ESSCA results with the baseline series, 2009–2012: rubber allergens

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Summary

Background. Allergic contact dermatitis caused by rubber allergens is common, and causes significant patient morbidity. Contemporary data are important to allow appropriate preventive measures and identification of contact allergy trends.
Objectives. To describe the pattern of patch test reactivity to rubber allergens, including those in the European baseline series.
Methods. Data collected by the European Surveillance System on Contact Allergies (ESSCA) network between 2009 and 2012 from 12 European countries were analysed.
Results. Contact allergy to thiuram mix declined over the studied time period, with an overall prevalence of 1.87%. The prevalence of allergy to carba mix was 2.29%, and was significantly increasing. Prevalence rates of sensitization to other rubber allergens were largely unchanged. Statistical analysis with the MOAHLFA index confirmed the strong links between rubber allergy and occupational hand dermatitis.
Conclusions. Changing patterns of allergy to rubber additives have been identified. Inclusion of carba mix in the European baseline series may be appropriate.

Key words: contact allergy; dithiocarbamates; mercaptobenzothiazoles; *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine; occupational contact allergy; rubber; surveillance; thiurams.

Allergic contact dermatitis caused by rubber additives is common and of clinical importance. Rubber chemical additives may be present as remnants from the production process, usually vulcanization accelerators such as dithiocarbamates, thiurams, and 2-mercaptobenzothiazole (MBT) derivatives. Alternatively, they can be added to enhance the properties of the final product; examples are antioxidants and antiozonants – so-called 'black rubber' chemicals.

Currently, the European baseline series (EBS) recommends the inclusion of thiuram mix 1% pet., *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine (IPPD) 0.1% pet., mercapto mix 2.0% pet., and MBT 2.0% pet. (1).

On the basis of data collected by the European Surveillance System on Contact Allergies (ESSCA) (www.essca-dc.org) network, this study describes the pattern of patch test reactivity to rubber allergens in the EBS.

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Methods

This retrospective analysis is based on data collected by the ESSCA network during the study period (January 2009 to December 2012). For time trend analyses concerning selected allergens, additional data from 2004 to 2008 were used.

The ESSCA network has already been described in previous publications (2). The current clinical sample has been described in detail in a previous publication (3). Briefly, clinical and demographic data, along with patch test results, of all patients patch tested in the departments participating in the ESSCA for suspected allergic contact dermatitis are documented electronically in the local departments, by the use of diverse data capture software and, partly, the multilingual software WINALLDAT/ESSCA provided by the ESSCA (4). Data are pooled in the ESSCA data centre in Erlangen with R (version 3.1.1) software (5), according to standard operating procedures (6).

Patch testing was performed according to ICDRG recommendations (7). The maximum patch test reaction between D3 and D5 (inclusive) was aggregated as the patch test outcome. Reactions designated as either +, ++ or +++ were classified as positive; all others were classified as non-positive. The rubber allergens contained in the EBS and additional allergens listed in Table S1, provided that they were tested in consecutive patients, were analysed for this study. Different test concentrations were sometimes used, depending on local policy, with the corresponding results being separately analysed. When the TRUE Test® baseline series was used, results were analysed separately, for better comparability. Details of 'mercapto', 'carba' and 'black rubber' mix constituents are given in Table S1. In cases of multiple consultations within the 4-year study period, the most recent consultation was chosen for analysis.

The associations between positive reactions to the different rubber allergens and (i) age group (adjusted for sex) and (ii) time trend (adjusted for age and sex) were quantified with log-binomial regression analysis, yielding estimates of the prevalence ratio (PR) with accompanying 95% confidence intervals (CIs) derived from the profile likelihood method. Descriptive analysis followed pertinent guidelines (8, 9), with R (version 3.1.1) software (5).

Results

Data from 53 departments in 12 European countries are included. Over the 4-year study period, 63 530 consultations were registered with the ESSCA, yielding 59 922 applications of the baseline series and at least one reading at D3–D5 after application of patch tests. Owing to multiple consultations of some patients, this number was reduced to 59 728 single consultations of these patients.

Table 1(a) and (b) shows the overall results for positive reactions to rubber allergens, with age-standardized and sex-standardized prevalence rates with accompanying 95% CIs. Data were analysed separately for patch testing with investigator-loaded allergens and patch testing with the TRUE Test® baseline series. The vast majority of patch tests were performed with investigator-loaded, petrolatum-based or water-based allergens, as shown in Table 1(a). These were all assumed to be tested in consecutive patients, be it only in certain periods (e.g.

