

UK rates of occupational skin disease attributed to rubber accelerators, 1996–2012

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Summary

Background. Natural and synthetic rubbers containing rubber accelerators are well-known causes of allergic contact dermatitis (ACD). Latex contact urticaria (CU) has been widely reported, especially when powdered latex glove use was commonplace. Consequently, interventions to reduce latex exposure by altering glove manufacture were introduced.

Objective. This study aimed to analyse trends in UK-reported incidence of occupational skin disease associated with rubber accelerators.

Method. We analysed cases reported to EPIDERM (part of The Health and Occupation Research network) of occupational ACD caused by natural and synthetic rubber products, between 1996 and 2012.

Results. For the studied period, a decreasing incidence of ACD associated with rubber products was found, with an average annual change of -1.2% [95% confidence interval (CI) -3.1 to 0.7]. The number of cases of latex CU ($n = 580$) significantly declined. The number of cases of ACD caused by mercapto mix and mercaptobenzothiazole ($n = 177$) and thiuram mix ($n = 603$) also declined. Reports of ACD associated with carba mix and its constituents ($n = 219$) increased significantly, by an average annual percentage of 10.1% (95% CI $6.1-14.2$). Twenty-six cases of ACD caused by rarer rubber compounds were identified, highlighting skin disease attributable to less widely recognized chemicals.

Conclusions. These data show a falling reported incidence of occupational ACD attributed to rubber chemicals, but within this a significant rise attributable to the constituents of the carba mix. Clinicians should recognize the changing diversity of chemicals used in rubber manufacturing, and consider including carba mix in their baseline series and testing beyond this in suspect cases to avoid false-negative results.

Key words: allergic contact dermatitis; contact urticaria; epidemiology; latex; occupational; rubber; rubber accelerators.

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Natural and synthetic rubbers containing rubber accelerators are well-known causes of occupational skin disease.

In 1992, in response to growing concerns about the spread of blood-borne viruses, guidance was produced (1) to reduce exposure to body fluids through 'universal precautions'. The subsequent widespread use of personal protective equipment, such as powdered latex gloves, led to an increase in reported latex-induced occupational skin disease, including allergic contact dermatitis (ACD) and latex contact urticaria (CU) (2).

International and national interventions to reduce occupational exposure to latex (3–5) have been shown to coincide with a downward trend in latex-induced occupational ACD (although not all occupational skin disease), especially among healthcare workers (6–10). This decline in ACD may be associated with the use of low-protein powder-free latex gloves and latex alternatives.

Altered glove composition as a consequence of manufacturers' efforts to decrease exposure to latex may have an impact on the causes and rates of ACD seen in clinical practice. Rubber accelerators are added during the manufacturing process to speed up rubber vulcanization, but residual amounts remain in gloves and are released during use, potentially leading to type IV sensitization. Chemicals including carbamates, thiurams and benzothiazoles are commonly used vulcanizing agents. In addition, antioxidants designed to reduce rubber deterioration, such as so-called 'black rubber' chemicals, may be included in rubber processing.

This study aimed to analyse changing trends in the UK-reported incidence of occupational skin disease associated with rubber accelerators since 1996. Reactions to all rubber products were included in the analysis. This analysis was carried out with data collected within The Health and Occupational Research network (THOR) (11).

Patients and Methods

This study analysed incident case reports, originating from clinical specialists in dermatology, of ACD and CU associated with natural and synthetic rubber products that were returned to a UK-wide surveillance scheme (EPIDERM) between 1996 and 2012. EPIDERM was established in 1993 (12), and is a component of THOR; EPIDERM reporters are asked to submit new cases of occupational skin disease seen in their clinical practice during their allocated reporting period [which can be every month ('core' reporters), or for one, randomly chosen month per year ('sample' reporters)]. The collated variables include diagnosis, employment, suspected

Table 1. Number of actual cases of allergic contact dermatitis attributed to rubber agents, 1996–2012

