

Patch testing with rubber series in Europe: a critical review and recommendation

Katharine L. Warburton¹, Wolfgang Uter², Johannes Geier³, Radoslaw Spiewak⁴, Vera Mahler⁵, Marie-Noëlle Crépy⁶, Marie-Louise Schuttelaar⁷, Andrea Bauer⁸ and Mark Wilkinson¹

¹Department of Dermatology, Chapel Allerton Hospital, Leeds, LS7 4SA, UK, ²Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, 91054 Erlangen, Germany, ³Information Network of Departments of Dermatology (IVDK), University Medical Centre, 37075, Goettingen, Germany, ⁴Department of Experimental Dermatology and Cosmetology, Jagiellonian University Medical College, 30-688 Krakow, Poland, ⁵Department of Dermatology, University Hospital of Erlangen, 91054 Erlangen, Germany, ⁶Department of Occupational Diseases, Centre Hôtel-Dieu, AP-HP, Paris University Hospital, 75004 Paris, France, ⁷Department of Dermatology, University Medical Centre Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands, and ⁸Department of Dermatology, University Allergy Centre, University Hospital Carl Gustav Carus, Technical University Dresden, 01307 Dresden, Germany

doi:10.1111/cod.12736

Summary

Background. Rubber additives constitute an important group of contact allergens, particularly in certain occupations.

Objectives. To collect information regarding the current practice of using a 'rubber series' in Europe, and discuss this against the background of evidence concerning the prevalence of allergy in order to derive a recommendation for a 'European rubber series'.

Methods. The following were performed: (i) a survey targeting all members of the COST action 'StanDerm' consortium, (ii) analysis of rubber contact allergy data in the database of the European Surveillance System on Contact Allergies, and (iii) a literature review.

Results. Information from 13 countries was available, from one or several departments of dermatology, and occasionally occupational health. Apart from some substances tested only in single departments, a broad overlap regarding important allergens was evident, but considerable variation existed between departments.

Conclusions. An up-to-date 'European rubber series' is recommended, with the exclusion of substances only of historical concern. A 'supplementary rubber series' containing allergens of less proven importance, requiring further analysis, is recommended for departments specializing in occupational contact allergy. These should be continually updated as new evidence emerges.

Key words: clinical epidemiology; contact allergy; patch testing; rubber additives; standardization.

Correspondence: Dr Mark Wilkinson, Department of Dermatology, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK. Tel: +44 113 3924357. E-mail: mark.wilkinson15@nhs.net

Conflicts of interest: J. Geier has received reimbursements for scientific advice from the German association of manufacturers of protective gloves and skin protectors (Bundesverband Handschutz e.V.). M.-N. Crépy has received lecture fees from GlaxoSmithKline (alitretinoin). R. Spiewak is an advisor to Instytut Dermatologii sp. z o. o., and owns shares in the company. S. M. Wilkinson has attended a drug advisory board meeting for GlaxoSmithKline (alitretinoin). V. Mahler has received a speaker's fee from SmartPractice Germany, and has served on a medical advisory board on medical gloves for Hutchinson Santé, France. W. Uter has accepted travel reimbursement and honoraria for presentations given to cosmetic industry (associations), and has received a lecture fee from Almirall Hermal for an educational lecture on contact allergy. The other authors do not declare a conflict of interest pertinent to this study.

Accepted for publication 27 October 2016

Rubber products, comprising natural (rubber latex) or synthetic elastomers, are widely used in everyday and working life. Rubber additives, either as remnants from the production process (such as accelerators) or those deliberately added to enhance the product characteristics (such as antioxidants), constitute an important group of contact allergens. At present, four of 30 allergens recommended in the European baseline series (1, 2) are rubber additives, namely, thiuram mix 1% pet., 2-mercaptobenzothiazole (MBT) 2% pet., mercapto mix (with four constituents, including MBT) 2% pet., and *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine (IPPD) 0.1% pet.. Many departments patch test with special 'rubber series' in patients for whom rubber allergy is initially suspected, or in those who react positively to one of the rubber mixes of the baseline series. Commercial suppliers of patch test materials cater for this need by providing ready-to-order test series termed 'rubber additive series' or 'rubber additives'. Information on suppliers of patch test materials is available from the ESCD website (see: www.escd.org).

The most frequent rubber exposures leading to sensitization to rubber components are from protective gloves (3, 4), often used in an occupational context. The appropriate testing and identification of allergens is essential for secondary and tertiary prevention and the medico-legal consequences of occupational disease.

The present article reviews current practice regarding the use of rubber patch test series, and discusses the findings in relation to information on contact allergy prevalence, to derive a proposed 'European rubber series'.

Methods

The first aim of this study was to collect information on current practice regarding the set of allergens, together with their test concentrations and vehicles, used as part of the 'rubber series' in dermatological (including occupational dermatology) departments across Europe. For this purpose, the following approaches were used:

- (1) The database of the European Surveillance System on Contact Allergies (ESSCA) (www.essca-dc.org), containing patch test results obtained since 2002 and information on the patch test series used to obtain these, was searched to identify rubber series allergens. The results of this search from 2013 to 2014 are reported in a separate publication (5), detailing the frequencies of reactions to individual allergens.
- (2) Members of the StanDerm (COST action TD1206) consortium (www.standerd.eu), which provides nearly complete geographical coverage of Europe,

were requested by e-mail to fill in a simple electronic questionnaire (spreadsheet) listing the allergens used locally in their rubber series.

