Bull. Environ. Contam. Toxicol. (1995) 55:320–324

Environmental Contamination and Toxicology

Respiratory Effects and Skin Allergy in Workers Exposed to Tetrachloroisophthalonitrile

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Received: 30 July 1994/Accepted: 3 January 1995

Tetrachloroisophthalonitrile (TCPN) is an agricultural and horticultural fungicide used in many parts of the world. It has been widely reported as inducing allergic contact dermatitis (Bach and Pedersen, 1980; Bruynzeel and van Ketel, 1986; Liden, 1990). It has also been classified as a strong skin allergen with the guinea pig maximization test. (Matsushita and Aoyama, 1981). However, little information has been documented on its possible effects on the bronchopulmonary system.

This study was conducted to assess the prevalence of respiratory symptoms and the status of spirometric lung function among employees engaged in TCPN manufacturing. In addition, skin symptoms were also examined.

METHODS AND MATERIALS

Twenty eight workers (nineteen men and nine women) in the TCPN manufacturing workshop of a pesticide plant were investigated. The participation of the work force in this study was 93.3% (28/30), and two workers were absent at the time of the study owing to vacation. Workers were exposed to TCPN for about 8 hr/d, six days per week in a 500 m^2 room. Mean duration of TCPN exposure was 3.8 yr. Additional eighteen reference (REF) workers (twenty men and six women), who were working as office workers or repair workers in the same plant, but had no history of TCPN exposure, were also surveyed. Personal details of the workers are shown in Table 1. There were no significant differences in age, height, weight, and smoking habits between the TCPN workers and the REF workers.

Air sampling in the TCPN workshop was taken with a FC-A-3 dust sampler (Hongwei Inc, China) fitted with cellulose ester membrane filter with a diameter of 37 mm and a pore size of 8.0 um, and placed at a height of 1.5 m in five selected positions of the room. Samples were drawn at a rate of 20 L/min. Samplings were made four times; 1, 3, 5 and 7 hr after the beginning

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of the workshift one day before the lung function tests, and 20 samples were collected. The mean concentration of TCPN during the eight hour shift, determined through chromatographic method (Chen et al, 1986), was 0.72 mg/m^3 (0.34-1.21 mg/m^3). This value was similar to the two values obtained three and six months before this survey.

Interviews were administered by an experienced occupational physician who was blind to the exposure status of the workers. The presence of signs and symptoms suggestive of respiratory diseases was recorded with a Japanese version of the British Medical Research Council questionnaire with additional questions on occupational asthma. All interviewees were also asked about any skin reactions (such as skin rash and itching). Diagnoses were established by the physician at the interviews based on the questionnaire results. Among them, chronic cough and/or phlegm were defined as cough and/or phlegm production on most days for at least 3 months in a year; chronic bronchitis was defined as cough and phlegm for a minimum of 3 months a year and for not less than 2 successive years.

Table 1. Comparison of demographic variables in TCPN workers and REF workers

Demographic variables	TCPN workers (n=28)	REF workers (n=18)
Age (yr; M±SD)	25.6±5.9	24.8±3.3
Height (cm; M±SD)	160.7±5.5	159.9±6.3
Weight (kg; M±SD)	55.0±4.8	53.8±4.1
TCPN exposure (yr; M±SD)	3.8±2.1	0
Smoking habits (%)		
Non-smoker	78.6	77.8
Ex-smoker	0	5.6
Current smoker	21.4	22.2

The forced expiratory flow-volume test was performed using an electronic spirometer (Minato Medical Device Co., AS-4, 500). The best of three acceptable curves was used in deriving the forced expiratory vital capacity (FVC), the forced expired volume in 1 sec (FEV_1), the FEV_1/FVC multiplied by 100 (%FEV_1), the maximum mid-expiratory flow (MMF) and the peak expiratory flow (PEF). Smokers were asked to refrain from smoking for at least one hour before measurement. The flow-volume study was conducted by an examiner who was blind to whether or not the examinees were TCPN workers.

All the TCPN workers and the REF workers were patch tested with 0.05% TCPN diluted in petrolatum. Patch testing was carried out according to the internationally accepted method (Fregert 1981). Finn Chamber (Epitest, Finland) on Scanpor tape (Norgesplaster, Kristiansand, Norway) was used. Readings were carried out at 48 hr, 30 min after removal of the patches.

Simultaneously, 5% formaldehyde, 0.1% toluene diisocyanate and 0.01% potassium dichromate were used as controls.

