

Sensitization to thiourea derivatives among Finnish patients with suspected contact dermatitis

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Background: Thiourea derivatives in rubber products may induce contact sensitization and allergic contact dermatitis. Sensitization is most often from neoprene rubber, but the multitude of possible sensitizing products has remained poorly characterized.

Objective: The aim of this study was to collect information on the occurrence of thiourea-related contact allergy and to show novel sources of sensitization.

Patients and methods: A mixture of dibutyl-, diethyl-, and diphenylthiourea was included in patch test baseline series in five Finnish dermatology clinics during 2002–2007. In addition, an extended series of rubber chemicals was tested in patients with suspected rubber allergy. Sources of sensitization to thioureas were analysed in sensitized patients.

Results: Thiourea mix yielded positive patch test reactions in 59 of 15 100 patients (0.39%); 33/59 patients were also tested with individual rubber chemicals. Diethylthiourea was positive in 24/33, diphenylthiourea in 5, and dibutylthiourea in 1 patient. The most common sources of sensitization included various neoprene-containing orthopaedic braces, sports equipment, and foot wear.

Conclusions: The sources of sensitization to thiourea chemicals were detected in most cases. These sources comprise a heterogeneous group of products extending from orthopaedic materials to sports equipment.

Key words: allergic contact dermatitis; dibutylthiourea; diethylthiourea; diphenylthiourea; rubber additives; thioureas. © John Wiley & Sons A/S, 2010.

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Thioureas are widely used accelerators in the manufacture of synthetic rubber products, especially neoprene and foam rubber (1). They are also present as antioxidants to preserve rubber products from drying and oxidation. Diphenylthiourea (DPTU), diethylthiourea (DETU), and dibutylthiourea (DBTU) are tested in special series of rubber chemicals, if rubber allergy is suspected. Neoprene (or polychloroprene), a widely used synthetic rubber, is manufactured via thiourea-mediated polymerization of chloroprene (2-chlorobutadiene) monomers. Neoprene products are highly flexible, durable, and resistant to damage caused by physical and chemical stress. Based on different polymerization accelerators, curing methods, and components, four different neoprene subtypes (T, W, S, and G) exist with differing physical and chemical properties. Vulcanizates of the G-type neoprenes have, for instance, the best

tear strength, while the W-types have the best compression and heat durability. In addition, raw polymers of the G-types do not necessarily require accelerators, whereas all the other subtypes (i.e. W, G, and S) require accelerators in their processing (neoprene – polychloroprene, Technical Information, DuPont Dow Elastomers L.L.C., Wilmington, DE, USA/www.dupont-dow.com).

Allergic contact dermatitis because of thiourea sensitization from orthopaedic joint braces, protective clothing, swim suits, and various sports equipment has been reported (2–8). Even computer wrist rests have previously been documented to cause thiourea-related allergic contact dermatitis following prolonged exposure (9). In earlier reports, photocopy papers and photography products that have contained thioureas as fixatives have caused allergic contact dermatitis (10). Thiourea

sensitization from neoprene gloves is possible but not frequent, and occupational sensitization to thiourea compounds has been infrequent (11).

Because the occurrence of rubber products containing thioureas may be common today, a mixture of three thiourea chemicals was added to the Finnish patch test baseline series in 2002. We have analysed the occurrence of positive patch test reactions to thiourea chemicals and sources of sensitization among Finnish general dermatology patients with suspected contact allergy during a 6-year period.

Patients and Methods

A total of 15 100 patients were patch tested with the Finnish baseline series (Chemotechnique Diagnostics, Vellinge, Sweden) and a thiourea mixture in five central hospital dermatology clinics since 2002. The mixture of the three thiourea chemicals consisted of 0.5% (wt/wt) DETU, 0.5% DBTU, and 0.5% DPTU in petrolatum (pet.). In all, 1500 patients with suspected allergy to rubber compounds were further tested with the rubber chemical series (Chemotechnique Diagnostics) containing DETU (1.0%, pet.), DBTU (1.0%, pet.), and DPTU (1.0%, pet.) among other rubber additives.

Patch test products were applied onto the upper back in Finn Chambers® (Epitest Ltd Oy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Venesla, Norway), removed after 2 days, and interpreted 1–3 days after the removal according to the International Contact Dermatitis Research Group criteria.

Results

Patch test reactions to the mixture and to DETU, DPTU, and DBTU

A positive patch test reaction to the thiourea mixture was seen in 59 patients (0.39%) (Tables 1 and 2). These patients included 30 females and 29 males, aged 52.6 and 42.1 years (mean), respectively. A majority (35/59) of the reactions were 2+ or more, and one, initially interpreted as a doubtful reaction, was eventually regarded as an allergic one because DETU yielded a 2+ reaction.