The second aim was to provide a recommended European rubber series. The allergens identified with the above methods were combined with a literature review. Publications in the last 15 years were screened via PubMed, with the search terms 'rubber allergy' and 'glove allergy', in order to identify reports containing relevant information (actual patch test results, and aspects raised in the discussion of these, were also used). Substances that were to be regarded (i) as proven, common contact allergens or (ii) as more rare allergens, but with widespread exposure, would qualify for inclusion in the European rubber series. Other substances with less evidence concerning importance as contact allergens clinically, but with widespread exposure, which also need further investigation, would be included in a supplemental test series, used predominantly in specialized departments and scientifically evaluated in the short term. This approach mirrors that used by Uter et al. for the hair cosmetic series in Europe (6).

Results

StanDerm survey information was obtained from 18 departments, covering 13 European countries. ESSCA database information yielded rubber series data from 23 departments, covering seven of the 12 European countries that participate, as some other departments and countries contribute only baseline series data. The set of substances identified with the above combined strategies are shown in Table 1. The current use of these substances is shown in Table 1 by providing information on the number of countries (represented by one or several departments) using the respective substance. Some single departments used additional chemicals in their rubber series, predominantly resins, which were not included in this analysis. Similarly, other elastomers (such as polyurethane and PVC) are not dealt with in this review.

Discussion

The suggested composition of a basic European rubber series, considered to be optimal at the time of writing, is summarized in Table 2, with possible extensions being shown in Table 3. It is important to always consider more extended patch testing with preservatives, stabilizers, plasticizers, and other markers beyond the allergens included in this particular series, which should be based on the patient's history. The need to continually review and adapt such a series, to maintain good diagnostic relevance, is of ongoing significance.

Table 1. Substances used in rubber production that have been employed in a 'rubber series' in more than one department in Europe, grouped according to class and function

Name	Maximum concentration (%)	Other names	CAS no.	n	Remarks
Accelerators					
Thiurams					
Tetramethylthiuram disulfide	1		137-26-8	13	*
Tetramethylthiuram monosulfide	1		97-74-5	13	*
Tetraethylthiuram disulfide (disulfiram)	1		97-77-8	13	*
Dipentamethylenethiuram disulfide	1		94-37-1	12	
Dipentamethylenethiuram tetrasulfide	0.25		120-54-7	2	
Dithiocarbamates					
Zinc diethyldithiocarbamate	1		14324-55-1	12	
Zinc dibutyldithiocarbamate	1		136-23-2	11	
Zinc dimethyldithiocarbamate	1		137-30-4	6	
Zinc dibenzoyldithiocarbamate	1		14726-36-4	2	
Benzothiazoles					
2-Mercaptobenzothiazole	2		149-30-4	9	†
N-cyclohexyl-2-benzothiazyl sulfenamide	1		95-33-0	12	†,‡
Dibenzothiazyl disulfide	1		120-78-5	11	
Morpholinylmercaptobenzothiazole	1	2-(4-morpholinylmercapto) benzothiazole	102-77-2	11	
Guanidines					
1,3-Diphenylguanidine	1		102-06-7	12	
Thioureas					
Dibutylthiourea	1	N,N'-dibutylthiourea	109-46-6	10	†
Diphenylthiourea	1	N,N'-diphenylthiourea	102-08-9	9	†
Diethylthiourea	1	N,N'-diethylthiourea	105-55-5	6	
Thiourea	0.1		62-56-6	6	‡
Antidegradants					
'Black rubber' chemicals					
N,N'-diphenyl-p-phenylenediamine	1		2350-01-8	10	
N-isopropyl-N-phenyl-4-phenylenediamine	0.1		101-72-4	9	
N-cyclohexyl-N-phenyl-4-phenylenediamine	1		101-87-1	8	‡
N,N-di-2-naphthyl-4-phenylenediamine	1	Di-β-naphthyl-p-phenyl enediamine	93-46-9	5	
Other antioxidants					
4,4'-Diaminodiphenylmethane	0.5		107-77-9	9	§
N-phenyl-2-naphthylamine	1	Phenyl-β-naphthylamine	135-88-6	7	
2,2,4-Trimethyl-1,2-dihydroquinoline	1		147-47-7	5	
4,4'-Dihydroxybiphenyl ether	0.1	4,4'-Dihydroxydiphenyl	92-88-6	3	
Butylated hydroxyanisole	2		9009-68-1	3	‡
Monobenzene	1	Monobenzylether of hydroquinone, 4-(benzyloxy)phenol	103-16-2	2	
Bonding agents					
Methenamine	2	Hexamethylene tetramine	100-97-0	9	
Retarders					
Cyclohexyl thiophthalimide	1	N-(Cyclohexylthio)phthalimide	17796-82-6	10	
Dodecyl mercaptan	0.1		112-55-0	7	
Stabilizers					
Ethylenediamine dihydrochloride	1		333-18-6	3	
4-tert-Butylcatechol	0.25	p-tert-Butylcatechol	98-29-3	2	
Plasticizers					
Di-2-ethylhexyl-phthalate	5		117-81-7	4	‡
Dibutylphthalate	5	Di-n-butylphthalate	84-74-2	3	‡
Dimethylphthalate	5		131-11-3	2	‡

n, number of countries reporting actual use of rubber substance within their 'rubber series'.