Table 1. (a) Overall results with the rubber allergens available in (a) petrolatum and (b) TRUE Test®

Allergen	n tested	% +	% ++/+++	% ? +/IR	% positive	% pos.std	95%CI
(a)							
Carba mix	16 744	1.8	0.5	0.83	2.31	2.29	2.06–2.52
Mercaptobenzothiazole	57 186	0.32	0.26	1.09	0.58	0.60	0.53–0.66
Mercapto mix (CBS, MBTS, MOR)	23 436	0.5	0.22	2.65	0.72	0.72	0.61–0.83
Mercapto mix (MBT, CBS, MBTS, MOR)	29 856	0.25	0.23	0.26	0.49	0.51	0.43–0.59
IPPD	53 369	0.36	0.31	1.29	0.67	0.66	0.59–0.73
PPD ('black rubber') mix (IPPD, CPPD, DPPD)	795	0	1.01	0	1.01	0.95	0.27–1.63
Thiuram mix	56 136	1.02	0.93	1.2	1.98	1.87	1.76–1.98
Zinc diethyldithiocarbamate	14 224	0.47	0.18	1.25	0.65	0.64	0.5–0.78
(b)							
Carba mix	2436	0.37	0.16	1.69	0.53	0.48	0.22–0.75
Mercaptobenzothiazole	2361	0.64	0.17	0.14	0.8	0.76	0.41–1.11
Mercapto mix (CBS, MBTS, MOR)	2361	0.76	0.17	0.22	0.93	0.91	0.52–1.3
PPD ('black rubber') mix	2436	0.29	0.49	0	0.78	0.78	0.42–1.14
Thiuram mix	2362	1.14	0.42	0.14	1.57	1.48	1–1.97

CBS, *N*-cyclohexylbenzothiazyl sulfenamide; CPPD, *N*-cyclohexyl-*N*′-phenyl-*p*-phenylenediamine; DPPD, *N*,*N*′-diphenyl-*p*-phenylenediamine; IPPD, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine; IR, irritant reaction; MBTS, dibenzothiazyl disulfide; MOR, morpholinyl mercaptobenzothiazole; MBT, 2-mercaptobenzothiazole; PPD, *p*-phenylenediamine; % pos.std., proportion of positives, directly age-standardized and sex-standardized; 95%CI, 95% confidence interval to the standardized prevalence.

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in the context of the DKG monitor series) or by a subset of departments only, or both. 2435 of the consecutive patients were patched tested with TRUE Test® in five departments [Groningen (n = 1468), Madrid, Princesa (n = 604), León (n = 244), Amsterdam VU (n = 101), and Murcia (n = 18)]; these results are shown in Table 1(b).

Table 2 shows the results presented in Table 1(a) stratified for patients with occupational contact dermatitis versus patients in whom occupational causation was explicitly denied. Thereby, 16 109 patients for whom no definite statement was made or in whom occupational causation was considered to be 'unclear' were excluded from this analysis, as in a previous study on occupation-related contact dermatitis (10).

Table 3 shows the pattern of the MOAHLFA index (11, 12) in patients reacting positively to a rubber allergen as compared with those with a negative test result. With extension of this standard analysis format, addressing two main sites of contact (and contact dermatitis) to rubber products, that is, not only the hands but also the feet, the prevalence of positive reactions only to mercapto compounds in patients with foot dermatitis was consistently and markedly higher than that for the other rubber allergens. Moreover, for patients with foot dermatitis who reacted positively to MBT, the age was significantly lower than in positive patients in whom other anatomical sites were affected ($p = 0.045$, Wilcoxon test).

A subdivision of test results by country is shown in Table S2(a–g). This shows (i) some variation in contact allergy prevalence rates and (ii) that some patch test preparations are used alternatively, notably carba mix versus zinc diethyldithiocarbamate (ZDEC) and the two mercapto mixes. The 'black rubber mix' is hardly tested beyond TRUE Test®.

Table 2. Results with the rubber allergens in petrolatum stratified for patients with occupation-related contact dermatitis ('Occ+') versus patients in whom this was not the case ('Occ−')

	Occ+			Occ−		
Allergen	n tested	% pos.std	95%CI	n tested	% pos.std	95%CI
Thiuram mix	7202	4.91	4.41–5.42	30 339	1.33	1.2–1.46
Zinc diethyldithiocarbamate	3543	1.35	0.95–1.74	8614	0.29	0.17–0.42
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine	6542	1.01	0.77–1.26	29 516	0.53	0.45–0.62
Mercapto mix (MBT, CBS, MBTS, MOR)	2613	1.02	0.63–1.41	12 948	0.48	0.36–0.6
Mercapto mix (CBS, MBTS, MOR)	4458	1.01	0.71–1.32	15 920	0.62	0.48–0.75
Mercaptobenzothiazole	7243	1	0.77–1.23	31 308	0.56	0.47–0.64
Carba mix	1854	5.52	4.47–6.57	13 233	1.82	1.58–2.05
PPD ('black rubber') mix	380	1.5	0.23–2.77	415	0.39	0–0.92

CBS, *N*-cyclohexylbenzothiazyl sulfenamide; MBT, 2-mercaptobenzothiazole; MBTS, dibenzothiazyl disulfide; MOR, morpholinyl mercaptobenzothiazole; PPD, *p*-phenylenediamine; % pos.std., proportion of positives, directly age-standardized and sex-standardized; 95%CI, 95% confidence interval to the standardized prevalence.

