Rubber

14

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Contents

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14.1 Types of Rubber and Allergens: Frequent Allergens: Consumer/Occupational Exposures

14.1.1 Consumer/Occupational Exposures

Rubber materials are ubiquitous in daily life [11, 34] (Tables 14.1 and 14.2). Most rubber allergies are work related [9, 27, 34]. Allergic contact dermatitis may occur due to synthetic rubber even with the use of latex-safe products [9]. The most frequent rubber exposure leading to sensitization against rubber components is protective gloves [9, 17, 32, 34] which are covered in Chap. 18 of this book. Diagnosing an allergy to one or several rubber components may lead to challenging implications for secondary prevention measures and the individual's ability to work in specific occupational environments (Table 14.2) [12].

14.1.2 Types of Rubber

Rubber elastomers can be divided in the following classes [22]:

(i) General-purpose rubber: natural (NRL), polyisoprene, styrene-butadiene, butyl, ethylene-propylene, and polybutadiene rubber
(ii) Solvent-resistant rubber: polysulfides, nitrile, polychloroprene, polyurethanes, and epichlorohydrin rubber
(iii) Heat-resistant rubber: silicone, chlorosulfonated polyethylene, polyacrylates, and fluoroelastomers

Table 14.1 Examples of rubber exposures

Environment or purpose of use	Product
Medical	Protection gloves, finger cots, catheters, tubes, stopper, sealings, splints, wound dressings, bandages, condoms, hot water bag, implants (mostly silicone)
Laboratory	Protections gloves, Peleus (pipet) ball, stopper
Construction	Cable material, rubber grips of tools, sealing, insulation, hoses, buckets
(Vehicle) production and repair	Tires, rubber grips of tools, cables, insulation
Cleaning	Gloves, rubber sponge, hoses
Household	Rubber bands, cell phone covers, kitchen devices, baking and ice cube molds (mostly silicone)
Sport	Balls, mats, flooring, handles of sport instruments, diving equipment and wet suits, swimming goggles, currycomb
Clothing	Bras, waistband of trousers, cuffs, socks, stockings, suspenders, wristbands
Shoes	Sport shoes, rubber boots, shoe soles
Toys and children's items	Dolls, ducklings, balls, erasers, swings, pacifiers, craft supplies (e.g., for making of wristbands; e.g., Loom (mostly silicone))

Nowadays, natural rubber latex supplies 25 % of the rubber market, whereas synthetic rubbers constitute the remaining 75 % [5]. Blends between natural and synthetic rubber materials exist [5]. Styrene-butadiene is now the major synthetic rubber produced. In comparison with natural rubber, it is weaker and less resistant to fatigue, but it has the merit of ageing more slowly [22]. Since most rubberized materials are unlabeled, it is difficult to determine whether a product contains

Table 14.2 Frequent contact allergens (rubber additives added to natural or synthetic rubber during the manufacturing process)

Rubber additive	Contained in rubber	Other exposures	Impaired occupational fields
Thiurams	Yes (e.g., protection gloves, rubber form products (e.g., tires, hoses, sealing rings, clothing))	Pesticides, fungicides, germicides, insecticides, insect repellents, preservatives (wood, paints, greases, etc.)	Rubber production, productive industries with unavoidable contact to rubber form products (e.g., assembly lines, tires, hoses)
		Tetraethylthiuram disulfide (TETD, disulfiram) as medication (Antabus®) for alcohol withdrawal and as chelating agent used for nickel intoxication	Production of pesticides, farming; floristry may be impaired, if thiuram-containing fungicides cannot be avoided
			In the medical field, in construction; for cleaning and hairdressing, most frequently thiuram-free protection gloves may be used as a surrogate
Mercaptobenzothiazole and its derivatives	Yes (e.g., protection gloves, shoe soles, tires, industrial rubber)	Glues (neoprene based), antifreeze, automotive cooling systems, refrigerants, cutting fluids/greases, detergents (granulated and tablets), paint, fungicides, pesticides, germicides, veterinarian medicaments, leather industries and shoemaking	Leather processing industries, shoe and rubber production. Metal industries may be impaired if MBT-containing cutting fluids cannot be exchanged
			In the medical field and construction, most frequently MBT-free protection gloves may be used as a surrogate
Dithiocarbamates	Yes (e.g., protection gloves, medical products, condoms, rubber boots, rubber covered tools, sealings, cable insulation)	Fungicides (zinc dimethyldithiocarbamate (Ziram), zinc ethylene-bis-dithiocarbamate (Zineb), Maneb (mangan-ethylene-bis-dithiocarbamate))	Rubber production, productive industries with unavoidable contact to dithiocarbamate-containing rubber form products (e.g., assembly lines, tires, hoses)
			Farming and gardening, as well as production and processing of biocides may be impaired