All chemical substances in pet. as vehicle. For countries where more than one department contributed data, all were in concordance for substances used in their rubber series, except for Italy and Germany.

*Used in Trieste, but not Genoa.

†Used in Genoa, but not Trieste.

‡Used in Osnabrück, but not Bern.

§Used in Bern, but not Osnabrück.

Table 2. Suggested European rubber series; all allergens are available as commercial patch test preparations

	% (all in pet.)
Tetramethylthiuram disulfide	1.0
Tetramethylthiuram monosulfide	1.0
Tetraethylthiuram disulfide (Disulfiram)	1.0
Dipentamethylenethiuram disulfide	1.0
Zinc dibutyldithiocarbamate	1.0
Zinc diethyldithiocarbamate	1.0
1,3-Diphenylguanidine	1.0
2-Mercaptobenzothiazole	2.0 (as part of the baseline series)
<i>N</i> -cyclohexyl-2-benzothiazyl sulfenamide	1.0
Dibenzothiazyl disulfide	1.0
Morpholinylmercaptobenzothiazole	1.0
Dibutylthiourea	1.0
Diphenylthiourea	1.0
Diethylthiourea	1.0
<i>N</i> -isopropyl- <i>N</i> -phenyl-4-phenylenediamine	0.1 (as part of the baseline series)
<i>N</i> -cyclohexyl- <i>N</i> -phenyl-4-phenylenediamine	1.0
<i>N,N'</i> -diphenyl- <i>p</i> -phenylenediamine	1.0
<i>N,N</i> -di-2-naphthyl-4-phenylenediamine	1.0
Cyclohexyl thiophthalimide	0.5
Own gloves	'as is' (both sides)

General considerations for including substances in a test series

There is a need to continually adapt this series. Sensitivities closely follow glove and occupational exposures, which may change if legislation comes into place limiting the use of some chemicals (as has happened previously in terms of primary prevention reducing allergic contact urticaria caused by natural rubber latex) (7). An awareness of potential new sensitizers is vital. These are often described through case reports initially, with further studies on larger numbers of patients being required to provide data regarding patch test concentrations and vehicles.

Accelerators

A range of chemicals are used to speed up the process of rubber vulcanization, and these constitute the most frequent contact allergens among rubber chemicals. Slow accelerators are thiourea derivatives and amines; moderately fast accelerators are 1,3-diphenylguanidine (DPG), mercaptobenzothiazoles, and sulfonamides; and very fast accelerators are thiurams, dithiocarbamates, and thio-phosphates (8).

Table 3. Allergens suggested as temporary additions to a European rubber series for monitoring purposes

	% (all in pet.)
<i>N</i> -phenyl-2-naphthylamine	1.0
4,4'-Diaminodiphenylmethane	0.5
Methenamine	1.0 or 2.0 (optimum concentration yet to be clarified)
Cetylpyridium chloride	0.1 (optimum concentration yet to be clarified)
Ethylenediamine dihydrochloride	1.0
4- <i>tert</i> -Butylcatechol	0.25

Country-specific legislation may apply; for example, the Swedish Work Environment Agency's provision on Chemical Hazards in the Working Environment (AFS 2014:43) does not permit *N*-phenyl-2-naphthylamine to be used in concentrations of 1% and above without authorization.

Thiurams. The most frequently tested rubber chemicals by country were the thiurams, which would seem appropriate, given their well-documented status as rubber allergens (4, 9–11). A recent ESSCA study (11) from 2004 to 2012 found the prevalence of sensitization to thiuram mix to be 1.87%, although the prevalence was steadily declining, as thiurams in manufactured gloves have been largely replaced by dithiocarbamates (3, 9, 12).

The four constituents of the thiuram mix (tetramethylthiuram disulfide, tetramethylthiuram monosulfide, tetraethylthiuram disulfide, and dipentamethylene thiuram disulfide), are currently tested as a mix within the European baseline series at 1% in pet., although the data suggest that ~20% of thiuram-sensitized patients are missed by the mix (4), so individual components should be tested as part of the rubber series when rubber allergy is suspected. Five countries reported testing these chemicals at the same concentration as used in the thiuram mix (0.25%); the remainder tested each chemical at 1% in pet. as part of their rubber series. Consistently, both the thiuram mix and the carba mix cause more reactions than the single ingredients combined (5). Regarding the thiuram mix, there has been criticism that patch testing with the single thiurams in the same concentration as they are used in the mix, that is, 0.25%, will result in the underdiagnosis of contact allergy. However, the present, albeit limited, results obtained with single thiurams tested at 1% pet. do not show a greater concordance with the mix (5, 13). Thus, it seems warranted to further study the clinical implications of thiuram mix reactions supported by positive reactions to a single constituent or single constituents as compared with isolated reactions to the mix.