Table 3. MOAHLFA index of patients with positive versus negative reactions to the rubber allergens

Allergen	Result	% M	% O	% A	% H	% L	% foot	% F	% A
Thiuram mix	Positive	37.8	35.1	23.1	38.1	4.3	1.9	9.8	67.3
	Negative	33.2	13.1	21.3	21.3	4.7	2.1	13.9	60.8
ZDEC	Positive	46.2	52.7	32.3	28.0	5.4	0	2.2	67.7
	Negative	38.6	25.1	22.2	19.6	2.7	1.1	4.8	68.0
Carba mix	Positive	49.5	27.5	28.8	38.6	9.1	3.1	12.7	65.3
	Negative	31.8	10.7	28.7	25.6	6.1	2.9	22.5	59.1
MBT	Positive	40.2	23.1	28.2	34.8	1.6	8.2	6.0	52.2
	Negative	33.5	13.3	22.0	21.3	4.9	2.1	14.0	59.9
Mercapto mix (CBS, MBTS, MOR)	Postive	37.5	27.4	22.0	26.2	3.0	8.9	5.4	63.1
	Negative	35.4	19.2	22.9	22.0	4.4	1.8	11.2	65.2
Mercapto mix (CBS, MBTS, MOR, MBT)	Positive	45.0	20.6	28.2	38.2	1.5	8.4	9.9	52.7
	Negative	31.5	9.5	20.4	21.3	4.9	2.2	16.0	57.6
IPPD	Positive	36.7	20.7	20.7	24.6	2.4	1.5	10.4	60.4
	Negative	33.6	12.9	22.5	20.7	4.8	2.2	14.3	60.0

M, male; O, occupational dermatitis; A, atopic dermatitis; H, hand dermatitis; L, leg dermatitis; F face dermatitis; and A, age 40 years and above; CBS, *N*-cyclohexylbenzothiazyl sulfenamide; IPPD, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine; MBT, 2-mercaptobenzothiazole; MBTS, dibenzothiazyl disulfide; MOR, morpholinyl mercaptobenzothiazole; ZDEC, zinc diethyldithiocarbamate.
The prevalence of feet as the main affected anatomical sites has been added. Note that patient populations are disjunct concerning allergens tested alternatively, for example mercapto mix 1% and 2%, and ZDEC and carba mix.

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Coupled reactivity between selected rubber allergens was examined for pet.-based allergens only. The cross-tabulation results are shown in Table 4(a–e).

Figure 1 shows the risk of sensitization to some rubber allergens at different ages. For the analysis of an 'age gradient', three outcomes were considered: positive (versus negative) reactions to (i) thiuram mix, (ii) carba mix, or ZDEC (tested alternatively, i.e. in disjunct subgroups of patients), and (iii) 2-mercaptobenzothiazole, mercapto mix 1%, or mercapto mix 2% (the latter two allergen preparations having been tested alternatively).

Table 4. Coupled reactivity between different rubber compounds in those patients tested with both allergens quantified by the odds ratio (OR) with accompanying exact 95% confidence interval (CI)

(a) Thiuram mix (1% pet.) versus zinc diethyldithiocarbamate (ZDEC, 1% pet.)

		ZDEC	
		n positive	n negative
Thiuram mix	n positive	61	324
	n negative	26	13 757

(b) Thiuram mix (1% pet.) versus carba mix (3% pet.)

		Carba mix	
		n positive	n negative
Thiuram mix	n positive	132	197
	n negative	253	16 144

(c) MBT (2% pet.) versus mercapto mix (CBS, MBTS, MOR; 1% pet.)

		Mercapto mix 1%	
		n positive	n negative
MBT	n positive	79	65
	n negative	88	23 185

(d) MBT (2% pet.) *versus mer*capto mix (CBS, MBTS, MOR, MBT; 2% pet.)

		Mercapto mix 2%	
		n positive	n negative
MBT	n positive	76	75
	n negative	55	27 157

(e) IPPD (0.1% pet.) versus PPD (1% pet.)

		PPD	
		n positive	n negative
IPPD	n positive	66	173
	n negative	1454	39 181

CBS, *N*-cyclohexylbenzothiazyl sulfenamide; IPPD, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine; MBT, 2-mercaptobenzothiazole; MBTS, dibenzothiazyl disulfide; MOR, morpholinyl mercaptobenzothiazole; PPD, *p*-phenylenediamine; ZDEC, zinc diethyldithiocarbamate.
(a) OR: 99.4 (95%CI: 61.0–166.3); (b) OR: 42.7 (95%CI: 32.9–55.5); (c) OR: 320.4 (95%CI: 212.3–490.6); (d) OR: 493.1 (95%CI: 321.3–791.1); (e) OR: 10.3 (95%CI: 7.6–13.8).