Agents	Search terms	Number of actual cases
Thiuram mix	Thiuram Tetramethylthiuram monosulfide Tetramethylthiuram disulfide Tetraethylthiuram disulfide Dipentamethylenethiuram disulfide	603
Carba mix	Carba Dithiocarbamates Zinc diethyl dithiocarbamate Zinc dibutyl dithiocarbamate Diphenylguanidine (DPG)	219
Mercapto mix and mercaptobenzothiazole	Mercapto Mercaptobenzothiazole (MBT) <i>N</i> -cyclohexyl-2-benzothiazolesulfenamide Dibenzothiazyl disulfide Morpholinyl mercaptobenzothiazole	177
IPPD	'Black rubber', <i>N</i> -isopropyl- <i>N'</i> -phenyl- <i>p</i> -phenylenediamine (IPPD)	84
Other agents	Cyclohexylthiophthalimide Diaminodiphenylmethane Dithiodimorpholine Thiourea Hexamethylenetetramine Total other	14 2 1 4 5 26

agents, and demographic data. The time period chosen for this study excluded the pilot period for EPIDERM (1993–1995 inclusive). On average, 190 dermatologists per year reported to EPIDERM over the time period 1996–2012. The British baseline series includes carba mix 3% pet., thiuram mix 1% pet., mercapto mix 2% pet., mercaptobenzothiazole (MBT) 2% pet., and *N*-isopropyl-*N'*-phenyl-*p*-phenylenediamine (IPPD) 0.1% pet. Other rubber chemicals were tested at the discretion of the reporting physician.

Case reports of ACD attributed to rubber agents reported to EPIDERM between 1996 and 2012 were identified with the search terms outlined in Table 1 and grouped as indicated.

Statistical analysis

To investigate the change in incidence of reports associated with rubber accelerators over time, the STATA™ software command *xtnbreg* was used, which

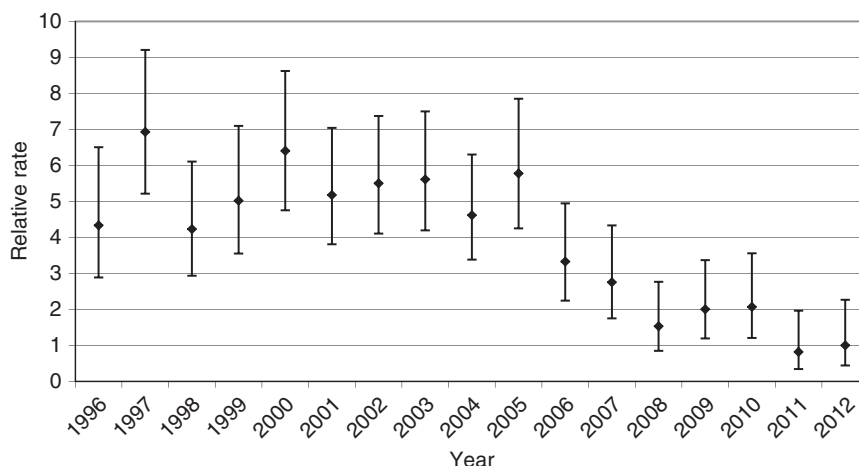


Fig. 1. Relative rates (with 95% confidence intervals) by year for contact urticaria attributed to latex reported to EPIDERM 1996–2012.

fits longitudinal, negative binomial (i.e. over-dispersed) models with a beta-distributed random intercept term (13). These models are also known as multi-level models with a hierarchical structure, whereby the repeated reporting occasions over time are nested within individual reporters. The dependent variable was the number of cases, including zeros, per reporter per month. This method is able to correctly allow for variation in the number of reports between reporters (e.g. core versus sample and attributable to non-response). The main predictor of interest, calendar time, was represented either as a categorical variable with 2012 as the base year for comparison, or as a continuous variable with a scale of years. Variables representing 'season', 'reporter type' ('core' or 'sample'), 'first month as a new reporter' and 'first month as a new "core" reporter' were also included.

Ethics

Multicentre Research Ethics Committee approval has been granted to THOR (Reference number MREC 02/8/72).

Results

CU associated with latex exposure

In total, between 1996 and 2012, 580 cases of CU were reported to EPIDERM in which latex was cited as the causal agent. An average annual reduction in case reporting of 7.8% [95% confidence interval (CI) −9.9 to −5.6] was found over this time period. This is shown in Fig. 1, with relative rates by year; 2012 was set as the year for comparison with other years (that is, the relative rate for 2012 was 1).

