Eur J Dermatol 2016; 26(6): 523-30

Marie-Noëlle CREPY

Department of Occupational Diseases,
Paris University Hospital,
Centre Hôtel-Dieu, AP-HP 1,
Parvis Notre-Dame, 75004 Paris,
France

Reprints: M.-N. Crepy
<marie-noelle.crepy@orange.fr>

Rubber: new allergens and preventive measures

Natural rubber latex (NRL) and rubber accelerators are well-known causes of occupational skin diseases. The latest epidemiological data on rubber allergy show that rubber additives are still among the allergens most strongly associated with occupational contact dermatitis, however, a decrease in NRL allergy has been confirmed. A review of recent publications on rubber allergens based on the Pubmed database is presented. New glove manufacturing processes have been developed, such as low-protein natural rubber gloves, vulcanisation accelerator-free gloves, or specific-purpose gloves containing antimicrobial agents or moisturisers. Several websites provide information on allergens found in gloves and/or glove choice according to occupation.

Article accepted on 1/4/2016

Key words: rubber, latex, allergy, allergen, glove, contact dermatitis

The word caoutchouc (commonly called rubber in English) is derived from the Amerindian phrase cao (wood) tchu (crying). In 1839, Charles Goodyear's discovery of the vulcanisation of rubber revolutionised the use and applications of rubber. Over 20,000 plant species can produce latex but *Hevea brasiliensis* (Willd. Ex A. Juss), a plant belonging to the Euphorbiaceae family, remains the main worldwide source of natural rubber latex [1]. The proportion of synthetic rubber is increasing; in 2011, global natural rubber production reached 10 million tons a year, while that of synthetic rubber was over 15 million tons [1].

There are many recent technological innovations and these go far beyond the field of dermato-allergology. This article is a review of the latest epidemiological data on rubber allergy and an update on rubber allergens and new manufacturing processes of gloves, since these data can be of interest to dermatologists, allergists, and occupational physicians. The data suggest that some examples of alternative gloves should be recommended to allergic subjects.

Update on epidemiology

Rubber additives

A descriptive study based on the national register of occupational diseases was carried out in Denmark in 2010. It included 1,504 patients and found that rubber additives are the main causes of allergic contact dermatitis (ACD). Rubber additives and epoxy were reported to induce 40% of the cases of occupational ACD [2, 3].

Pesonen *et al*. analysed the patch test results to the allergens in the European baseline series in 44,277 patients with and without occupational contact dermatitis; the data was collected from the European Surveillance System on Contact Allergy (ESSCA) from 2002 to 2010 [4]. Rubber additives are the allergens most strongly associated with occupational contact dermatitis; the results are shown in *table 1*. Positive patch test reactions to thiuram mix are found mostly in workers who wear waterproof (occlusive) protective gloves, such as domestic helpers, cleaners, healthcare workers, housekeepers, restaurant workers, bricklayers, and stonemasons.

The information provided by glove manufacturers and the search for the constituents of medical gloves show that most international rubber glove companies have replaced thiurams by dithiocarbamates and/or mercaptobenziothiazole derivatives [5, 6]. However, thiurams remain the rubber allergens that most frequently yield positive patch test results [7]. In a retrospective study (2002-2010) of patients suffering from occupational dermatitis carried out in Germany by Geier *et al*., 3,448 (24.4%) were tested for suspected glove allergy [8]. Among these, healthcare workers represented the largest group (n=1,058). The allergens most frequently yielding positive patch test results were thiurams (13%), dithiocarbamates (3.5%), 1,3-diphenylguanidine (3%), mercaptobenziothiazole and/or its derivatives (3%), and thioureas (0.4%). When comparing their results with those from 1995 to 2001, the authors concluded that the situation has remained unchanged. On the contrary, other more recent studies have shown a decrease in the prevalence of positive patch tests to thiuram mix [9-12].

In the UK, Warbuton *et al*. analysed cases of occupational allergic contact dermatitis induced by rubber additives reported to EPIDERM (an occupational skin disease surveillance network) between 1996 and 2012 [12]. The British baseline series includes thiuram mix 1% pet. (containing tetramethylthiuram disulphide or TMTD, tetramethylthiuram monosulfide or TMTM, tetraethylthiuram disulphide or TETD and dipentamethylenethiuram or PTD), carba mix 3% pet. (containing zinc diethyldithiocarbamate or ZDEC, zinc dibutyldithiocarbamate or ZDBC and 1,3-diphenylguanidine), mercapto mix 2% pet. (containing 2-mercaptobenzothiazole or MBT, N-cyclohexyl-2-benzothiazolesulfenamide or CBS, morpholinylmercaptobenzothiazole or MOR, and dibenzothiazyl disulfide or MBTS), mercaptobenzothiazole (MBT) 2% pet., and N-isopropyl-N′-phenyl-p-phenylenediamine or IPPD 0.1% pet. The other allergens tested vary from

doi:10.1684/ejd.2016.2839

To cite this article: Crepy MN. Rubber: new allergens and preventive measures. *Eur J Dermatol* 2016; 26(6): 523-30 doi:10.1684/ejd.2016.2839

Table 1. Risk of occupational contact dermatitis (OCD) associated with allergy to test substances; Pesonen *et al.* [4].