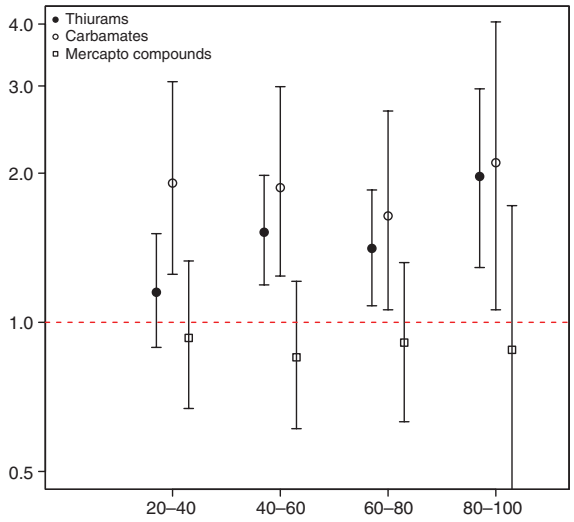

Fig. 1. Risk of sensitization to thiurams (thiuram mix), dithio carbamates (carba mix or zinc diethyldithiocarbamate) and 'mercapto compounds' (mercaptobenzothiazole, mercapto mix 1%, or mercapto mix 2%) in five age groups, expressed as prevalence ratios with accompanying 95% confidence intervals. The youngest age group (≤20 years) serves as a reference.

Figure S1 shows the time trend of positive reactions to rubber agents of the EBS from 2004 to 2012, including only those countries contributing to the ESSCA since 2004. This analysis is based on between 15 698 (mercapto mix 1%) and 49 670 (thiuram mix) additional patient consultations in the period 2004–2008. Prevalence rates are standardized for age and sex, and provided with 95% CIs. It should be noted that not all countries test the 'carba mix' or the 2% 'mercapto mix', so the trend results may not be entirely comparable.

Discussion

Prevalence and time trends in rubber allergy 2004–2012

Figure S1 summarizes the time trends of allergy to rubber additives from patient data collected by the ESSCA from 2004 to 2012. In agreement with other studies (13–18), the prevalence of allergy to thiuram mix declined over the studied time period of 2004–2012 (PR: 0.961, $p < 0.001$), with a prevalence in this study of 1.87% (95%CI: 1.76–1.98). Previous analysis of trends in contact sensitization in Poland in 1996–2009 showed a significant decline in the prevalence of allergy to thiurams only in women ($p = 0.033$) (19). After earlier widespread use in rubber gloves and associated high rates of sensitization, it has been observed that thiurams in

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manufactured gloves have now been largely replaced by dithiocarbamates (17, 20, 21).

The age-standardized and sex-standardized prevalence of allergy to carba mix in this study was 2.29% (95%CI: 2.06–2.52), and the prevalence was significantly increasing (PR: 1.042, $p = 0.00254$), a trend that has been noted in other studies (21, 22). The prevalence was higher in a 2009–2010 study from the North American Contact Dermatitis Group, which reported a prevalence of 4.6% positive patch test reactions to carba mix (sample size, 4308 patients; only 10% cases were occupational) (23). In our study, there was no increase in the prevalence of sensitization to ZDEC, which is a component of carba mix that, in some departments, is tested individually in the baseline series without carba mix. Dithiocarbamate-free gloves are difficult to source (17), which may explain the increase in the prevalence of sensitivity to carba mix; this is discussed in more detail below. It has been stated that the prevalence of positive patch test reactions in consecutively tested patients should normally exceed 0.5–1% for an allergen to be eligible for inclusion in a baseline series (24). The findings of this study suggest that carba mix should be included in a baseline series. The low prevalence of positive reactions to ZDEC, as compared with the carba mix, indicates that this allergen is a poor marker of contact allergy to dithiocarbamates, notwithstanding some discussion regarding the diagnostic validity of the mix (see below).

On review of 25 studies published between 1973 and 2004, a weighted average for the frequency of sensitization to mercaptobenzothiazole compounds of 1.7% (588/33 675) was calculated (25), although the evidence suggests a general decline in the prevalence of allergy to MBT and its derivatives in the last 30 years (25). This finding is in keeping with the results of this study, in which the age-standardized and sex-standardized prevalence rates of allergy were 0.60% for mercaptobenzothiazole, 0.72% for three-component mercapto mix, and 0.51% for four-component mercapto mix. The time trend analysis in this study shows that the sex-adjusted and age-adjusted prevalence was largely unchanged between 2004 and 2012, as shown in Figure S1.

The prevalence of allergy to IPPD did not significantly change over the studied time period, and the prevalence remained low, at 0.66%.