RESULTS AND DISCUSSION

Table 2 presents the prevalence of clinical symptoms in the TCPN workers and the REF workers. The TCPN workers experienced higher prevalences of respiratory symptoms than did the REF workers, being significantly different for nose and throat irritation ($p<0.01$), chronic cough and phlegm ($p<0.05$), chest tightness ($p<0.01$), and shortness of breath and wheezing at work ($p<0.05$). Six TCPN workers (21.4 %), who complained of asthma-like symptoms such as wheezing and shortness of breath at work, had a duration of employment in TCPN workshop varying from 1 to 7 yr, being not significantly longer than the other TCPN workers without the symptoms. Skin symptoms were not found in the TCPN workers at the time of examination, however, three TCPN workers complained that they had skin rashes and itching on the neck, hands and legs in the summer which recurred every year; these symptoms did not appear if they were away from the workplace in summer.

Table 2. Prevalence of clinical symptoms in TCPN workers and REF workers

Symptoms	TCPN workers (n=28)		REF workers (n=18)	
	No	%	No	%
Eye irritation	12	42.9**	0	0
Nose irritation	13	46.4**	1	5.6
Throat irritation	13	46.4**	2	11.2
Chronic cough	8	28.6*	1	5.6
Chronic phlegm	8	28.6*	1	5.6
Chronic bronchitis	3	10.7	1	5.6
Chest tightness	9	32.1**	0	0
Shortness of breath at work	6	21.4*	0	0
Wheezing at work	6	21.4*	0	0
Skin reactions	0	0	0	0

*$p<0.05$, **$p<0.01$, compared with the REF workers (Fisher's exact test)

Table 3 presents the values of lung functions. There was no significant difference between the TCPN workers and the REF workers with regard to FVC, PEF and MMF. However, the TCPN workers demonstrated significant reductions in FEV_1 and $\%FEV_1$ in comparison with the REF workers ($p<0.05$ for FEV_1, $p<0.01$ for $\%FEV_1$, Student's test). Moreover, the complaint of asthma-like symptoms was in accordance with the decrease in FEV_1 and $\%FEV_1$, as the six TCPN workers possessing these symptoms displayed a much greater decline in FEV_1 and $\%FEV_1$ than those of the other TCPN workers without the symptoms.

Table 3. Lung functions of TCPN workers and REF workers (M±SD)

	TCPN workers (n=28)	REF workers (n=18)
FVC (L)	3.39±0.57	3.56±0.71
FEV_1 (L/sec)	2.29±0.95*	2.94±0.66
% FEV_1 (%)	72.8±11.8**	83.7 ±8.7
PEF (L/sec)	4.08±1.42	4.38±0.84
MMF (L/sec)	2.92±0.67	3.25±1.01

*p<0.05, **p<0.01, compared with REF workers (Student's t test)

The results of patch testings are shown in Table 4. Two TCPN workers were positive to 0.05% TCPN. They complained of skin symptoms such as rashes and itching on the neck, hands and legs in the summer which recurred every year. One REF worker showed positive reaction to 5% formaldehyde, but had no any skin symptoms or past history of contact dermatitis.

Table 4. Patch test results

Substances	Conc.* (%)	Positive reaction	
		TCPN workers (n=28)	REF workers (n=18)
TCPN	0.05	2	0
Formaldehyde	5	0	1
Toluene diisocyanate	0.1	0	0
Potassium dichromate	0.05	0	0

*All substances were diluted in petrolatum

Our study found that the TCPN workers had more respiratory symptoms, including irritation symptoms, chronic cough and phlegm, chest tightness, and asthma-like symptoms such as shortness of breath and wheezing at work as compared to the REF workers. Also, the lung function tests revealed a significant decrement of FEV_1 and %FEV_1 in them, particularly in the six TCPN workers with asthma-like symptoms at work, suggesting a typical obstructive ventilatory disturbance. Based on these findings, we supposed that TCPN exposure-related asthmatic hazards might have occurred among the TCPN workers. The executive board of the plant denied permission for us to perform a TCPN inhalation challenge test on the workers.

It is not clear whether immunological reactions are present in this disorder. Skin test and hapten specific antibody have been proposed to be sensitive indexes for the diagnosis of immunologically mediated occupational asthma (Grammer et al., 1989; Baur, 1990; Cockcroft, 1990), However, because we could not find a solvent of TCPN, we could not prepare the TCPN-protein conjugates required for both the skin test and the evaluation of TCPN specific antibody by RAST or ELISA.

Skin allergy was verified in two TCPN workers. They had positive reactions to TCPN patch testing and TCPN-related skin symptoms in the summer. The results were consistent with many reports cited above (Bach and Pedersen, 1980; Bruynzeel and van Ketel, 1986; Liden, 1990).

In conclusion, this study suggested that the workers in the TCPN manufacturing workshop suffered from an excess of respiratory symptoms including irritation, chronic cough and phlegm, chest tightness, and asthma-like symptoms and abnormal lung function. Moreover, two cases of skin allergy were observed. The average TCPN concentration in the environment was 0.72 mg/m^3, which possessed apparent irritant effects to the respiratory route as experienced by the workers and our examiners; however, it can not be regarded as high or low as no exposure standard of TCPN in air has been documented. We hope that our data will be useful for the establishment of an occupational exposure limit to TCPN in the future.

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