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Should carba mix be reintroduced into the European baseline series?

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Carba mix was removed from the European baseline series in 1989, owing to the opinion that many concomitant reactions with thiurams were found, resulting in very few cases being missed by exclusion of carba mix (1). However, carba mix is still included in the TRUE Test[®]. Recent studies have reported an increasing prevalence of contact allergy to, and allergic contact dermatitis caused by, carba mix (2,3). We aimed to evaluate the trend in the prevalence of contact allergy and associated clinical relevance to rubber chemicals in Odense, Denmark, in the period 1994–2013, based on TRUE Test[®] allergens as part of the European baseline series.

Methods

All patients patch tested at the Department of Dermatology and Allergy Centre, Odense University Hospital in the period 1994–2013 were included. All patients were patch tested with the rubber allergens carba mix, mercaptobenzothiazole, mercapto mix, thiuram mix and black rubber mix by the use of TRUE Test[®]. Patch tests were performed according to ICDRG guidelines (4), with readings on day (D)3/D4 and D7. Reactions designated as either +, ++ or +++ were classified as positive. At the last reading, clinical relevance was assessed by a dermatologist according to the history of exposure to rubber materials such as gloves, fungicides, and pesticides,

together with evaluation of the dermatitis pattern. Relevance was confirmed even if testing with the constituents of carba mix gave negative results but a history of clinical correlation with glove dermatitis existed, which, of course, entails the risk of over-interpreting clinical relevance. According to the manufacturer's information, the TRUE Test[®] carba mix 250 µg/cm² contains diphenylguanidine (purity ≥96%), zinc dibutyldithiocarbamate (purity ≥96%), and zinc diethyldithiocarbamate (purity ≥96%) in equal proportions. In 2015, we also tested with carba mix 3% pet. from Trolab[®], SmartPractice; these data were compared with the TRUE test[®] results separately. The χ^2 -test for trend was used to assess changes over time. The study was approved by the Danish Data Protection Agency.

Results

A total of 9741 patients were patch tested, and 579 (5.9%) had at least one positive reaction to a rubber allergen. Figure 1 shows the trend in contact allergy to the different rubber allergens in the period 1994–2013. Contact allergy to thiuram mix declined significantly in the period, that is, from 3.8% in 1994–1997 to 2.5% in 2010–2013 ($p < 0.05$), while the prevalences for the other rubber allergens were stable.

The overall prevalence of contact allergy to carba mix in the study time period was 3.6%. Of the 351 patients who reacted to carba mix, 56% (196) had concomitant reactions to thiuram mix, 6.8% (24) to mercapto mix, and 5.1% (18) to mercaptobenzothiazole. Of those who reacted to carba mix, 40% (142/351) had reactions to carba mix without concomitant reactions to thiuram mix, mercapto mix, or mercaptobenzothiazole, with an increasing trend over time (Table 1). Clinical relevance of reactions to any of the ingredients in carba mix was found in 33% (47/142) of those with isolated reactions

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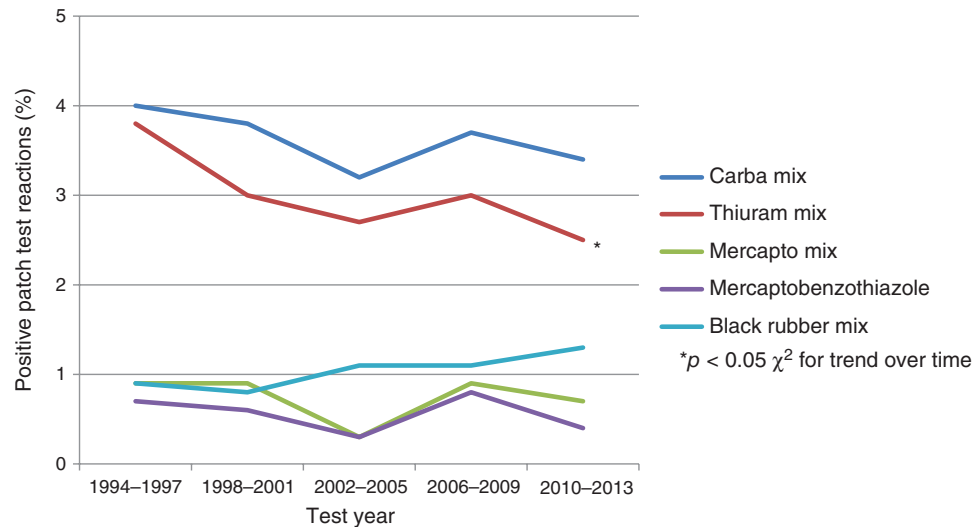


Fig. 1. Trend in the prevalence of sensitization to rubber allergen in Odense, Denmark from 1994 to 2013.