TRUE Test® versus investigator-loaded allergens

The differences in positive reactions to rubber allergens between TRUE Test® and investigator-loaded allergens in pet. were minimal, with the exception of carba mix, to which 0.48% reacted positively in TRUE Test® (n = 2436) and 2.29% reacted positively with investigator-loaded allergens (n = 16 744), which is a statistically significant difference. As shown in Table S1, it is notable that the dose in mg/cm^2 of TRUE Test® is much lower than the dose applied in pet., which may account for the low frequency of reactions to carba mix with TRUE Test®. A similar finding was made in a recent study investigating fragrance mix I (26). However, this difference in applied concentrations did not appear to have affected the rates for other rubber allergens, although a comparison based on our data is difficult, as different sets of patients had been tested with either TRUE Test® or investigator-loaded test systems. An interesting observation, as seen in Table 1(a), is the proportion of positive (+) reactions to carba mix being 1.8%, that is, accounting for 78% of all positive reactions. This may be an indication of an irritant response, or may represent weak sensitization. Conversely, if carba mix is only tested with TRUE Test®, a proportion of relevant sensitizations may be missed. The diagnostic validity of the two preparations can, however, only be assessed if verification tests such as the repeated open application test are employed.

MOAHLFA

Focusing on the patient characteristics according to the MOAHLFA index (12), no strong age or sex influence was seen for any of the rubber allergens. This lack of a sex association has previously been observed in occupational studies (14, 27). Facial dermatitis is negatively associated with all rubber allergens. There is, however, a clear link with hand dermatitis (particularly in the case of four-component mercapto mix and thiuram mix) and occupation. Moreover, all benzothiazole derivatives are strongly associated with dermatitis of the feet, confirming their importance in shoe dermatitis (28–30).

Occupational influence

Allergic contact dermatitis caused by rubber additives is especially prevalent in professions with a frequent need to wear watertight protective gloves, for example domestic helpers, healthcare workers, and restaurant workers, as well as in the rubber manufacturing and building industry (10, 14, 31, 32). The findings of this study fully support this occupational association; Table 2 shows non-overlapping CIs between occupation-positive and occupation-negative contact dermatitis caused by all rubber additives except 'black rubber' mix (for which small numbers were tested, and thus the precision of the prevalence estimates is limited) and the three-component mercapto mix. The recent study of occupational dermatitis by the ESSCA network 2002–2010 (10) investigating patterns of reactivity to allergens of the baseline

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series found that rubber additives comprised four of the top five allergens associated with occupational dermatitis, namely thiuram mix, MBT, IPPD, and mercapto mix.

Regarding mercapto compounds, in a multifactorial analysis of sensitization in construction workers, sensitization to MBT was significantly more frequent (1.37% versus 0.79%) (33). Approximately 20% of patients with occupational dermatitis registered in the Information Network of Departments of Dermatology (IVDK) in the years 1995–2001 were patch tested because of suspected rubber glove allergy (17). Although there were indications that thiurams would be replaced increasingly by mercapto compounds, the frequencies of sensitization to thiurams remained high (~15% of this specific subgroup tested), and the frequency of sensitization to any of the mercapto compounds was rather low (~3%) (17). In a trend analysis of IVDK data covering the period 1995–2002, there was a difference in the frequency of sensitization to MBT between hairdressers and female clients [odds ratio (OR): 1.97; 95%CI: 0.32–16.55] (34). In a larger study from Spain, including 4680 patients patch tested with the standard series and rubber additives, 686 cases were identified as being sensitized to rubber compounds, among them 83 (12%) cases sensitized to MBT (35). Although almost two-thirds of this group reacted to thiurams, 12% reacted to MBT, indicating that MBT must be regarded as an important occupational and non-occupational rubber allergen (35). Among 4433 patients consecutively tested with standard series in an occupational institute in Poland in 1996–2009, only 0.8% reacted to MBT (19).

By country

As with previous ESSCA studies (2, 10, 36, 37), the proportion of cases varied between different countries. The distinct focus of certain departments, for example those with an occupational remit (The Finnish Institute of Occupational Health, Osnabruck and Heidelberg in Germany, and Lodz in Poland), is a confounder of between-country comparison.

The range of prevalence of sensitization to thiuram mix was notably broad, ranging from 0.5% in Lithuania to 3.68% in Austria. The particularly low level of sensitization to thiurams in Lithuania is a pattern previously recognized in the 2007–2008 ESSCA baseline series patch test data study (2). The Netherlands has a particularly high prevalence of sensitization to carba mix, at 5.63%. Neither of these patterns, nor the reverse, is reflected in the prevalence of sensitization to other rubber additives, thus ruling out a simple explanation. Regional and comparative analyses of glove uge and chemicals in gloves may be helpful in deciphering this pattern.

