

Allergic patch test reactions caused by the rubber chemical cyclohexyl thiophthalimide

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Rubber chemicals are among the most common occupational contact sensitizers. The most common rubber sensitizers are thiurams, thiazoles, carbamates and paraphenylenediamine derivatives. Here we present data on a less-well-known rubber chemical, N-(cyclohexylthio)phthalimide (CTP; CAS 17796-82-6). This chemical is currently the most widely used vulcanization retarder, but data on allergic contact dermatitis caused by CTP are lacking. We conducted a survey of 310 patients who had been patch tested with 30 rubber chemicals including CTP. 11 (3.5%) showed an allergic patch test reaction provoked by CTP, and 9.0% by thiurams. 4 of the patients reacted only to CTP and not to other rubber chemicals, whereas the other 7 concomitantly reacted to other rubber chemicals. After analyzing the patch test data of these 11 patients, it was concluded that CTP probably did not cross-react with the other rubber chemicals. Therefore the patch test results may indicate independent sensitization to CTP and other rubber chemicals. Because very little data on the components of rubber chemicals in rubber products are available, the source of the putative sensitization to the rubber vulcanization retarder CTP is unknown.

Key words: N-(cyclohexylthio)phthalimide (CAS 17796-82-6); cyclohexyl thiophthalimide; phthalimides; rubber chemicals; occupational; allergic contact dermatitis; patch testing; thiurams.

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Rubber chemicals are among the most common occupational sensitizers (1-6), and protective gloves are the most common cause of occupational rubber allergy in our patients (7, 8). To diagnose allergic contact dermatitis caused by rubber chemicals, specific rubber chemical series have been developed. The rubber chemical series currently used in our Department contains 30 chemicals (Table 1). The most common causes of rubber allergy are the accelerators, such as thiurams, thiazoles, thio-carbamates, and the antioxidants, e.g., paraphenylenediamine derivatives (1, 2, 5, 7-9). Thioureas are less frequent causes of rubber chemical allergy (10, 11), and then there are less-well-known chemicals in the rubber series, such as N-(cyclohexylthio)-phthalimide (CTP, CAS 17796-82-6, Fig. 1) (9, 12). N-(cyclohexylthio)phthalimide is included in the rubber series of Trolab, Hermal Kurt Herrmann, Reinbeck/Hamburg, Germany, and is manufactured from Monsanto's Santogard® PVI; other trade names of CTP are Vulkalent® (Bayer) and Rhenogran® (Rhein-Chemie). In the present report, we have analyzed data on allergic patch test reactions caused by CTP.

Materials and Methods

The patient material comprised all patients who were patch tested with the rubber chemical series at the Finnish Institute of Occupational Health from January 1991 to February 1995. All the patients were also patch tested with a modified European standard series, and many of the patients also with other anamnesticly relevant series (data not given). Patch testing was performed on the back and scored according to standardized methods as previously described (4), with 2 days' occlusion, the 1st reading on day 2, and 2 further readings 1-4 days later. Altogether, 310 patients were patch tested with the rubber series during the observation period.

CTP patch testing (1% pet; suggested by the ICDRG (13)) was carried out with the commercial patch test substance purchased from Trolab, Hermal Kurt Herrmann, Reinbeck/Hamburg, Germany, manufactured from Monsanto's Santogard® PVI (9, 10) (Table 1). Other rubber chemicals were from Chemotechnique Diagnostics AB, Malmö, Sweden, and Epikon Oy, Helsinki, Fin-

Table 1. Patch test results (with the currently used rubber chemicals patch test series at the Finnish Institute of Occupational Health) of 11 patients with allergic patch test reaction to cyclohexyl thiophthalimide

	%	1	2	3	4	5	6	7	8	9	10	11
Chemotechnique												
tetramethylthiuram disulfide	1.0			+		+++						++
tetramethylthiuram monosulfide	1.0			++		+++						+++
tetraethylthiuram disulfide	1.0											+++
dipentamethylenethiuram disulfide	1.0											+++
N-cyclohexyl-N-phenyl-4-phenylenediamine	1.0											
N,N-diphenyl-4-phenylenediamine	1.0											
N-isopropyl-N-phenyl-4-phenylenediamine	0.1											
N-cyclohexylbenzothiazyl sulphenamide	1.0					+++						
dibenzothiazyl disulfide	1.0					+++						
morpholinylmercapto benzothiazole	1.0					+++						
diphenylguanidine	1.0											
zinc diethyldithiocarbamate	1.0											++
zinc dibutyldithiocarbamate	1.0											
N,N-di-beta-naphtyl-4-phenylenediamine	1.0											
N-phenyl-2-naphtylamine	1.0											
hexamethylenetetramine	2.0		+									
diaminodiphenylmethane	0.5				+++			++				
diphenylthiourea	1.0								++			
zinc dimethyldithiocarbamate	1.0					+++						++
2,2,4-trimethyl-1,2-dihydroquinoline	1.0											
diethylthiourea	1.0											
dibutylthiourea	1.0											
dodecylmercaptan	0.1											
thiourea	0.1											
*Trolab												
monobenzone (hydroquinone monobenzyloether)	1.0											
ethylenethiourea	1.0											
dithiodimorpholine	1.0											
piperazine	1.0											
cyclohexyl thiophthalimide	1.0	+	+	++	++	+	++	+	+	+	++	+++
*Epikon												
4,4-dihydroxydiphenyl (DOD)	0.2											

All test substances in petrolatum; empty area=negative. *. Source of patch test substance.

land, and Trolab, Hermal Kurt Herrmann, Reinbeck/Hamburg, Germany (Table 1).