ACD associated with rubber agents

Between 1996 and 2012, thiuram mix and its ingredients were the most commonly identified rubber agents causing ACD ($n = 603$ cases), followed by carba mix and its ingredients ($n = 219$), benzothiazoles ($n = 177$), IPPD ($n = 84$), and other agents ($n = 26$), as shown in Table 1.

Over this time period, an average annual percentage change of −1.2% (95% CI −3.1 to 0.7) in the reported incidence of work-related ACD attributed to rubber agents was found.

Trends for ACD associated with individual mixes

A decreasing incidence in ACD cases was shown between 1996 and 2012, associated with exposure to both thiuram mix (average annual percentage change of −2.20%; 95% CI −4.5 to 0.1) and benzothiazoles (average annual percentage change of −3.2%; 95% CI −6.9 to 0.6), although this was not statistically significant at the 95% level. This is shown in Figs. 2 and 3 as relative rates by year; 2012 was set as the year of comparison for other years (that is, the relative rate for 2012 was 1).

In comparison, relative rates for ACD associated with exposure to carba mix and its ingredients showed an increasing incidence, with an average annual percentage increase of 10.1% between 1996 and 2012 (95% CI 6.1–14.2), as shown in Fig. 4.

ACD cases associated with exposure to IPPD and 'other' accelerators had insufficient numbers for statistical modelling of average annual percentage change. The details of more diverse rubber accelerator chemicals associated with 26 reported cases are given in Table 1.

Discussion

This study aimed to investigate changing trends in UK-reported CU caused by latex and ACD associated with

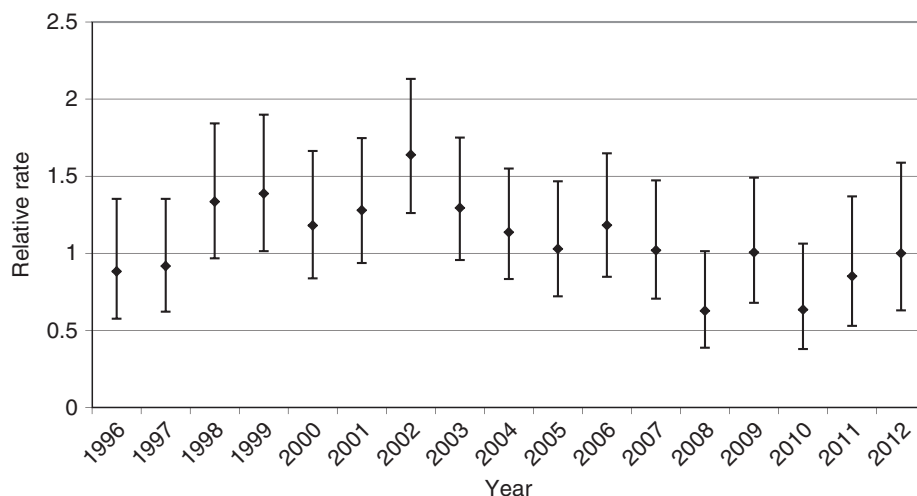


Fig. 2. Relative rates (with 95% confidence intervals) by year for allergic contact dermatitis (ACD) attributed to thiuram mix and its constituents, as reported to EPIDERM 1996–2012.