(continued)

Table 14.2 (continued)

Rubber additive	Contained in rubber	Other exposures	Impaired occupational fields
Thioureas	Yes (e.g., neoprene products (e.g., wet suits, other sport equipment), thermoplastic coatings, foam rubber products)	Anticorrosives, antioxidants, acidic detergent, cleaning products, paint/glue remover, fungicides, pesticides, PVC adhesives/tapes	Rubber production, productive industries with unavoidable contact to thiourea containing products
N-isopropyl-N′-phenyl-phenylenediamine (IPPD)	Yes (used as antioxidant and antiozonant agent in statically and dynamically highly challenged natural or synthetic rubber products; mostly in the industrial environment; gives the black color to industrial rubber; e.g., in tires, car parts, conduction belts, cable insulation, hoses, and tubes, sealings; milking machines; protection and diving gear). Non-occupational exposures are rare: squash balls, motorbike handles, wrist watch bands, eyelash formers, orthopedic supports, underwear	Rubber cement, acrylates, gasoline, cross-reactive components in hair dyes	Black rubber production and assembly lines (tools with covered handles, tubes, hoses, tires.), car repair (with contact to black rubber tubes and tires)

natural or synthetic rubber [5]. The existing overlap between ingredients in "rubber" and "plastic" further complicates the matter [5]. Whereas completely cured plastic materials are rare sensitizers, fully cured rubber products produce allergic reactions since the sensitizers in rubber can leach out over time [5].

14.1.3 Rubber Components

Two main groups of compounds different in nature have to be distinguished as allergen sources in rubber: (1) proteins from natural rubber latex (NRL) which may lead to type I allergies (presenting as contact urticaria and rarely also protein contact

dermatitis) and (2) rubber additives which are added to natural rubber latex as well as to synthetic rubber elastomers during the manufacturing process (e.g., vulcanizing agents (e.g., sulfur or sulfur donors, organic peroxides, phenol resins, metal oxides), accelerators (e.g., thiurams, benzothiazoles, guanidines, dithiocarbamates), activators (e.g., zinc oxide), retarders (e.g., organic acids, cyclohexylthiophtalimide, N-nitrosodiphenylamine), fillers (e.g., China clay), antidegradants (antioxidants (e.g., phenylenediamines, quinolines, hydroquinones, butylhydroxytoluene (BHT), phosphites), antiozonants (e.g., PPD derivatives)) to enhance the technical properties of the final product, plasticizers (e.g., phthalate esters in rubber tires), processing aids (e.g., mineral oils, solvents, talc), tackifiers, stabilizers (e.g. casein), pigments (inorganic pigments and organic dyes and lacquers), among others) [22, 5], some of which may lead to type IV allergies (allergic contact dermatitis). Hundreds of different rubber additives may be used in different blends; in a particular rubber product, however, around a dozen different components may be used [22].

Vulcanizing agents are necessary to induce cross-linking of natural as well as synthetic rubber elastomers during the process of rubber manufacturing [9, 22]. The most common vulcanizing agent in general-purpose use is sulfur. Common sulfur donors are morpholine, dithiocarbamates, dithiophosphonates, and tetraethylthiuram disulfide and tetramethylthiuram disulfide [30]. The reaction between sulfur donors and rubber is slow. To speed up the process, a group of chemicals is used as accelerators: slow accelerators are thiourea derivatives and amines; moderately fast accelerators are 1,3-diphenylguanidine, mercaptobenzothiazoles, and sulfonamides; very fast accelerators are thiurams, dithiocarbamates, and thiophosphates [30]. While some synthetic rubbers (e.g., butyl and nitrile) can be polymerized with organic peroxides without the addition of sulfur, others (e.g., styrene-butadiene) require much greater amounts of sulfur donors (e.g., 2-MBT, thiurams) than natural rubber [5].