Dipentamethylenethiuram tetrasulfide (DPTT) 0.25% pet. is a thiuram chemical that is tested in the rubber

series of two countries. Only one positive reaction has been reported in the literature, in 1996 in a study of 19 Japanese farmers wearing rubber boots (14). No positive reactions were found in recent ESSCA rubber series data (5). It therefore does not seem appropriate to include DPTT in a European rubber series.

Dithiocarbamates. This group of chemicals includes zinc diethyldithiocarbamate (ZDEC), zinc dibutyldithiocarbamate (ZDBC), zinc dimethyldithiocarbamate (Ziram), and zinc dibenzylthiocarbamate. The former two agents are tested alongside DPG as part of the carba mix in some centres. The prevalence of positive reactions to carba mix is steadily increasing (3, 11), with some experts calling for its inclusion in the European baseline series (15). However, the carba mix is a controversial allergen mix, as it is difficult to test. It is marginally irritating, and therefore can potentially cause false-positive reactions (16). The increasing prevalence of positive reactions to the carba mix is likely to represent true sensitization, as it is not clear why irritation caused by the carba mix should increase over time. In the case of a positive test reaction to carba mix, retesting has to be performed, because the responsible allergen, DPG or a dithiocarbamate, is still unknown. While the debate continues, we recommend including ZDEC and ZDBC in a rubber series.

The existing evidence, however, would suggest that DPG may be the responsible component. Thiuram disulfides and dithiocarbamates constitute a redox pair in equilibrium and in which the thiurams are better markers for sensitization to the dithiocarbamate/thiuram redox pair (17). A recent study has also shown no clinical advantage of testing with carbamates over thiurams to detect allergy to these compounds (18).

Recent data (5) have shown 0.32% positive results in patch testing with Ziram in cases of suspected rubber allergy ($n = 625$). However, there is no literature in the last 15 years regarding its relevance in rubber allergy, and it probably represents historical relevance only. It is therefore excluded from our recommended series.

Zinc dibenzylthiocarbamate is currently included in the rubber series of only two countries. A 2003 study (19) investigated the relevance of testing with this chemical. It was concluded that patch testing at 1% pet. would provide no further information on patients with suspected rubber allergy. There were no positive reactions in 1380 patients tested. Therefore, it is excluded from our rubber series recommendation.

1,3-Diphenylguanidine. DPG is not a carbamate, despite its inclusion in the carba mix; this is a source of potential confusion. To keep the diagnostic procedure short and to

avoid confusion, it may be preferable to patch test with DPG and ZDEC instead of the carba mix, or – for study purposes – to at least apply carba mix together with its three ingredients (5). This appears to be already occurring in the majority of the European countries that submitted data. DPG is recognized to cause irritant reactions, and further work on an optimal patch test concentration may be needed (18). However, allergy to DPG may account for the observed increase in contact allergy to the carba mix (see above), as a consequence of its increased use in gloves, and is recommended for inclusion.

Triphenylguanidine has also been reported to be increasingly present and to cause contact allergy from exposure to surgical gloves (20), but there are, as yet, insufficient data to recommend its inclusion.

Benzothiazoles. The four constituents of the mercapto mix [MBT, *N*-cyclohexyl-2-benzothiazyl sulfenamide (CBS), dibenzothiazyl disulfide (MBTS), and morpholinylmercaptobenzothiazole (MOR)] are tested as part of the European baseline series at 2% pet., and MBT is tested separately at 2% pet. MBT derivatives are metabolized or converted to MBT in the skin, and MBT is the allergen responsible for contact allergy in this chemical group (21). Chemical analyses of patch test preparations showed that the concentration of MBT was unstable in the four-component mix. In contrast, the concentrations of CBS, MBTS and MOR proved to be stable in the three-component mix without MBT. Therefore, Hermal (Trolab) switched from the four-component mix ($4 \times 0.5\%$, including MBT) to a three-component mercapto mix ($3 \times 0.33\%$, without MBT) in 1995 (22). Several studies have shown that patch testing with either MBT alone or a mercapto mix alone would miss 20–30% of patients sensitized to benzothiazoles (23–25). A combination of MBT and the three-component mercapto mix in the baseline series identifies 86% of patients (4), and was therefore recommended for screening purposes (24, 26). It is recommended that MBT and its derivatives CBS, MBTS and MOR be tested separately as part of a rubber series to maximize allergy identification in this group.

Compound allergy. During vulcanization, new compounds can be formed by reactions between thiurams/dithiocarbamates and/or mercaptobenzothiazoles (27). 2-Dimethylthiocarbamyl benzothiazole sulfide (DMTBS) (CAS no. 3432-25-5, molecular weight 254) is such a newly formed component, with proven patch test positivity in relation to rubber (17). Clinicians should be aware of the potential for compound allergy, and to

test with patient glove samples, but DMTBS is not recommended for inclusion in a rubber series, owing to a lack of data on the wider applicability of the allergen.