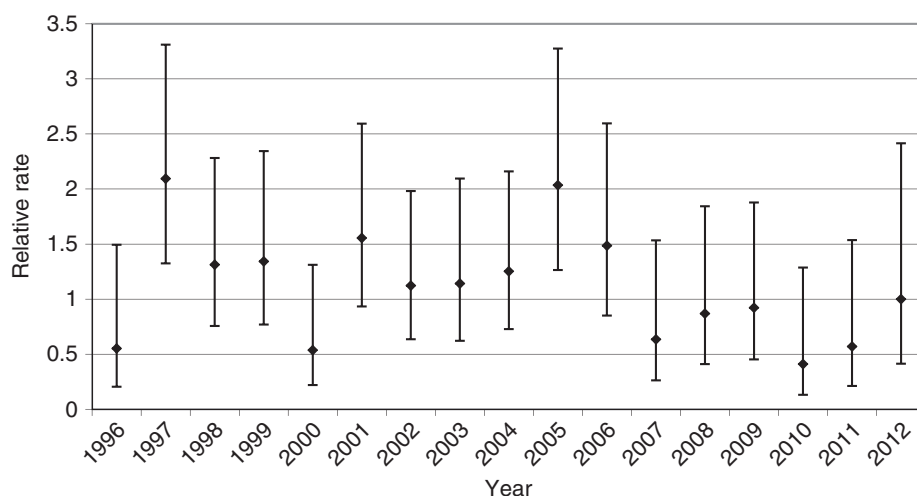


Fig. 3. Relative rates (with 95% confidence intervals) by year for allergic contact dermatitis attributed to benzothiazoles, as reported to EPIDERM 1996–2012.

rubber accelerators, as reported to EPIDERM from 1996 to 2012. EPIDERM data collection is based on incident case reporting to a UK-wide surveillance scheme for occupational skin disease.

This study shows a statistically significant decline in type I immediate hypersensitivity (CU) associated with latex exposure from 1996 to 2012. This is a trend that has previously been reported in other epidemiological studies of urticaria (8, 14), and has also been observed in respect to occupational asthma (15). Within the EPIDERM dataset, the most apparent decline in CU associated with latex exposure was from 2006 onwards, which is likely to have coincided with interventions aimed at reducing

exposure to sensitizing latex gloves. This is in keeping with a previous EPIDERM-based study, which showed a downward trend in all cases of CU associated with latex exposure when three time periods were compared between 1996 and 2007 (6).

Thiurams are comparatively cheap and well-established rubber vulcanizing agents. Worldwide, thiurams have been considered to be the most common rubber contact allergen chemicals causing type IV hypersensitivity reactions (16). Our study confirms this finding, with cases of ACD associated with thiuram mix totalling 603, more for than all other agents combined, over the study time period. However, this finding could indicate

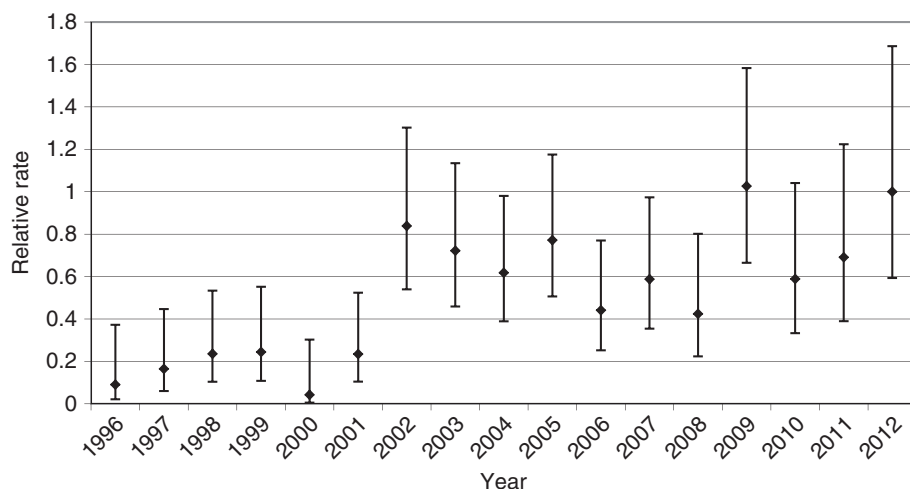


Fig. 4. Relative rates (with 95% confidence intervals) by year for allergic contact dermatitis attributed to carba mix and its constituents, as reported to EPIDERM 1996–2012.

more awareness of the association between these chemicals and ACD, and subsequent increased patch testing rates for thiuram mix ingredients plus underreporting of other possible chemical exposures.

In recent years, the sensitization frequency associated with thiuram mix and its constituents has appeared to decline in both occupational and non-occupational studies (14, 17–21). This decline is mirrored in this study's findings in an occupational cohort, with an average annual percentage change of -2.20% (95% CI -4.5 to 0.1) between 1996 and 2012, and with the highest relative rate in 2002. Glove analysis studies (22, 23) have shown that thiurams are infrequently detected in analysed gloves, supporting the observations of Geier et al. (20) that thiurams are now frequently replaced with other rubber accelerators by most international rubber-glove manufacturers, thus providing an explanation for the reduction in clinical cases of ACD associated with thiuram exposure.