However, silicone rubber, which is fully saturated, cannot be vulcanized with sulfur or sulfur donors. Instead, peroxides are necessary to achieve cross-linking [30]. Silicones are relatively nonreactive and highly biocompatible. Hypersensitivity reactions to silicone polymers have only rarely been reported [37].

14.1.4 Most Important Rubber Allergens

In patients with suspected rubber allergy, contact allergies (type IV allergies) to rubber additives are frequent, whereas type I allergies (presenting as contact urticaria syndrome) to natural rubber latex (NRL) proteins are much less frequent.

14.1.4.1 Type IV Allergens: Rubber Additives

The rubber accelerators (thiurams, carbamates, thiazoles and thioureas) and antioxidants (mainly derivatives of PPD) constitute the most frequent contact allergens among the rubber chemicals; reactions to other components of rubber (except for phenol formaldehyde resins (used as tackifiers/reinforcing agents) and epoxy resins (used as stabilizers) are rare [5]. The accelerators cause the greatest amounts of

sensitivity among users of rubber products (Fig. 14.1); in contrast, workers involved in the manufacture of rubber are more likely allergic to the amine antioxidants (e.g., IPPD) [5]. Allergic reactions to the synthetic rubber monomers/polymers themselves may occur and, however, are very rare (Fig. 14.2).

Thiurams and Dithiocarbamates

Thiurams are still the most frequently recognized rubber accelerator [15, 17, 31] with prevalences of sensitization to the thiuram mix between 2.0 and 2.7 % in patch test clinics throughout Europe, with exception for Italy, Lithuania, and the Netherlands where it is considerably lower. The thiurams used industrially include tetramethylthiuram monosulfide (TMTM), tetramethylthiuram disulfide (TMTD), tetraethylthiuram disulfide (TETD), and dipentamethylenethiuram disulfide (PDT).

In a recent analysis of data from the ESCCA network, contact allergens with the strongest association to occupational dermatitis (i.e., those with a risk of occupational dermatitis $\geq$1.75) were thiurams, epoxy resin, mercapto rubber chemicals, and N-isopropyl-N′-phenyl-p-phenylenediamine (IPPD), followed by a number of antimicrobials. Concordantly, thiurams, mercapto rubber chemicals, and IPPD were defined as predominantly occupational allergens [27].

As occupational subgroups mainly at risk of contact sensitization to thiurams except for rubber industry workers, healthcare workers (physicians, nurses, and related), food processors (cooks, meat and fish processors), and professional cleaners were identified [32]. Whereas between 1992 and 2006 a significant decline of sensitization prevalence could be identified in healthcare workers, no significant trend was determined in food processors and professional cleaners [32]. A predominance of exposure via gloves was illustrated by the pattern of sites associated with an increased risk; however, footwear also seems to have some relevance for elicitation of contact dermatitis due to thiurams [32].

Thiurams, dithiocarbamates, and mercaptobenzothiazoles have fungicide effects and for this reason are used in agriculture. They have been also described in adhesives, paints, cutting oils, and veterinary medications [5]; however, these exposures seem to be outdated in the European Union [12]. Due to its potential carcinogenicity and known sensitizing potency, 2-mercaptobenzothiozole is not being used anymore in cutting oils in Germany [http://www.kss-komponenten.de/, last accessed 20 Dec. 2014].

Currently, none of the veterinary medications listed in the EudraPharm weblist (European Union Drug Regulating Authorities Pharmaceutical Database; summarizes all medicinal products authorized in the European Union; http://www.eudrapharm.eu/eudrapharm/) contains thiurams, dithiocarbamates, or mercaptobenzothiazole. The exposure may vary in countries outside the EU. In the Green Book (FDA-Approved Animal Drug Products, Sect. 2.0 – Active Ingredients), one 2-mercaptobenzothialzole-containing product for the treatment of dogs is listed (Sulfodene™ medication for dogs), whereas no thiuram- or dithiocarbamate-containing veterinary drugs were found (http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/UCM2006464; last accessed 20 Dec. 2014).