The patch test result was considered allergic (positive) when it elicited at least erythema with infiltration (+). Reactions inducing erythema without infiltration (++) were not interpreted as allergic.

Results

11 (3.5%) out of the 310 patients had an allergic patch test reaction caused by CTP (Fig. 2). Furthermore, 30 reactions were considered doubtful or irritant. For comparison, thiurams gave an allergic patch test reaction in 28 of these 310 patients (9.0%). The patch test results with the rubber chemical series are given in Table 1. None of the other 29 chemicals were positive in all patients with an allergic patch test reaction caused by CTP (Table 1). 4 of the patients reacted only to CTP and not to other rubber chemicals, whereas the other 7 concomitantly reacted to other rubber

chemicals. Table 2 shows that the most common known rubber exposure of the patients was protective gloves used at work. Patient no. 3 also had a history of condom allergy, and his own condoms, as well as several rubber chemicals, elicited an allergic patch test reaction (Table 1). Data on the other causes of the patients' rubber chemical allergy have not been included in the present results.

Discussion

CTP is the active ingredient in Monsanto's Santogard® PVI (14, 15). According to information kindly given by Hermal, the purity of the raw material has been determined as 94–96%. Accordingly, it is possible to state only that the patch test preparation of CTP induced allergic reactions, and not necessarily CTP. This same problem, i.e., impurities are present in most patch test substances, relates to most currently published research reports on allergic contact dermatitis. Though aware of the above problem, the allergic patch test reac-

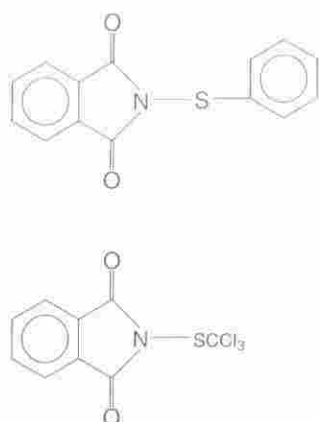


Fig. 1. Chemical structures of 2 phthalimides used for patch testing: the rubber chemical cyclohexylthiophthalimide (CTP, top), and the fungicide captan (N-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide, bottom).

tions caused by CTP are called CTP allergy in the present report.

During rubber processing, it is necessary to prevent premature vulcanization. This is achieved by the addition of vulcanization retarders, of which the predominant one currently is CTP (9, 12). It delays the onset of accelerated sulfur vulcanization (14) and is especially used in the processing of solid rubber products to prevent the rapid onset of curing. It is probably not used in the compounding of natural rubber latex gloves, although it may be present in gloves made of minced dry rubber latex (according to information kindly provided by SmartPractice, Arizona, USA). We came across one material safety data sheet (MSDS) that declared CTP, namely a rubber sheet used in the repairing of tyres. According to the MSDS, the rubber sheet contained CTP and N-tert.-butyl-2-



Fig. 2. Allergic patch test reaction of patient 11 caused by cyclohexylthiophthalimide (CHTPI) and zinc dimethyldithiocarbamate (ZnDMTC). The 3-day reading.

Table 2. Known exposure to rubber chemicals of 11 patients with allergic patch test reactions caused by cyclohexyl thiophthalimide

Patient no.	Occupation	Rubber exposure
1	assistant nurse	protective gloves
2	sales woman (furniture)	protective gloves
3	bricklayer	protective gloves condoms
4	glassblower	glassblower's pipe
5	dentist	protective gloves Nobecutan® rubber boots polishing discs
6	home helper	protective gloves
7	electrician	protective gloves
8	cleaner	protective gloves
9	cleaner	protective gloves
10	nurse	protective gloves
11	cleaner	protective gloves

benzothiazol sulfenamide, together less than 0.5%. CTP is produced by oxidative coupling of phthalimide and cyclohexyl mercaptan (15). One mercaptan, namely dodecylmercaptan, is included in our rubber chemical series (substance 23, Table 1) but was negative on patch testing in all our 11 patients.