Thioureas. The thioureas are predominantly used in the production of chloroprene products and foam rubbers (8), and are only rarely relevant in occupational glove allergy (4, 9). Dibutylthiourea and diphenylthiourea are more commonly tested than diethylthiourea and thiourea in current European practice (Table 2). Recent analysis of ESSCA data (5) has shown that the proportion of positive reactions to diethylthiourea (0.92%) are higher than those to the more commonly tested dibutylthiourea (0.45%), and diphenylthiourea (0.22%), possibly suggesting the desirability of a more targeted approach based on pretest suspicion. A North American Contact Dermatitis Group Study (28) assessed allergy to 'mixed dialkyl thioureas' (MDTUs) (ie, diethylthiourea and dibutylthiourea) from 1994 to 2004, showing positive reactions in 1.0% (21 898 patients tested). Only 24.9% of these patients also reacted to another rubber allergen, highlighting the importance of thiourea-specific testing. Additionally, MDTU will detect only 75% of relevant thiourea reactions (3, 29). Hence, the regular inclusion of these separate chemicals would be worthwhile. It would seem reasonable to not routinely test for thiourea 1% pet. as part of a European rubber series; the data returned from one European centre showed no positive reactions in 18 patients tested (5), and recent relevant literature is lacking.

Antidegradants

These groups of chemicals are added to rubber to inhibit degradation by oxygen and/or ozone, and represent another important cause of rubber contact allergy. Antidegradants are usually divided into non-colouring and colouring substances. The former comprise substituted phenols, benzofuranes, and others. The latter include derivatives of *p*-phenylenediamine (30). These are well-recognized and important sensitizers, being used in industrial rubber and black rubber. Although the prevalence of sensitization to IPPD is low (<1% in most studies), it is included in the baseline series to act as a screening agent for this chemical group on the basis of a recommendation from 1995 (31). However, recent data from the ESSCA (5) clearly show that this strategy will underdiagnose sensitization to this class of allergens. Therefore, other black rubber agents should be included in a rubber series; these include *N*-cyclohexyl-*N*-phenyl-4-phenylenediamine, *N,N'*-diphenyl-*p*-phenylenediamine, and *N,N*-di-2-naphthyl-4-phenylenediamine,

all at 1% pet. These three agents are also available as a mix from various manufacturers.

N-phenyl-2-naphthylamine is another *p*-phenylenediamine derivative. Recent ESSCA data (5) suggest a sensitization prevalence of 0.18% (all ++/+++ reactions) among 559 patients tested. It is also currently included in the rubber series of seven countries. However, there is no recent literature confirming its role in rubber allergy. We suggest that it should be included in a supplementary rubber series for further investigation.

The antioxidant 4,4-dihydroxydiphenyl (DOD) is routinely tested in three surveyed countries, and forms part of the Trolab rubber series at 0.1% pet. (32). A recent study including Information Network of Departments of Dermatology data of 36 338 patients patch tested for DOD (33) has suggested that allergy to this chemical is of historical importance only, and that the majority of positive reactions were probably irritant or represented old sensitization only. Thus, it should be omitted from current rubber patch test series.

4,4'-Diaminodiphenylmethane (MDA), which is currently included in nine countries' rubber series, is used as a curing agent in a wide array of products, with the most relevance being for isocyanate or polyurethane occupational exposure. The prevalence of positive patch test results varies from 0.8% to 8.5% (34), although recent data, obtained in the context of rubber series testing (5), showed 1.43% positive reactions in 491 patients when MDA was tested at 0.5% pet. Whether these are specifically relevant to its use in rubber remains to be seen, as there is a very limited amount of literature specifically on its relevance in rubber allergy. Some experts have questioned the relevance of MDA in shoe dermatitis (35). It would seem sensible to include this in a supplementary rubber series for further evaluation.

Three countries reported testing with 2,2,4-trimethyl-1,2-dihydroquinoline (ETMDQ) and butylated hydroxyanisole (BHA) in their rubber series. However, neither of these allergens has been included in our suggested rubber series. There are no data on prevalence from recent publications. The involvement of ETMDQ in rubber-related allergy was only reported in one small 20-year-old case series (14), in relation to rubber boots: it may be worth considering as part of a shoe series, but further data are lacking. The involvement of BHA in glove allergy was reported in one case report from 1991 (36).

Monobenzylether of hydroquinone (monobenzene) is an antioxidant that is used rarely in the rubber industry, and reports of allergic reactions in the context of rubber appear to be historical. Leukoderma can occur after contact with this chemical. Uter et al. (5) showed a prevalence of 0.82% positive reactions when the chemical

was tested as part of a rubber series at 1% pet. in 2185 European patients. All of these positive reactions were classed as weak (+). These data suggest that it is not necessary to include this allergen in a routine rubber series.

Bonding agents

Methenamine is a frequently tested chemical in the European countries surveyed. This agent has certainly been of historical importance in rubber allergy, with the data being predominantly from the 1990s. However, the literature of the last 15 years suggests that its main role as an allergen is as a preservative in cosmetic agents, with there being limited data on its role in rubber products. A recent ESSCA analysis of rubber series chemicals (5) showed 0.62% positivity when it was tested at 2% pet. ($n = 487$) and 0.41% positivity when it was tested at 1% ($n = 2193$). These figures are much lower than those from the Mayo Clinic rubber series data (2000–2007) (37), which showed 3.9% clinically relevant positive patch test reactions ($n = 773$). The prevalence may vary between regions, or the relevance of this chemical may be decreasing in the context of rubber allergy. We would suggest using methenamine in a supplementary rubber series, with ongoing analysis of its significance. The optimal test concentration has also yet to be clarified.