Table 1. Proportion of positive test reactions to carba mix, together with isolated carba mix reactions (without concomitant reactions to thiuram mix, mercapto mix, and mercaptobenzothiazole)

	Year					Total
	1994–1997	1998–2001	2002–2005	2006–2009	2010–2013	
Positive patch test reactions to carba mix	4.0% (78/1952)	3.8% (73/1914)	3.2% (62/1947)	3.7% (69/1876)	3.4% (69/2028)	3.6% (351/9717)
Positive patch test reactions to carba mix without reactions to other rubber allergens	35% (27/78)	32% (23/73)	48% (30/62)	42% (29/69)	48% (33/69)	40%* (142/351)
Clinical relevance in patients with isolated carba mix reactions	22% (6/27)	22% (5/23)	37% (11/30)	34% (10/29)	45% (15/33)	33% (47/142)
Positive reactions to single allergens in the mix in patients with isolated carba mix reactions	14% (3/22)	5% (1/19)	13% (2/16)	23% (6/26)	25% (6/24)	17% (18/107)
Doubtful reactions to single allergens in the mix in patients with isolated carba mix reactions	18% (4/22)	37% (7/19)	25% (9/16)	38% (10/26)	25% (6/24)	34% (36/107)

* $p < 0.05$ (χ^2 for trend over time).

to carba mix, as determined by exposure history and dermatitis pattern.

Patch testing with single allergens included in the mix was performed in 250 of the 351 patients who reacted to carba mix. Reactions to zinc diethyldithiocarbamate were found in 24% (61/250), reactions to diphenylguanidine in 15% (38/250), and reactions to zinc dibutyldithiocarbamate in 3.6% (9/250). Only 2 patients had reactions to more than one of the three ingredients in carba mix: 1 to all three, and 1 to the two carbamates.

Among those with isolated reactions to carba mix, 17% (18/107) had positive reactions to one of the three ingredients of the mix, and 34% (36/107) had doubtful reactions (Table 1). Among the 47 patients with isolated reactions to carba mix that were determined to be clinically relevant, 34 were tested with the three individual ingredients: 8 had positive reactions, 12 had doubtful reactions, and 14 had negative reactions.

In 2015, 406 patients were tested both with carba mix from TRUE Test® and with carba mix 3% pet. The numbers of positive reactions to carba mix were similar with

TRUE Test® (4.4%) and with carba mix in pet. (4.7%); 3.0% (12/406) reacted to both carba mixes. The number of doubtful reactions was higher for carba mix in pet. (8.1%) than for carba mix in TRUE Test® (4.4%).

Discussion

The prevalence of contact allergy to rubber allergens was stable in the period 1994–2013, except for a decline in the prevalence of contact allergy to thiuram mix. Carba mix was the rubber allergen with the highest prevalence (3.6%) during the study period. A recent UK study on occupational rubber contact allergy showed a decreasing incidence of occupational allergic contact dermatitis caused by rubber chemicals in total, but a relative increase in reactions to carbamates (2). The same trend has recently been reported in a multicentre European study (3), supporting our results.

Cross-reactivity to various rubber accelerators occurs. However, 40% of patients who reacted to carba mix did not react to other rubber accelerators, and would have

been missed if carba mix had not been present in the baseline series at the department. One-third of these reactions were clinically relevant, although, in testing with the individual ingredients in the mix, not all patients had positive reactions. In total, 17% of patients with isolated carba mix sensitization had positive reactions to at least one of the three ingredients in the mix, and 34% had doubtful reactions. False-positive reactions to carba mix occur, but some of the missing positive reactions to the constituents of carba mix could be explained by pseudo-compound allergy (comparing patch test results obtained with different vehicles) (5). Furthermore, there is a need for studies testing carba mix together with all three ingredients separately to re-evaluate the reliability of the mix and establish the optimal test concentration for the mixture and for the individual ingredients. Our results add further arguments for reintroducing carba mix into the European baseline series.

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