Tetraethylthiuram disulfide (i.e., disulfiram; *Antabus*™) has also been used as an oral medication to support the treatment of chronic alcoholism by producing an

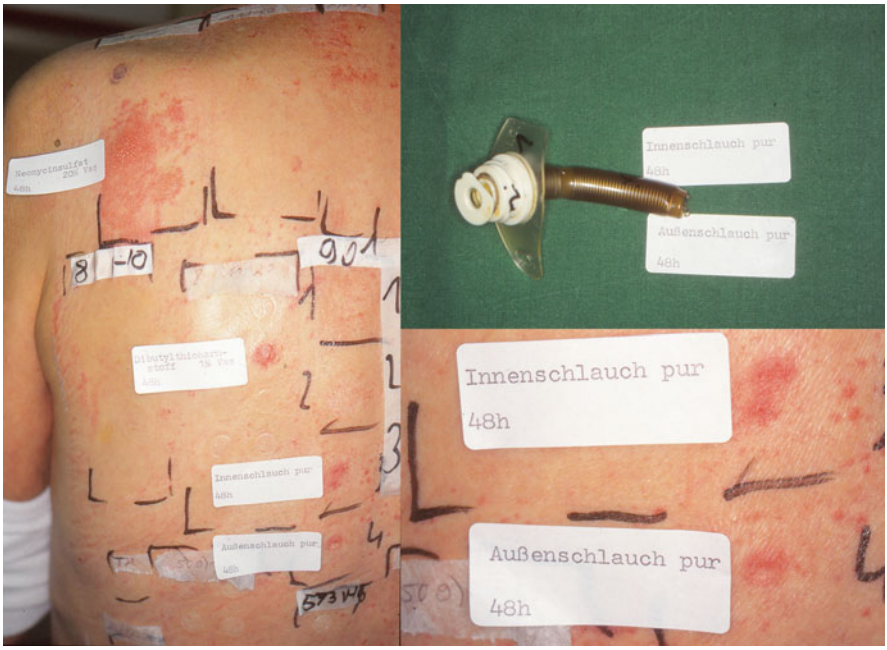

Fig. 14.1 Positive patch test reactions to dibutylthiourea, inner tube (Innenschlauch), and outer tube (Außenschlauch) of the tracheal cannula causing allergic contact dermatitis in a 56-year-old female patient with tracheostoma following surgery for hypopharyngeal carcinoma 6 year earlier. Additionally, a type IV sensitization to neomycin was diagnosed

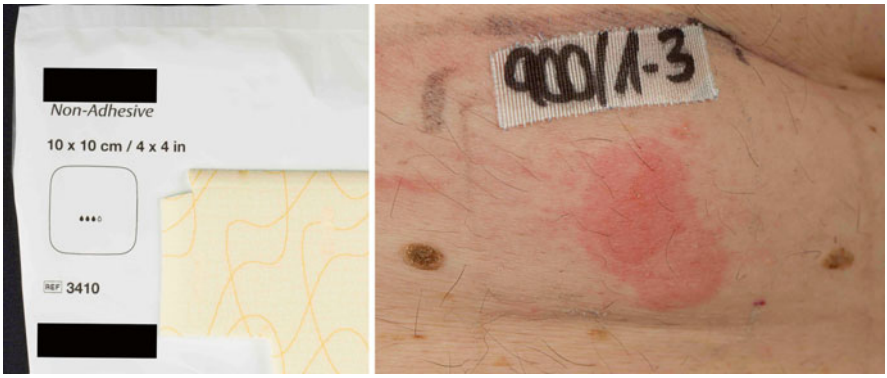

Fig. 14.2 Positive patch test reactions to a polyurethane wound dressing causing acute allergic contact dermatitis in a 70-year-old male patient. According to the manufacturer, no accelerators are used during the production process, and this case was the first case of contact dermatitis to this kind of wound dressing ever reported. The patient exhibited concomitant type IV sensitizations to several rubber chemicals (mercapto mix (CBS, MBTS, MOR) without MBT, 1,3-DPG, cyclohexylthiophtalimide, tert-butyl hydroquinone) which were after meticulous research of the manufacturer not used during the production process. A rare case of type IV sensitization to the polyurethane polymers may be assumed

acute sensitivity to alcohol. According to EudraPharm weblist (last accessed 20 Dec. 2014) in Europe, Antabus™ is currently only still available in Finland.