Retarders

Retardant chemicals are used to slow the process of rubber vulcanization.

Cyclohexyl thiophthalimide (CTP) is a potent retarder for sulfur-cured elastomers. Its highest efficiency is obtained with sulfenamide-type accelerators, but it is also effective with thiazoles (MBTS and MBT), and is mostly used in the production of thick rubber goods such as tyres. It is currently included in the rubber series of 10 countries, at various concentrations (one country at 0.25%, four at 0.5%, and five at 1%, all in pet.). Testing can be difficult, owing to irritant reactions at higher concentrations and cross-reactivity with thiurams (38). Work from the German Contact Dermatitis Research Group (39) suggested that testing at 1% would elicit false-positive irritant reactions, whereas 0.25% would miss the majority of true allergies; it was therefore concluded that testing at 0.5% pet. was most appropriate. Recent ESSCA data have shown a prevalence of 0.49% positive reactions to CTP 0.5% pet. in 2053 patients, as compared with 1.72% in 58 patients tested with 1% pet., again suggesting a higher rate of false-positives with the higher concentration. Therefore, in a European rubber series, testing at 0.5% is suggested.

Dodecyl mercaptan is included in the rubber series of seven countries. However, there is no recent literature supporting continued use, and recent data (5) showed no positive reactions in 488 patients when it was tested at 0.1% pet. We therefore do not include it in the suggested rubber series.

Stabilizers

Although ethylenediamine dihydrochloride is more commonly used as a stabilizer in topical medicaments, can be used industrially as a rubber latex stabilizer. It was removed from the European baseline series in 1995 (31), and since that time evidence of its role in rubber allergy has been lacking. Recent European data suggest a low level of positivity (0.69% positive at 1% pet. in 2027 patients). Another stabilizer, 4-*tert*-butylcatechol, is also used industrially in rubber production, but is more frequently found in resins. It is a potent sensitizer, and, in 2003, Hillen et al. (40) found the optimum test concentration to be 0.25%. Recent European data on use in the rubber series suggests a slightly higher sensitization prevalence (1.12% positive at 0.25% pet. in 1971 patients). Although these data may represent old or non-rubber sensitizations, we suggest inclusion in a supplementary rubber series for further evaluation.

Plasticizers

A range of chemicals are used in the rubber industry to improve flexibility, for example in seals, conveyer belts, hoses, and tubing; allergy to them in the context of rubber is most likely to be industrial. Phthalates were reported to be included in up to four countries' rubber series; di-2-ethylhexyl phthalate (four countries), dibutyl phthalate ($n = 3$), and dimethyl phthalate ($n = 2$). No case reports or sufficient clinical data are available in the recent literature about their relevance in rubber. One US study (41) investigating urinary levels of these three chemicals (rather than skin disease) found them to be of relevance in rubber boot and hose manufacture only; even in these apparently highly exposed workers, no cases of contact allergy have been reported. We suggest that these chemicals should be excluded from a European rubber series, given the lack of data.

Pieces of glove

Patch testing with pieces of rubber or glove 'as is' is necessary to identify contact allergy to the material that the patient is actually exposed to, although identification of the exact allergen may not be possible (5). This technique

has been reported in the rubber series of two countries surveyed. Small glove pieces moistened with water, ethanol or acetone can be tested in chambers, and it is worth testing both sides of the glove. However, patients should not wear gloves for which they have had negative patch test results if they have had positive reactions to a chemical listed as present in the glove (3).

Where there is strong suspicion of contact allergy but test results are negative, the use of glove extracts may be invaluable to increase the concentration of allergens present within the patch test material. The choice of solvent may, however, be crucial (42).

In the case of gloves, allergens may be present that are unrelated to the rubber, and that have been included to impart additional properties. Some examples are as follows.

Antimicrobials. Cetylpyridium chloride is a quaternary ammonium compound that is used as an antimicrobial agent in many products, including gloves. Several case reports in the 1990s highlighted this as an allergen, with more recent studies also showing its importance as a clinically relevant allergen in rubber gloves (42). Four countries surveyed are currently including it in their rubber series at 0.01–0.1% pet. This allergen has been included in a supplementary European rubber series; further information about optimum test concentrations needs to be obtained in further studies.

Antiseptics in surgical gloves are becoming more commonplace. Although, as yet, contact allergy to these additional agents, such as chlorhexidine gluconate (GAMMEX® Non-Latex Antimicrobial Gloves; Ansell, Iselin, NJ, USA) and dodecyl dimethylammonium chloride, has not been reported in direct relation to rubber glove use, their role should be considered in occupational glove allergy testing.

Moisturizers. Some rubber gloves are internally coated with a moisturizer (e.g. Vileda® Comfort and Care,

Comfort plus, extra-absorbent; Vileda, Verviers, Belgium). A 2014 case report (43) used gas chromatography/mass spectrometry to chemically analyse the gloves responsible for a case of allergic contact dermatitis, and showed the presence of fatty acids and quaternary ammonium compounds (specifically dodecyl trimethylammonium chloride), which are surfactants used as stabilizers or wetting agents.