Allergens	OCD + (%+)	OCD - (%+)	PR (95% CI)
Thiuram mix	5.63	1.35	4.23
2-MBT	1.42	0.52	2.91
N-isopropyl-N′-phenyl-p-phenylenediamine (IPPD)	1.05	0.41	2.62
Mercapto mix (CBS, MBTS, and MOR)	1.32	0.62	2.46

CBS: N-cyclohexyl-2-benzothiazylsulfenamide; MBTS: dibenzothiazyle disulphide; MOR: morpholinylmercaptobenzothiazole.

one dermatologist to another. Thiurams remain the agents that most frequently cause ACD (603 cases), followed by carba mix (219 cases), mercapto mix (177 cases), IPPD (84 cases), N-cyclohexylthiophtalimide (a vulcanisation retarder) in 14 cases, hexamethylenetetramine (five cases), thioureas (four cases), diaminodiphenylmethane (two cases), and dithiodimorpholine in one case. The authors reported a decreasing incidence in ACD induced by thiurams, mercapto mix, and mercaptobenzothiazole, while the incidence of ACD induced by carba mix, which contains 1,3-diphenylguanidine, increased. Several studies have confirmed the increasing prevalence of positive patch test results with 1,3-diphenylguanidine [7]. It has been suggested that this was due to rubber latex gloves being replaced by synthetic rubber gloves [7, 13].

Latex

Preventive measures against latex allergy, in particular the use of low-protein, low-allergen, powder-free natural rubber latex (NRL) gloves, has markedly reduced latex allergies in healthcare workers [12, 14-16]. Recently, Blaabjerg *et al*. investigated the prevalence of NRL sensitisation between 2002 and 2013 in an allergy centre in Denmark (n=8,580) [15]. Latex sensitisation was defined by positive prick test results, whereas clinical NRL allergy was defined by immediate symptoms when exposed to NRL (contact urticaria, angioedema, rhinoconjunctivitis, asthma, gastrointestinal symptoms, anaphylaxis, worsening of hand eczema, or pruritus) combined with a positive prick test reaction. The prevalence of clinical NRL allergy decreased from 1.3% in 2002-2005 to 0.5-0.6% in 2006-2013 (p<0.004). Similarly, based on prick tests, the prevalence of NRL sensitisation decreased from 6.1% in 2002-2005 to 1.9% in 2006-2009, and then to 1.2% in 2010-2013 (p<0.0001). Of the NRL-sensitised patients, 64% also had a positive prick test reaction to birch pollen and 52% had a history of reaction to oral intake of fruit or vegetables (mainly kiwis, bananas, tomatoes, carrots, and avocados). Gloves (75%) and balloons (33%) were the main culprit materials.

Latest news on allergens

Rubber vulcanisation additives and antioxidants

The real haptens in thiurams and dithiocarbamates remain unknown. Hansson *et al*. tested 24 patients with known contact allergy to rubber accelerators (thiurams, dithiocarbamates, and/or mercaptobenzothiazoles) with a series of 21 compounds identified based on the chemical analyses of vulcanised rubber products (*table 2*) [6]. Diphenylguanidine, p-phenylenediamine oxidants, and thioureas were not included in the study. The baseline series included allergens usually found in the TRUE Test® or Chemotechnique® series, as well as potentially sensitising molecules (*table 2*). Zinc dibenzyldithiocarbamate in 1% pet. from the former Trolab® series, currently marketed by SmartPratice®, was not tested. Thiuram monosulfides induced stronger and more frequent patch test reactions than the corresponding thiuram disulfides. In this study, a positive reaction to a dithiocarbamate was always accompanied by a positive reaction to the corresponding thiuram, except in one case.

Table 2. List of allergens tested with the rubber series of Hansson *et al.* [6].

Chemical family	Marketed allergens	Additional allergens
Thiurams	Tetramethylthiuram monosulfide (TMTM) Tetramethylthiuram disulfide (TMTD) Tetraethylthiuram disulfide (TETD) Dipentamethylenethiuram disulfide (DPTD)	Tetraethylthiuram monosulfide (TETM) Dipentamethylenethiuram monosulfide (DPTM) Tetrabutylthiuram monosulfide (TBTM) Tetrabutylthiuram disulfide (TBTD)
Dithiocarbamates	Zinc dimethyldithiocarbamate (ZDMC) Zinc diethyldithiocarbamate (ZDEC) Zinc dibutyldithiocarbamate (ZDBC)	Methyl N,N-dimethyldithiocarbamate (MeDMC) Methyl N,N-diethyldithiocarbamate (MeDEC) Zinc pentamethylene-dithiocarbamate (ZPD)
Benzothiazoles	2- mercaptobenzothiazole (MBT) N-cyclohexyl-2-benzothiazylsulfenamide (CBS) Morpholinylmercaptobenzothiazole (MOR) Dibenzothiazyle disulphide (MBTS)	2- (methyl)mercaptobenzothiazole (MBT)
Products of thiurams and mercaptobenzothiazoles during vulcanisation		Dialkylthiocarbamyl benzothiazole Sulfide (DMTBS) Diethylthiocarbamylbenzothiazole sulfide (DETBS)