Benzothiazoles are rarer causes of ACD, and are found in a variety of occupational exposure sources. Although nitrile gloves and shoes remain the most common sources of MBT, many industrial chemicals and veterinary preparations also contain this compound. Our study found 177 cases of ACD associated with MBT and related chemicals in natural and synthetic rubber from 1996 to 2012, with trends analysis indicating declining rates. This finding is consistent with other reports in the literature that the frequency of ACD is declining (24). Clinicians should be aware that both MBT and mercapto-mix should be used in patch testing to avoid false-negative results (25). The European and British baseline series include mercapto-mix with MBT, although mercapto-mix without MBT has proven more stable and is used in some centres (25, 26).

This study shows a significant rise in the frequency of occupational contact allergy attributable to carba mix and its ingredients between 1996 and 2012, with an average annual percentage increase of 10.1% (95% CI 6.1 – 14.2). In the United Kingdom, carbamates are routinely tested as a carba mix in the baseline series, which includes 1,3-diphenylguanidine (1,3-DPG), zinc dibutyl dithiocarbamate, and zinc diethyl dithiocarbamate.

Other work had also suggested this trend associated with carba mix (23), but until now this had not been shown statistically. A recently published study from the North American Contact Dermatitis Group reporting the 2009–2010 patch test results found prevalence rates of 3.1% and 4.6% positive patch test reactions to thiuram mix and carba mix respectively (sample size of 4308 patients), a reversal in the frequency of positive results between the two mixes (27). It should be noted that only 10% of these cases were occupational. However, this finding was not supported by a large 2012 retrospective analysis of prevalence, in which, of all occupational ACD patients, 13% were sensitized to thiurams and 3.5% to dithiocarbamates, with no change in time trends (16). This was a study from Germany, where zinc diethyl dithiocarbamate is the only carbamate tested within the baseline series, and this may explain why no change was shown. Other recent reports have highlighted increasing sensitization to 1,3-DPG (part of the carba mix) attributable to gloves (28–30).

The increase in carbamate sensitivity is likely to be related to the fact that many of the manufactured gloves that are free from MBT and thiurams now contain carbamates, therefore making it difficult to obtain carbamate-free gloves (20). In addition, studies have shown that, because of similar chemical structures, sensitization to dithiocarbamates is almost always found

concomitantly with thiuram sensitization, leading to the recommendation that carba mix should be removed from the standard series (31). This was disputed, with an analysis of 5986 patients showing that 84 cases of ACD caused by rubber would have been missed had the carba mix been excluded (32). Conversely, only approximately one-quarter of thiuram-positive patients also react to carbamates (16). As previously mentioned, carbamates are commonly tested as a carba mix. If carbamate allergy is strongly suspected, 1,3-DPG should be tested separately, as 1,3-DPG's tendency to act as a skin irritant (within the carba mix) may lead to false-positive results.

Although 84 cases of ACD associated with black rubber mix chemicals were identified in this study, the small number of case reports precluded the formal trends analysis that was applied in this study for other accelerators. Other studies have shown that IPPD sensitization remains relatively rare among healthcare workers (23), but that sensitization is more common in workers involved in industrial black rubber use.

Of interest in this study was the identification of a more diverse range of chemicals causing occupational ACD.

These specific chemicals are listed in Table 1, and were associated with 26 cases over the study period. It is likely that the true figure is underreported, with data being reliant on clinician identification and reporting. The use of these chemicals in association with the decreased use of latex and thiurams is important in relation to the rates of occupational skin disease. Accordingly, clinicians should consider patch testing for these rarer chemicals, which are not routinely included in baseline series.

Conclusion

This study shows a significant rise in occupational ACD attributable to carba mix and its ingredients since 1996. There was also a reduction in the number of cases associated with benzothiazoles and thiuram compounds. In addition, it is apparent that cases of skin disease attributable to less widely recognized rubber chemicals exist. Clinicians should recognize the changing and increasing diversity of chemicals used in rubber manufacturing, and consider including carba mix within the baseline series and testing beyond the baseline series to avoid false-negative results.

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