This highlights the need to routinely test glove pieces when investigating hand dermatitis in users of rubber gloves.

Conclusion

A two-part European rubber series is suggested; one set including allergens of proven importance for routine testing in all patients with suspected contact allergy to rubber; and another set including substances that, as yet, have less proven importance. The latter set should be tested in departments specializing in occupational or contact allergy, and the results should be scientifically evaluated so that a decision can be made on the inclusion of these allergens in the first, routine part of a European rubber series.

Acknowledgements

The following colleagues, in addition to the authors, contributed information about the composition of patch test series in their departments or national networks (shown in *italics*) and/or provided data to the ESSCA: W. Aberer, T. Agner, F. Ayala, A. Balato, B. Ballmer-Weber, A. Bircher, J. Brasch, P.-J. Coenraads, S. M. Cooper, P. Cousen, P. Elsner, T. Fuchs, R. Gallo, A. Giménez Arnau, H. L. Horne, S. M. John, M. Kieć-Świerczyńska, V. Kohanka, F. Laresse Filon, S. Ljubojević Hadžavdić, M. Matura, P. Mercader, M. Pesonen, V. Reljic, T. Rustemeyer, I. Ruiz, D. Simon, S. Urbancsek, and E. Weisshaar.

The authors acknowledge the support of Horizon 2020 COST Action TD1206 'StanDerm'.

References

- 1 Bruze M, Goossens A, Isaksson M. Recommendation to increase the test concentration of methylchloroisothiazolinone/methylisothiazolinone in the European baseline patch test series – on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2014; **71**: 35–40.
- 2 Isaksson M, Ryberg K, Goossens A, Bruze M. Recommendation to include a textile dye mix in the European baseline series. *Contact Dermatitis* 2015; **73**: 15–20.
- 3 Cao L Y, Taylor J S, Sood A et al. Allergic contact dermatitis to synthetic rubber gloves: changing trends in patch test reactions to accelerators. *Arch Dermatol* 2010; **146**: 1001–1007.
- 4 Geier J, Lessmann H, Mahler V et al. Occupational contact allergy caused by rubber gloves – nothing has changed. *Contact Dermatitis* 2012; **67**: 149–156.
- 5 Uter W, Warburton K, Weisshaar E et al. Patch test results with rubber series in the European Surveillance System on Contact Allergies (ESSCA), 2013/2014. *Contact Dermatitis* 2016; **75**: 345–352.
- 6 Uter W, Bensefa-Colas L, Frosch P et al. Patch testing with hair cosmetic series in Europe: a critical review and recommendation. *Contact Dermatitis* 2015; **73**: 69–81.
- 7 Wrangsjö K, Boman A, Lidén C, Meding B. Primary prevention of latex allergy in

