, air levels of MDI were easily detectable even after the first week of tract installation [11], a situation which may pose a potential health hazard for asthma exacerbation among these affected school children. Therefore, we have established a post-event monitoring team to follow up these affected school children on a yearly basis for the incidence of asthma and its possible exacerbation that may relate to this accident.

References

1. Ussetti P, Roca J, Agusti AG, Montserrat JM, Rodriguez-Roisin R, Agusti-Vidal A. Asthma outbreaks in Barcelona. Lancet. 1983;2:280-1.
2. Cullinan P, Harris JM, Newman Taylor AJ, Hole AM, Jones M, Barnes F, et al. An outbreak of asthma in a modern detergent factory. Lancet. 2000;356:1899-990.
3. Ivey MA, Simeon DT, Monteil MA. Climatic variables are associated with seasonal acute asthma admissions to accident and emergency room facilities in Trinidad, West Indies. Clin Exp Allergy. 2003;33:1526-30.
4. Wisnewski AV, Redlich CA. Recent developments in diisocyanate asthma. Curr Opin Allergy Clin Immunol. 2001; 1:169-75.
5. Krone CA, Klingner TD. Isocyanates, polyurethane and childhood asthma. Pediatr Allergy Immunol. 2005;16: 368-79.
6. Occupational Safety and Health Administration. Diisocyanates: method 42. Salt Lake City, UT: US Department of Labor; 1989. Available from: http://www.osha.gov/dts/sltc/methods/organic/org042/org042.html
7. National Institute for Occupational Safety and Health (NIOSH). Criteria for a recommended standard: occupational exposure to diisocyanates. DHEW (NIOSH) publication no. 78-215. Cincinnati: Department of Health, Education, and Welfare; 1978.
8. Boulet LP. Increases in airway responsiveness following acute exposure to respiratory irritants. Reactive airway dysfunction syndrome or occupational asthma? Chest. 1988;94:476-81.
9. Leroyer C, Perfetti L, Cartier A, Malo JL. Can reactive airways dysfunction syndrome (RADS) transform into occupational asthma due to "sensitisation" to isocyanates? Thorax. 1998;53:152-3.
10. Kern DG. Outbreak of the reactive airways dysfunction syndrome after a spill of glacial acetic acid. Am Rev Respir Dis. 1991;144:1058-64.
11. Chang FH, Lin TC, Huang CI, Chao HR, Chang TY, Lu CS. Emission characteristics of VOCs from athletic tracks. J Hazard Mater. 1999;70:1-20.