The series of the rubber chemicals was tested in 33/59 patients (56%) (Table 1). DETU was positive in 24/33 (73%) patients. DPTU reactions were seen in 5/33 patients (15%) and only one (3.0%) patient had a reaction to DBTU.

Four patients reacted to the thiourea mixture but had negative results for the individual thioureas in the rubber chemical series. One of these patients had no other patch test reactions, whereas all the other three reacted to thiuram chemicals.

Relevance of thiourea reactions and sources of sensitization

Twenty-six of 33 (79%) patients analysed with the rubber series had a history of dermatitis at the site of thiourea-containing material exposure indicating clinically relevant contact dermatitis caused by the source of sensitization (Table 1). Current relevance of thiourea reaction was found in 8/26 patients tested only with the thiourea mix (Table 2), while past relevance was found in 11/26 patients.

The most common probable or proven sources of sensitization were knee braces (14 cases), foot wear (7 cases), and various sports and fishing equipment. Positive patch test reactions to patients' own materials, however, were only seen in five cases. One patient developed occupational hand dermatitis in cleaning work. She reacted to DETU, diphenylguanidine, and also to the rubber handle of her cleaning trolley that she had used only 1 month. She had no previous exposure to rubber chemicals. In two other cases (a cutter in the insulation industry and a plastic worker), occupational sensitization was suspected.

Discussion

Thiourea sensitization was seen in 0.39% of the Finnish general dermatology patients with suspected contact allergy. In a recent report, 1.0% of the patients studied in the USA had positive patch test reaction to thioureas (12). The relevance of the past or present dermatitis was apparent or probable in a majority of the Finnish patients. In the USA, the number of clinically relevant cases was just slightly lower. Neoprene rubber and other thiourea-containing products may be more commonly used in the USA—for example, in sports wear products. Sensitization related to sports activities was also common among our patients—among male patients, in particular. Male patients were on average 10.5 years younger than the female correspondents, which reflects typical, for example, sports equipment related, sources of sensitization among male patients. There were no other clear demographic differences in our study material. Clinically relevant sensitization from orthopaedic braces is probably to occur regardless of age or sex.

A positive reaction to thiourea mixture without any reaction to separate thiourea chemicals was seen in four patients. Testing with higher than 1% concentrations of individual thioureas might have elicited allergic reactions in these patients as well. Alternatively, new reaction products in the mixture could have also yielded positive reactions in these cases. Possibility of skin irritation cannot be excluded with the 1.5% test concentration used, as serial dilution or end-point titration was not carried

Table 1. Patients patch tested with the baseline and rubber series^a

Patient	Gender/age	Thiourea				Other positive reactions to rubber chemicals				Symptoms	Proven or suspected sources	
		mixture	DBTU	DPTU	DETU							
1	F/57	2+	neg	1+	neg	b				External otitis	Ear phones	
2	M/40	1+	neg	neg	1+	b				Facial and leg/knee dermatitis	Knee brace, face mask	
3	F/51	2+	neg	2+	neg	b & MDA				Foot dermatitis	Shoe	
4	F/34	2+	neg	neg	3+	b & TMTM				Leg/arm dermatitis	Shoe, arm brace	
5	M/34	2+	neg	neg	2+					Leg/shoulder dermatitis	Fishing suit	
6	M/44	1+	neg	neg	2+					Fishing suit-associated dermatitis	Fishing suit	
7	F/40	1+	neg	neg	2+					Knee dermatitis	Knee brace	
8	M/52	2+	neg	neg	3+	Own knee brace				Knee/generalized dermatitis	Neoprene knee brace	
9	F/58	2+	neg	2+	neg	b & 2-MBT				Chest dermatitis	Stretchy bandage	
10	M/26	1+	neg	neg	neg	b & Thiuram-mix				Hand and knee dermatitis	Knee brace/gloves (football)	
11	M/54	1+	?	neg	2+					Leg stump dermatitis	Leg prosthesis	
12	F/69	2+	neg	neg	2+	b & Thiuram-mix, TMTM, TETD, TMTD, PTD, DTC				Arm/elbow dermatitis	Neoprene elbow brace	
13	M/33	1+	neg	neg	1+	b & DPG				Knee/hand/foot dermatitis	Knee brace/shoes/fishing glove	
14	M/48	1+	neg	neg	1+	b & DPG				Arm/elbow dermatitis	Elbow brace	
15	M/24	2+	neg	neg	3+					Foot dermatitis	Sport sandals/shoes	
16	F/37	2+	neg	neg	3+					Generalized dermatitis	Diving suit	
17	M/51	2+	1+	neg	2+	b & Own shin pad				Leg dermatitis	Goal keeper shin pad (football)	
18	M/17	2+	neg	neg	2+					Knee dermatitis	Knee brace	
19	F/66	3+	neg	2+	neg					Facial dermatitis	Make-up sponge	
20	M/61	2+	neg	neg	neg	b & Thiuram-mix, ZDEC, ZDBC, own knee brace				Knee dermatitis	Knee brace	
21	M/24	1+	neg	neg	1+	b				Hand/leg dermatitis	Shin pad (football)	
22	F/79	1+	neg	neg	neg	b & Thiuram-mix, TMTD, TMTM, TETD, PTD				Facial dermatitis	Unknown	
23	F/58	2+	neg	1+	neg	b				Hand dermatitis	Unknown	
24	F/26	1+	neg	neg	neg	b				Perioral dermatitis	Unknown	
25	M/40	2+	neg	neg	2+	b				Hand and arm dermatitis	Hand brace	
26	M/15	2+	neg	neg	2+	b				Hand/arm/back dermatitis	Hand brace	
27	F/54	2+	neg	neg	2+	b & Thiuram-mix, TMTM, own CPAP mask band				Scalp/cheek/neck dermatitis	CPAP mask/blue rubber band	
28	M/48	1+	neg	neg	2+	b				Foot/leg dermatitis	Shoes/knee brace	
29	M/46	2+	neg	neg	2+	b				Truss contact area dermatitis	Truss (hernia)	
30	M/38	2+	neg	neg	2+	b				Hand/finger dermatitis	Motor sledges gloves	
31	F/36	1+	neg	neg	1+	Thiuram-mix, TETD				Wrist dermatitis	Wrist brace	
32	M/19	2+	neg	neg	2+	Thiuram-mix, TMTM, TETD, own knee brace				Elbow/knee dermatitis	Elbow/knee brace (foot ball)	
33	F/20	3+	neg	neg	3+	DPG & rubber handle of a cleaning trolley				Hand dermatitis	Rubber handle of a cleaning trolley	