Positive patch test reactions to thiurams are frequently combined with positive patch test reactions to dithiocarbamates [6, 15]. Even though the use of thiurams as vulcanization accelerators in rubber glove production has been reduced and dithiocarbamates and mercaptobenzothiazole derivatives are now more commonly used [15, 21], positive patch test reactions to thiurams still are more common than positive reactions to dithiocarbamates [17, 31]. A possible explanation to this is that thiurams and dithiocarbamates constitute a redox pair in which a dithiocarbamate may oxidate into corresponding thiuram disulfide, and the thiuram may be reduced to reform the dithiocarbamate [6, 21]. Thiurams are considered to be better markers for sensitization to the dithiocarbamate/thiuram redox pair than the dithiocarbamates [21].

Historically, the predominant use of carbamates has been in pesticides and fungicides; however, during the last decade, the use as rubber chemical, especially in nitrile gloves, has increased [5]. Sodium dithiocarbamates are water soluble, whereas zinc dithiocarbamates are water insoluble. From the latter group zinc diethyldithiocarbamate (ZDEC), zinc dibutyldithiocarbamate (ZDBC), zinc dimethyldithiocarbamate (ZDMC), and zinc dipentamethylendithiocarbamate (ZPC) are clinically relevant contact allergens frequently contained in elastomers [30].

The prevalences of sensitization to ZDEC (derived from patch test clinics of the ESSCA network where it was tested as supplement to the standard series) varied from 0.3 % in Finland to 1.0 % in Switzerland [31].

Thiazoles

Thiazoles are derivatives of benzothiazoles compounded with sulfenamides [5]. The benzothiazoles include 2-mercaptobenzothiazole (MBT), dibenzothiazyl disulfide (MBTS), and the zinc salt of 2-mercaptobenzothiazole (ZMBT); the sulfenamides include N-cyclohexyl-2-benzothiazyl sulfenamide (CBS), N-tert-butyl-2-benzothiazyl sulfenamide (TBBS), and 2-(4-Morpholinyl mercapto) benzothiazole (MOR, MBS; MMBT). MBT, MBTS and CBS are the more widely used thiazoles [5]. Their use has increased in gloves during the last decade and MBT remains the most widely used accelerator for industrial rubber [5]. MBT was found to be the most frequent sensitizer in patients with shoe dermatitis [1].

The prevalences of sensitization to thiazoles are less frequent than it is to thiurams and dithiocarbamates. The prevalences of sensitization to MBT derived from patch test clinics of the ESSCA network varied in the different countries from 0.2 % in Lithuania to 1.3 % in Austria and Poland; the prevalences of sensitization to the mercapto mix (without MBT) varied from 0 % (Finland) to 1.0 % in Austria [31].

Thioureas

Thioureas include dibutylthiourea (DBTU), diethylthiourea (DETU), diphenylthiourea (DPTU), and ethylene thiourea (ETU). They are used in the production of synthetic rubbers, particularly neoprene products and foam rubbers [3, 23, 5]. Thioureas are only rarely used as accelerators in protective rubber gloves [17]. The most frequent source of relevant positive patch test reactions have been

reported to be shoes and medical devices (Fig. 14.1) before gloves [9]. Allergic contact dermatitis to thioureas has occasionally been noted from exposure to rubber, especially neoprene. Thiourea accelerators may decompose to give isothiocyanates [22].

p-Phenylenediamine Derivatives

Among over 100 existing antioxidants, the most important sensitizers are phenylenediamine derivatives: N-isopropyl-N′-phenyl-4-phenylenediamine (IPPD), N-phenyl-N′ cylohexl-4-phenylenediamine (CPPD), N-N′ diphenyl-4-phenylenediamine (DPPD), and N-(1-3 dimethylbutyl)-N′-phenyl-4-phenylenediamine (DMPPD). They are contained in industrial rubber and rubber of black color. Although they are strong sensitizers, the sensitization prevalence to phenylenediamine derivatives is low probably due to automation in the production process [5]. IPPD is included in the baseline series and is an uncommon contact allergen with sensitization prevalences ranging from below 1 % to 1 % [31].