Age

The risk of sensitization to select rubber additives according to age was analysed to assess newly acquired sensitizations in young adults versus pre-existing 'old' sensitizations, especially to thiurams, whose overall rates are declining. Previous analyses of data from the IVDK network specifically concerning allergy to thiurams from 1992 to 2006 (14) found a distinct general risk gradient related to increasing age. Our dataset has shown that the risk of sensitization to thiurams (thiuram mix) and carbamates (carba mix or ZDEC) is increased in older age groups, with some overlap in CIs, but that age does not appear to influence sensitization to 'mercapto compounds' (2-mercaptobenzothiazole, mercapto mix 1%, or mercapto mix 2%). However, despite the fairly large size of our clinical sample, most of the results are non-significant, and should thus not be over-interpreted. The pattern that we observed with mercapto compounds was mirrored in previous studies of 4055 patients by Nethercott et al. (25, 38). It is likely that these results are attributable to the strong occupational link with rubber chemical allergy; younger age groups either have not yet entered the workforce or are yet to be exposed in the workplace, but possibly are exposed to non-age-specific sources, such as in footwear. In addition, tighter legislation and controls regarding glove use and changing composition may be influential.

Coupled reactivity

Coupled reactivity between different rubber compounds is well known. ZDEC, zinc dibutyldithiocarbamate and diphenylguanidine (DPG) are contained in the 'carba' mix. Debate about the use of the carba mix has been extensive, owing to many ('redundant') concomitant reactions with thiurams (39), a finding that was repeatedly confirmed (35, 40, 41). A 2001 study found that the OR for reactions to ZDEC and thiuram mix being associated was 166.43 (41), a finding also confirmed in this study, which calculated the OR as 99.4 (95%CI: 61.0–166.3). Therefore, it was recommended to remove the carba mix from the baseline series (42), which was disputed (43). An analysis of 5986 patients tested showed that 84 cases of contact dermatitis caused by rubber would have been missed had the carba mix been excluded (43).

In this study, a strong correlation was found between sensitization to ZDEC and sensitization to thiuram mix [OR 99.4 (95%CI: 61.0–166.3)], and, to a lesser extent, between sensitization to carba mix and sensitization to thiuram mix [OR 42.7 (95%CI: 32.9–55.5)]. However, it is of note that 253 patients who reacted positively to carba mix and 26 patients who reacted positively to ZDEC did

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not react to thiuram mix. This finding suggests a need to include carba mix in the baseline series.

The striking difference between the overall prevalence rates of contact allergy to ZDEC and contact allergy carba mix (0.65% versus 2.29%) is of interest, given that ZDEC alone is tested in some centres as a representative of this group. There has been evidence suggesting that the carba mix caused more false-positive reactions, owing to the irritant effect of DPG (17, 44). However, a direct comparison is not possible in our data, as different departments tested ZDEC and carba mix, and as no verification test or unequivocal information on clinical relevance is available. Further studies would be required to clarify this.

The EBS includes mercapto mix with MBT, although mercapto mix without MBT has proven to be more stable, and is used in some centres (45, 46). The association between reactions to MBT and reactions to mercapto mix is clear from these data, with ORs of 320.4 (95%CI: 212.3–490.6) and 493.1 (95%CI: 321.3–791.1) with three-component mercapto mix, (1% pet.) and four-component mercapto mix (2% pet.), respectively. However, further study would be required to ascertain whether one mix is superior to the other.

Both IPPD (0.1% pet.) and *p*-phenylenediamine (1% pet.) are currently included in the baseline series, and, with a cross-reactivity OR of 10.3 (95%CI: 7.6–13.8), this appears to be appropriate, with comparatively little concomitant reactivity. However, it has been pointed out that concomitant reactivity is 'asymmetrical', in the sense that most patients who are allergic to IPPD will also react to *p*-phenylenediamine, but not vice versa (47).

Conclusions

This study has shown changing trends of sensitization to rubber allergens. Carba mix sensitivity has increased to a current prevalence of 2.29%, whereas allergy to thiuram mix is declining. Coupled reactivity exists between rubber additives, but a proportion of patients who reacted positively to carba mix and ZDEC did not react to thiuram mix. These findings suggest the need to add carba mix back into the EBS. There is a significant difference in the proportion of positive reactions to carba mix between investigator-loaded allergens and TRUE Test®, and clinicians should be aware of the possibility of false-negative and possibly also of false-positive results. As in previous European studies, there is inter-country variability of results, and the strong correlation of allergy to rubber additives with occupational hand dermatitis is confirmed.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Chemical constituents of carba, mercapto, thiuram and 'black rubber' mixes.

Table S2. Results with the rubber allergens patch tested in petrolatum, stratified for country.

Figure S1. Graphical illustration of time trend of positive reactions to rubber allergens 2004–2012, for those countries contributing since 2004.