F, female; M, male; neg, negative; DBTU, dibutylthiourea; DPTU, diphenylthiourea; DETU, diethyl thiourea; TMTM, tetramethylthiuram monosulfide; TETD, tetramethylthiuram disulfide; TMTD, tetramethylthiuram disulfide; PTD, dipentamethylenethiuram disulfide; CPPD, *N*-cyclohexyl-*N'*-phenyl-*p*-phenylenediamine; 2-MBT, 2-mercaptobenzothiazole; DTC, diethyldithiocarbamate; ZDEC, zinc diethyldithiocarbamate; ZDBC, zinc dibutylthiocarbamate; DPG, *N,N'*-diphenylguanidine; MDA, 4,4'-diaminodiphenylmethane.

^aPositive reactions to the thiourea mixture, individual thioureas, and other rubber chemicals are shown. The listed symptoms indicate the primary reason for patch testing. Proven or suspected sources of thiourea sensitization are shown.

^bOther non-rubber reactions.

Table 2. Patients patch tested with the baseline series^a

Patient	Gender/age	Thiourea mixture	Other positive reactions to rubber chemicals	Symptoms	Suspected sources
1	F/39	2+	^b	Knee dermatitis, external otitis	Knee brace
2	F/50	2+	^b & Black rubber mix	Hand dermatitis	Unknown
3	F/67	1+	^b	Stasis dermatitis	Unknown
4	F/42	1+		Hand dermatitis	Unknown
5	F/62	2+	^b	Hand dermatitis	Unknown
6	M/50	1+		Knee/leg dermatitis	Knee brace
7	F/70	1+		Facial/upper body dermatitis	Unknown
8	F/62	2+	^b	Hand dermatitis	Unknown
9	F/49	1+	^b	Hand dermatitis	Unknown
10	F/64	2+	^b	Genital/formerly leg dermatitis	Unknown
11	F/53	1+		Facial/formerly hand dermatitis	Unknown
12	M/61	2+	^b	Foot/facial dermatitis	Sport sandals/CPAP mask
13	M/63	2+	^b	Knee/foot dermatitis	Knee brace/sandals
14	F/46	1+	^b	Facial dermatitis	Unknown
15	M/42	2+		Hand/foot/leg & generalized	Unknown
16	F/72	1+		Leg ulcers/stasis dermatitis	Unknown
17	F/61	2+	^b	Hand/foot/dermatitis	Unknown
18	M/39	1+	^b	Leg/thigh dermatitis	Leg/knee brace
19	F/53	2+	^b	Arm/elbow dermatitis	Elbow brace
20	M/38	3+	^b & Black rubber mix	Hand dermatitis	Ice hockey equipment
21	F/61	1+		Hand/arm dermatitis	Unknown
22	M/66	1+		Knee/sides of trunk/arm	Knee brace
23	M/30	2+		Hand dermatitis	Motor cycle gloves
24	F/42	1+	^b	Finger tip dermatitis	Knee/arm braces
25	M/50	2+		Hand dermatitis	Unknown
26	M/44	2+		Knee dermatitis	Knee brace

F, female; M, male.