14.1.4.2 Type I Allergens: Natural Rubber Latex Allergens

Of the more than 240 natural rubber latex (NRL) polypeptides, 15 latex proteins (Hev b 1–15) have been officially recognized as allergens by the International Union of Immunological Societies (IUIS) (Table 14.3). Their clinical relevance and connection to the latex-fruit syndrome (cross-reactivity with homologous proteins contained in exotic fruits) have been reviewed [in 36]. Recently, Hev b 1, 2, 5, 6.01, and 13 were identified as major allergens in differently exposed subgroups [28]: Hev b 2, 5, 6.01, and 13 were identified as the major allergens (1) in latex-allergic healthcare workers (HCW) and (2) combined with Hev b 1 and Hev b 3 in latex-allergic patients with spina bifida (SB). (3) In latex-allergic patients without spina bifida who had undergone multiple surgeries (MS), only nHev b 2 and 13 seem to be major Hev b-allergen specificities (with a recognition ≥50 %), whereas IgE responses to rHev b 1, 3, 5, and 6.01 were present, but in <50 %. 8.3 % of the sera showed sIgE response to cross-reactive carbohydrate determinants (CCDs) [28]. Specific IgE binding to CCDs in vitro may be clinically irrelevant and may not induce cross-linking and histamine release in vivo [25]. However, also genuine latex allergens Hev b 2 and 13 are known to be extensively glycosylated. In contrast to glycosylated nHev b 2, unglycosylated rHev b 2 (produced in *E. coli*) was not able to bind specific IgE. In these glycosylated allergens, a combined IgE-binding site is conceivable, composed of a peptide and a carbohydrate epitope [28]. Consequently, in cases with positive IgE anti-CCD results in vitro, the clinical relevance must be critically evaluated within the context of the patient's symptoms [28].

14.2 When to Suspect Rubber Allergy: Clinical Signs

In a sensitized individual, the onset of contact urticaria as a reaction to natural rubber latex allergens will occur minutes to hours after contact, whereas an eczematous delayed-type reaction will occur 1–4 days after skin contact to the respective contact allergen source in the contact area. However, spreading of the skin lesions may

Table 14.3 Protein allergens from natural rubber latex (derived from the sap of the *Hevea brasiliensis* tree)

Identified allergens	Biochemical name	MW (kDa)	Recombinant protein for in vitro diagnostics commercially available
Hev b 1	Rubber elongation factor	14	X
Hev b 2	Beta-1,3-glucanase	34	
Hev b 3	Small rubber particle protein	24	X
Hev b 4	Lecithinase homologue	53–55	
Hev b 5	Acidic latex protein	16	X
Hev b 6	Hevein precursor	20	X
Hev b 7	Patatin-like protein	42	
Hev b 8	Profilin	15	X
Hev b 9	Enolase	51	X
Hev b 10	Superoxide dismutase (Mn)	26	
Hev b 11	Class I chitinase	30	X
Hev b 12	Nonspecific lipid transfer protein 1	9	
Hev b 13	Esterase	42	
Hev b 14	Hevamine	30	
Hev b 15	Serine protease inhibitor	7.5	

occur, depending on the strength of sensitization and the amount of allergen the individual has been exposed to.

Allergic contact dermatitis to rubber additives should be suspected in any patient who wears rubber gloves and presents with a diffuse or patchy dermatitis on the dorsal surface of the hands (skin over the metacarpal phalangeal joints, thenar, and hypothenar), wrists, and distal forearms. However, many patients present with nonspecific patterns of hand dermatitis [9]. Furthermore, contact allergy should be suspected in dermatitis in other locations in contact with rubber products (Table 14.1). In addition to common manifestations of acute, subacute, or chronic eczematous contact dermatitis which may be also airborne, translocated (due to indirect manual transfer e.g. to the face), or systemic due to ingestion, allergic contact dermatitis to rubber has also been described as occasionally presenting as hyperkeratosis (due to amine antioxidants), purpura (due to IPPD or thiuram derivatives), and leukoderma (due to hydroquinone) [5].