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Table S1. Chemical constituents of carba, mercapto, thiuram and 'black rubber' mixes

Mix and constituent compounds	Petrolatum concentration (%)* (wt/wt)	Petrolatum concentration (mg/cm^2)	TRUE Test® concentration (mg/cm^2)
Mercaptobenzothiazole	2.0	0.8	0.075
Mercapto mix (three-component)	1.0	0.4	0.075
N-Cyclohexylbenzothiazyl sulfenamide	0.33	0.13	0.025
Dibenzothiazyl disulfide	0.33	0.13	0.025
Morpholinyl mercaptobenzothiazole	0.33	0.13	0.025
Mercapto mix (four-component, European baseline series)	2.0	0.8	–
N-Cyclohexylbenzothiazyl sulfenamide	0.5	0.2	
Dibenzothiazyl disulfide	0.5	0.2	
Morpholinyl mercaptobenzothiazole	0.5	0.2	
2-Mercaptobenzothiazole	0.5	0.2	
Thiuram mix (four-component, European baseline series)	1.0	0.4	0.025
Tetramethylthiuram monosulfide	0.25	0.1	0.006
Tetramethylthiuram disulfide	0.25	0.1	0.006
Tetraethylthiuram disulfide	0.25	0.1	0.006
Dipentamethylenethiuram disulfide	0.25	0.1	0.006
'Carba' mix	3.0	1.2	0.25
Diphenylguanidine	1.0	0.4	0.08
Zinc dibutyldithiocarbamate	1.0	0.4	0.08
Zinc diethyldithiocarbamate	1.0	0.4	0.08
'Black rubber' or 'PPD' mix	0.6	0.24	0.075
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine	0.1	0.04	0.013
N-cyclohexyl-*N*′-phenyl-*p*-phenylenediamine	0.25	0.1	0.031
N,*N*′-diphenyl-*p*-phenylenediamine	0.25	0.1	0.031

PPD, *p*-phenylenediamine.

*Assuming 20 mg dispensed into an 8-mm Finn Chamber® for pet.-based allergens.

Table S2. Results with the rubber allergens patch tested in petrolatum, stratified for country

Country	n tested	% pos.std	95%CI
(a) Thiuram mix, 1% pet.			
AT	1113	3.68	2.47–4.89
CH	5004	2.23	1.8–2.67
DE	7437	2.99	2.57–3.41
DK	2555	2.46	1.39–3.52
ES	3361	1.55	1.13–1.96
FI	1053	2.51	1.56–3.46
IT	8254	1.33	1.09–1.58
LT	865	0.5	0–1.01
NL	2821	2.6	2.01–3.19
PL	2828	1.31	0.89–1.74
SI	5224	1.34	1.03–1.65
UK	15 586	1.77	1.56–1.98
(b) Carba mix, 3% pet.			
ES	3361	1.55	1.13–1.98
IT	407	2.58	0.98–4.19
NL	2813	5.63	4.77–6.49
UK	10 144	1.57	1.32–1.81
(c) Zinc diethyldithiocarbamate, 1% pet.			
AT	1109	0.62	0.09–1.15
CH	4976	0.6	0.37–0.83
DE	7434	0.73	0.52–0.94
FI	705	0.26	0–0.61
(d) Mercapto mix (MBT, CBS, MBTS, MOR), 2% pet.			
DK	2571	0.59	0.08–1.1
ES	1359	0.33	0–0.67
IT	5667	0.21	0.09–0.32
NL	2821	1.31	0.89–1.74
PL	2827	0.45	0.18–0.71
SI	5224	0.47	0.27–0.67
UK	9379	0.49	0.34–0.64
(e) Mercapto mix (CBS, MBTS, MOR), 1% pet.			
AT	1113	0.65	0.1–1.2
CH	4991	1.03	0.73–1.32
DE	7482	1.01	0.75–1.26
ES	1951	0.43	0.12–0.74
FI	1056	0.2	0–0.49
IT	855	0.23	0–0.56
LT	865	0.47	0–1.08
UK	5108	0.44	0.25–0.62
(f) Mercaptobenzothiazole, 1% pet.			
AT	1113	0.71	0.16–1.27
CH	4998	0.95	0.66–1.24
DE	7480	0.76	0.54–0.99
DK	2566	0.51	0.05–1
ES	3361	0.46	0.23–0.69
FI	1056	0.58	0.11–1.04
IT	9248	0.33	0.21–0.44
LT	865	0.47	0–1.08
NL	2821	1.21	0.8–1.62
PL	2828	0.54	0.25–0.83
SI	5224	0.52	0.31–0.73
UK	15 590	0.55	0.43–0.67
(g) *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine, 0.1% pet.			
AT	1109	1.31	0.65–1.97
CH	4977	0.74	0.5–0.99
DE	7441	0.95	0.71–1.19
DK	2572	0.6	0.07–1.13
ES	3077	0.43	0.19–0.67
IT	6846	0.72	0.52–0.92
LT	865	0.95	0.21–1.7
NL	2822	1.47	1.01–1.93
PL	2828	0.78	0.45–1.11
SI	5224	0.56	0.35–0.77
UK	15 579	0.34	0.24–0.43

AT, Austria; CH, Switzerland; DE, Germany; DK, Denmark; ES, Spain; FI, Finland; IT, Italy; LT, Lithuania; NL, Netherlands; PL, Poland; SI, Slovenia; CBS, *N*-cyclohexylbenzothiazyl sulfenamide; MBT, 2-mercaptobenzothiazole; MBTS, dibenzothiazyl disulfide; MOR, morpholinyl mercaptobenzothiazole; % pos.std., proportion of positives, directly age-standardized and sex-standardized; 95%CI, 95% confidence interval to the standardized prevalence.