^aPositive reactions to the thiourea mixture and to the rubbers chemicals in the baseline series are shown. The listed symptoms indicate the primary reason for patch testing. Suspected sources of thiourea sensitization are shown.

^bOther non-rubber reactions.

out in these four cases. On the other hand, we initially tested with a 0.75% thiourea mixture, too. Because false-negative results were seen with the 0.75% concentration, only the 1.5% concentration was left in the baseline series (J.L., L.A., T.H., A.L., T.R. & K.L. unpublished data). Nevertheless, all these four patients had also other concurrent reactions, and three of them reacted to thiurams as well, which all together may reflect their general rubber-related sensitization history.

In this material, cross-reactivity was not seen between the thioureas tested. Cross-reactions between individual thioureas seem to be rare as earlier suggested (13). From the individual thiourea chemicals, DETU elicited positive reactions most frequently. However, DPTU has been reported to be the major source of non-rubber thiourea contact sensitization (2). In our material, five patients were positive for DPTU and none of them had a history of having used leg or arm braces. DBTU yielded only one positive reaction in our material, and no cross-reactions were seen in that case either.

Concurrent reactions to other rubber chemicals were seen in 14/59 patients. Besides reactions to thiuram chemicals, also reactions to diphenylguanidine, carbamates, mercaptobenzothiazole, components of the black rubber mixture, and diaminodiphenylmethane were seen. Co-sensitization from the same source may have occurred in some cases, as thiuram disulfide is occasionally used to stabilize crystallizing neoprene (chloroprene polymers). One patient with a concomitant positive patch test reaction to thiuram chemicals and DETU also reacted to the continuous positive airway pressure (CPAP) mask band, but the neoprene appearing mask material did not elicit any reaction. Another patient had used orthopaedic braces and had brace-associated dermatitis. Although he also had facial dermatitis, he did not react to the neoprene appearing mask he had used in construction work. Facial neoprene masks, used for different purposes, however, could be potential sources of thiourea sensitization.

Testing with own materials has limitations which may occasionally lead to false-negative results. An occupational hand dermatitis had developed in a

cleaner following exposure to a cleaning trolley handle and in this case, a positive 3+ reaction was elicited by the handle material. A 3+ reaction to DETU was also seen and a positive reaction to diphenylguanidine. Apparently, the handle contains at least DETU and possibly also diphenylguanidine. Although DETU seemed to be the major allergen in this case, both rubber chemicals may have contributed to the occupational hand dermatitis. Other patients with diphenylguanidine and thiourea reactions had been sensitized to neoprene orthopaedic elbow or knee braces. In a similar way, six of eight patients with thiuram reactions had been exposed to various brace materials.

Hand dermatitis-related sensitization from neoprene sports gloves was seen in four patients. Earlier reports suggest that glove sensitization might be even more common (14). However, hand dermatitis was the main diagnosis in seven patients with unknown sources of sensitization. Earlier sensitization from gloves or from other sources has probably contributed to the hand dermatitis in these patients. In addition, occasional recurring exposure cannot be excluded. Foot wear is probably an important source of contact sensitization to thioureas, and although an actual foot dermatitis was only seen in eight patients, sensitization from shoes may have developed more often. Shoe insoles may contain thioureas, and testing with own shoe materials can be useful. In the present study, however, patients' own shoe materials were tested in a few cases and positive reactions were not detected.

Thiourea sensitization from fishing suits with neoprene-containing parts was seen in two patients. Diving suits have been reported as sources of thiourea sensitization (5, 15), but among our patients, only one case of sensitization from a diving suit was documented. Although there are many different types of clothing with neoprene-containing parts on the sports wear market, we could not find any patient sensitized from such clothing except patients sensitized from gloves or shoes.

In as many as 18 cases, the source of the sensitization remained unknown. The patients sensitized from unknown sources had most often hand dermatitis and occasionally leg or facial dermatitis. It appears that even a shorter period of exposure may lead to sensitization. Although the exact history and source of sensitization remained unrevealed, these patients were probably sensitized from shoes, gloves, make-up products, or other variable neoprene products in everyday life and hobbies. Besides sports wear and the related gloves or shoes, also other safety gloves, hand protection equipment, and protective clothing used in various spare time activities, that is, gardening, home repair, and

construction, might potentially act as sources of thiourea sensitization.

In conclusion, orthopaedic braces, sports equipment, foot wear, and certain gloves comprise a significant risk of thiourea sensitization. Sensitization, however, seems to develop from different patient aid products, and the chance of sensitization in domestic life and occupational environments should be considered, particularly in hand dermatitis patients. Patch testing with thiourea chemicals provides a significant contribution to the diagnosis of contact dermatitis in different patient groups.

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