- healthcare-spectrum of strategies including the European glove standardization. *Contact Dermatitis* 2012; **66**: 165–171.
- 8 Mahler V. Rubber. In: *Quick Guide to Contact Dermatitis*, Johansen J D, Lepoittevin J P, Thyssen J P (eds): Berlin and Heidelberg, Springer-Verlag, 2016: pp. 159–179.
 - 9 Geier J, Lessmann H, Uter W et al. Occupational rubber glove allergy: results of the Information Network of Departments of Dermatology (IVDK), 1995–2001. *Contact Dermatitis* 2003; **48**: 39–44.
 - 10 Uter W, Aberer W, Armario-Hita J C et al. Current patch test results with the European baseline series and extensions to it from the 'European Surveillance System on Contact Allergy' network, 2007–2008. *Contact Dermatitis* 2012; **67**: 9–19.
 - 11 Warburton K L, Bauer A, Chowdhury M M U et al. ESSCA results with the baseline series, 2009–2012: rubber allergens. *Contact Dermatitis* 2015; **73**: 305–312.
 - 12 Knudsen B B, Hametner C, Seycek O et al. Allergologically relevant rubber accelerators in single-use medical gloves. *Contact Dermatitis* 2000; **43**: 9–15.
 - 13 Geier J, Frosch P J, Schnuch A et al. Patch tests with thiurams at 0.25% pet. and 1% pet. are of equal diagnostic value. *Contact Dermatitis* 2002; **46**: 258–261.
 - 14 Nishioka K, Murata M, Ishikawa T et al. Contact dermatitis due to rubber boots worn by Japanese farmers, with special attention to 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (ETMDQ) sensitivity. *Contact Dermatitis* 1996; **35**: 241–245.
 - 15 Mortz C, Jensen E, Madsen J, Andersen K E. Should carba mix be reintroduced into the European baseline series? *Contact Dermatitis* 2016; **75**: 48–50.
 - 16 Sherertz E, Swarzt S. Careful with carba mix. *Am J Contact Dermatitis* 1994; **5**: 44–45.
 - 17 Hansson C, Pontén A, Svedman C et al. Reaction profile in patch testing with allergens formed during vulcanization of rubber. *Contact Dermatitis* 2014; **70**: 300–308.
 - 18 Aalto-Korte K, Pesonen M. Patterns of simultaneous patch test reactions to thiurams and dithiocarbamates in 164 patients. *Contact Dermatitis* 2016; **75**: 353–357.
 - 19 Geier J, Lessmann H, Rothe A et al. Patch testing with zinc dibenzylthiocarbamate. A multicentre study of the Information Network of Departments of Dermatology and the German Contact Dermatitis Research Group. *Contact Dermatitis* 2003; **48**: 209–211.
 - 20 Dahlin J, Bergendorff O, Vindenes H K et al. Triphenylguanidine, a new (old?) rubber accelerator detected in surgical gloves that may cause allergic contact dermatitis. *Contact Dermatitis* 2014; **71**: 242–246.
 - 21 Hansson C, Agrup G. Stability of the mercaptobenzothiazole compounds. *Contact Dermatitis* 1993; **28**: 29–34.
 - 22 Anonymous Mercapto mix. *Contact Dermatitis* 1995; **32**: 255.
 - 23 Diepgen T L, Bruynzeel D P, Andersen K E et al. Mercaptobenzothiazole or mercapto-mix: which should be tested in the standard series? *Contact Dermatitis* 2006; **55**: 36–38.
 - 24 Geier J, Uter W, Schnuch A et al. Diagnostic screening for contact allergy to mercaptobenzothiazole derivatives. *Am J Contact Dermatitis* 2002; **13**: 66–70.
 - 25 Geier J, Gefeller O. Sensitivity of patch tests with rubber mixes: results of the Information Network of Departments of Dermatology from 1990 to 1993. *Am J Contact Dermatitis* 1995; **6**: 143–149.
 - 26 Geier J, Uter W, Schnuch A et al. Both mercaptobenzothiazole and mercapto mix should be part of the standard series. *Contact Dermatitis* 2006; **55**: 314–316.
 - 27 Bergendorff O, Persson C, Lütke A et al. Chemical changes in rubber allergens during vulcanization. *Contact Dermatitis* 2007; **57**: 152–157.
 - 28 Warsaw E M, Cook J W, Belsito D V et al. Positive patch-test reactions to mixed dialkyl thioureas: cross-sectional data from the North American Contact Dermatitis Group, 1994 to 2004. *Dermatitis* 2008; **19**: 190–201.
 - 29 Anderson B E. Mixed dialkyl thioureas. *Dermatitis* 2009; **20**: 3–5.
 - 30 Fuchs T. *Gummi und Allergie*: Deisenhofen, Düstri, 1995.
 - 31 Bruynzeel D P, Anderson K E, Camarasa J G et al. The European standard series. European Environmental and Contact Dermatitis Research Group (EECDRG). *Contact Dermatitis* 1995; **33**: 145–148.
 - 32 Available at: www.smartpracticeeurope.com (last accessed December 2016).
 - 33 Frosch P J, Mahler V, Uter W. Dihydroxydiphenyl – a historical rubber contact allergen? *Contact Dermatitis* 2014; **73**: 364–380.
 - 34 Engfeldt M, Goossens A, Isaksson M et al. The outcome of 9 years of consecutive patch testing with 4,4'-diaminodiphenylmethane and 4,4'-diphenylmethane diisocyanate. *Contact Dermatitis* 2013; **68**: 98–102.
 - 35 Nardelli A, Taverne M, Drieghe J et al. The relation between the localization of foot dermatitis and the causative allergens in shoes: a 13-year retrospective study. *Contact Dermatitis* 2005; **53**: 200–206.
 - 36 Rich P, Belozor M L, Norris P et al. Allergic contact dermatitis 22 to two antioxidants in latex gloves: 4,4'-thiobis(6-tert-butyl-meta-cresol) (Lowinox 44S36) and butylhydroxyanisole. Allergen alternatives for glove-allergic patients. *J Am Acad Dermatol* 1991; **24**: 37–43.
 - 37 Bendewald M, Farmer S, Davis M. An 8-year retrospective review of patch testing with rubber allergens: the Mayo Clinic experience. *Dermatitis* 2010; **21**: 33–40.
 - 38 Huygens S, Barbaud A, Goossens A. Frequency and relevance of positive patch tests to cyclohexylthiophthalimide, a new rubber allergen. *Eur J Dermatol* 2001; **11**: 443–445.
 - 39 Geier J, Lessman H, Frosch P J et al. Contact sensitization to N-(cyclohexylthio)phthalimide. *Contact Dermatitis* 2003; **48**: 1–6.
 - 40 Hillen U, Frosch P J, Franckson T et al. Optimizing the patch-test concentration of para-tertiary-butylcatechol: results of a prospective study with a dilution series. *Contact Dermatitis* 2003; **48**: 140–143.
 - 41 Hines C J, Nilsen Hopf N B, Deddens J A et al. Urinary phthalate metabolite concentrations among workers in selected industries: a pilot biomonitoring study. *Ann Occup Hyg* 2009; **53**: 1–17.
 - 42 Pontén A, Hamnerius N, Bruze M et al. Occupational allergic contact dermatitis caused by sterile non-latex protective gloves: clinical investigation and chemical analyses. *Contact Dermatitis* 2013; **68**: 103–110.
 - 43 Vanden Broecke K, Zimerson E, Bruze M, Goossens A. Severe allergic contact dermatitis caused by a rubber glove coated with a moisturizer. *Contact Dermatitis* 2014; **71**: 117–119.