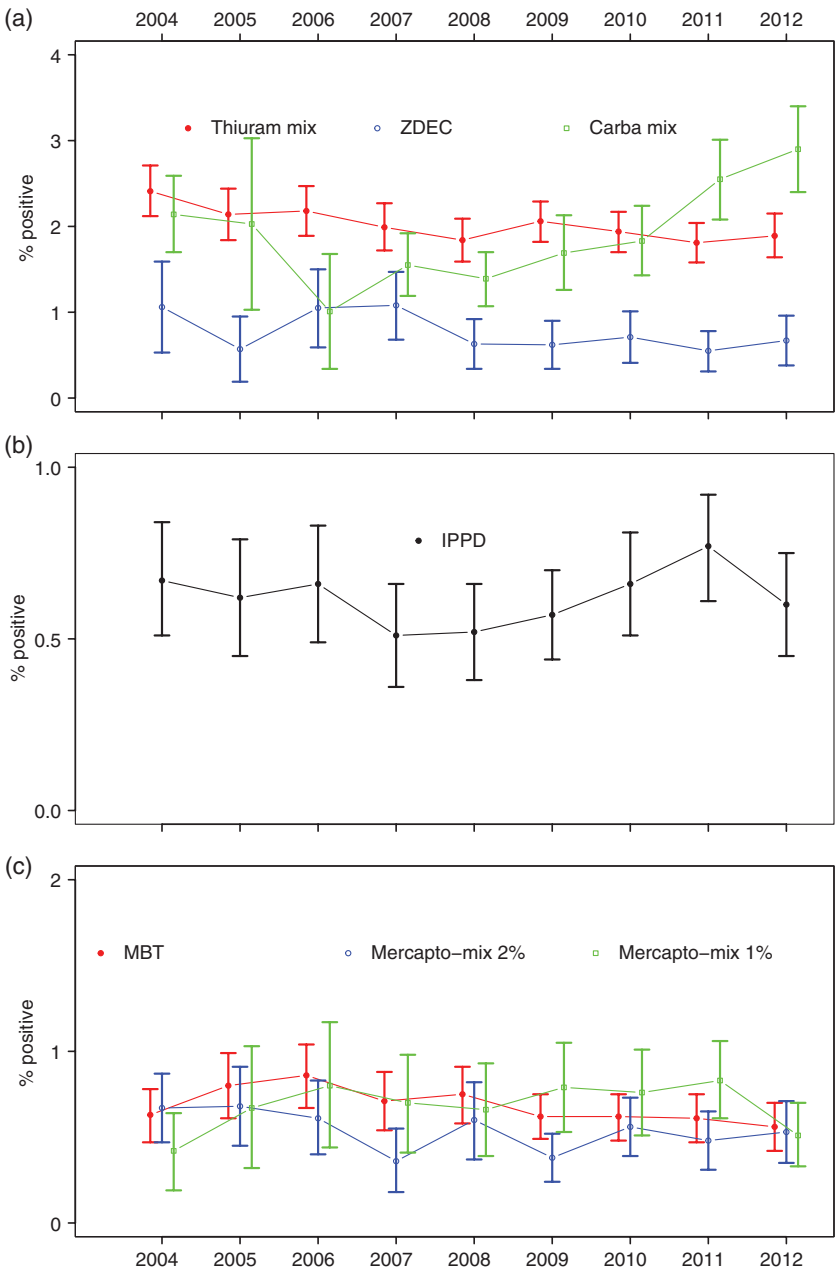

Fig. S1. Time trend of positive reactions 2004–2012, for those countries contributing since 2004. Prevalence rates are standardized for age and sex, and provided with 95% confidence intervals. The prevalence ratio (PR) with 2004 as the reference year and the corresponding *p*-value refer to the results of an age-adjusted and sex-adjusted log-binomial regression analysis. (a) Thiuram mix (PR: 0.961, $p < 0.001$), zinc diethyldithiocarbamate (ZDEC) (PR: 0.931, $p = 0.01249$), and carba mix (PR: 1.042, $p = 0.00254$). (b) *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine (IPPD) (PR: 1.008, $p = 0.64307$). (c) 2-Mercaptobenzothiazole (MBT) (PR: 0.966, $p = 0.02281$), mercapto mix 2% (PR: 0.952, $p = 0.02952$), and mercapto mix 1% (PR: 1.019, $p = 0.4397$).