In a literature survey, we did not find any reports of sensitization to CTP. Most cases of contact sensitization to thiophthalimides have been reported from fungicides (16–18). In fact, according to Italian experience, thiophthalimides, such as captan (Fig. 1), are the most common cause of pesticide allergy (16–18). According to Lisi et al. (16), thiophthalimides may cross-react with dithiocarbamates, but in our material, only 2 patients (nos. 5 and 11) also had allergic patch test reactions to dithiocarbamates, namely patient no. 5 to zinc dimethyldithiocarbamate, and patient no. 11 to both dimethyldithiocarbamate and zinc diethyldithiocarbamate (Table 1, Fig. 2).

CTP was positive in 3.5% of the patients patch tested with the rubber series. This is much more than the positive reactions caused by another group of rubber chemicals, the thiourea compounds (1.2%) in our material (11). CTP may

therefore be a significant sensitizer but, for the time being, the relevance of the reactions is not known. We were not able to determine any chemical in the rubber series that would probably cross-react with CTP. All the patients were allergic to other non-rubber chemicals too (data not given), but we did not observe any consistency in these reactions, i.e., we could not detect other cross-reacting chemicals. It seems therefore possible that the patients had sensitization to CTP from rubber products. The life-time exposure of people to rubber is so extensive that, at the moment, it is difficult to trace the origin of possible rubber sensitivity caused by CTP. The patients did not have any conspicuous occupational rubber chemical exposure, as shown in Table 2. It would be of great help in the future if rubber products were to be labelled with the chemicals they include.

In 30 patients, CTP induced a doubtful or irritant patch test reaction. The currently used patch test concentration (1% pet.) may therefore be too high, and one needs to be careful when evaluating whether the patch test reaction caused by CTP is irritant or allergic. The patch test concentration of CTP probably needs to be changed, but currently it is not known whether it should be increased or decreased; doubtful reactions may also be allergic. A dilution series might help to give more information about the nature of the patch test reactions caused by CTP. Hermal has kindly promised to send us CTP, and a study using a dilution series of CTP will then be undertaken.

References

- Romaguera C, Grimalt F. Statistical and comparative study of 4600 patients tested in Barcelona (1973-1977). *Contact Dermatitis* 1980; 6: 309-315.
- Themido R, Menezes Brandao F. Contact allergy to thiurams. *Contact Dermatitis* 1984; 10: 251.
- Kanerva L, Estlander T, Jolanki R. Occupational skin disease in Finland. An analysis of 10 years of statistics from an occupational dermatology clinic. *Int Arch Occup Environ Health* 1988; 60: 89-94.
- Heese A, Peters K-P, Koch H U, Hornstein O P. Allergologic evaluation and data on 173 glove-allergic patients. In: Mellström G, Wahlberg J E, Maibach H I (eds): *Protective gloves for occupational use*. Press Inc, Boca Raton, FL: CRC 1994: 185-205.
- Kanerva L, Jolanki R, Toikkanen J. Frequencies of occupational allergic diseases and gender differences in Finland. *Int Arch Occup Environ Health* 1994; 66: 111-116.
- Estlander T. Occupational skin disease in Finland. Observations made during 1974-1988 at the Institute of Occupational Health, Helsinki. *Acta Dermato-venereologica* 1990; suppl 155: 1-85.
- Estlander T, Jolanki R, Kanerva L. Dermatitis and contact urticaria from rubber and plastic gloves. *Contact Dermatitis* 1984; 14: 20-25.
- Estlander T, Jolanki R, Kanerva L. Allergic contact dermatitis from rubber and plastic gloves. In: Mellström G, Wahlberg J E, Maibach H I (eds): *Protective gloves for occupational use*. Boca Raton, FL: CRC, 1994: 221-239.
- Brandao F M. Rubber. In: Adams R M (ed): *Occupational skin disease*. Philadelphia: W.B. Saunders Co, Harcourt Brace Jovanovich, Inc., 1990: 469.
- Camarasa J G, Romaguera C, Condé-Salazar L, Pascal A M, Moran M, Alomar A, Grimalt F. Thiourea reactivity in Spain. *Contact Dermatitis* 1985; 12: 290.
- Kanerva L, Estlander T, Jolanki R. Occupational allergic contact dermatitis caused by thiourea compounds. *Contact Dermatitis* 1994; 31: 242-248.
- Greek B F. Rubber processing chemicals. *Chem Eng News*: 18 May 1987: 27-49.
- De Groot A C. Patch testing. *The concentrations and vehicles for 3700 chemicals*. Amsterdam: Elsevier, 1994: 85.
- Ash M, Ash I. *Concise encyclopedia of industrial chemical additives*. London: Edward Arnold, 1991: 517.
- Ashford R D (compiles). *Ashford's dictionary of industrial chemicals: properties, production, uses*. London: Wavelength publications, 1994: 1005 pp.
- Lisi P, Caraffini S, Asalve D. Irritation and sensitization potential of pesticides. *Contact Dermatitis* 1987; 17: 212-218.
- Lisi P, Caraffini S, Asalve D. A test series for pesticide dermatitis. *Contact Dermatitis* 1986; 15: 266-269.
- Lisi P. Pesticides in occupational contact dermatitis. *Clin Derm* 1992; 10: 175-184.

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