In type I allergy to natural rubber latex allergens, wheal and flare reactions in the contact area are characteristic; however, systemic manifestations may occur (contact urticaria syndrome stages 1–4 [35]) presenting as:

Cutaneous reactions only:

Stage 1: Localized urticaria and/or protein contact dermatitis/dermatosis and/or nonspecific symptoms (itching, tingling, burning, etc.)

Stage 2: Generalized urticaria

Extracutaneous reactions:

Stage 3: Bronchial asthma and/or rhinoconjunctivitis and/or orolaryngeal and/or gastrointestinal symptoms

Stage 4: Anaphylactoid (shock) reactions

14.3 How to Test? Basic Allergens and Supplements, Own Products

14.3.1 Patch Testing with Rubber Chemicals to Diagnose Suspected Contact Allergy

The general rules and caveats of patch testing covered in this book also apply for the patch testing with rubber chemicals.

14.3.1.1 Basic Allergens Included in the Standard Patch Test Series [ESCD-Recommendation; 7]

- Thiuram mix (TMTM, TMTD, TETD, PTD) 1 % pet.
- Mercapto mix (MBT, CBS, MBTS, MOR)[1] 2 % pet.
- 2-Mercaptobenzothiazole (MBT) 2 % pet.
- N-Isopropyl-N′-phenyl-4-phenylenediamine[2] 0.1 % pet.
- In some countries, as a supplement to the standard series a "carba mix 3 % pet." (mix of ZDEC 1 % pet., ZDBC 1 % pet., and DPG 1 % pet.) or zinc diethyldithiocarbamate (ZDEC) 1 % pet. is tested as one representative of this class of vulcanizing agents. This is not a frequent allergen; however, cross-reactivity to the antigenically closely related thiurams/thiuram mix is very prominent.

If positive test reactions are found to a mix, subsequent patch testing of its components is recommended to clarify the relevant contact allergen to advise the patient accordingly. In case of suspected rubber allergy, additional rubber allergens should be tested. Table 14.4 summarizes additional commercially available rubber chemicals frequently combined as "rubber series."

14.3.2 In Vivo and In Vitro Tests to Detect Specific IgE to Diagnose Suspected Contact Urticaria to Natural Rubber Latex Allergens

To diagnose a type I allergy to latex, in addition to an indicative clinical history skin prick test and/or intradermal test with latex fluids in combination with determination of specific IgE and a provocation test (e.g., glove use test) have been suggested [18].

In patients with a history of clinical reactivity to latex, latex-specific IgE assays remain useful, although they have a lower sensitivity than previously reported and should not be used for screening the general population [29]. In contrast, in patients

[1] The mercapto mix (CBS, MBTS, MOR) (1 % pet.) without 2-mercaptobenzothiazole (MBT) is being used by most ESSCA departments instead of the mercapto mix including MBT (2 % pet.) due to chemical instability of the 4-component mercapto mix [16, 31].

[2] In some countries, a "black rubber mix" (0.6 % pet.) (a mix of 0.25 % DPPD, 0.25 % CPPD, and 0.1 % IPPD) is used instead of *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine (IPPD).

Table 14.4 Additional commercially available rubber chemicals (frequently combined as rubber series)

Function accelerators	Chemical name	Test conc. and vehicle
Accelerators		
Thiurams	Tetramethylthiuram disulfide (TMTD)	0.25 % pet.
	Tetramethylthiuram monosulfide (TMTM; thiram)	0.25 % pet.
	Tetraethylthiuram disulfide (TETD; disulfiram)	0.25 % pet.
	Dipentamethylenethiuram disulfide (PTD)	0.25 % pet. (or 1.0 % pet)
Dithiocarbamates	Zinc diethyldithiocarbamate (ZDEC)[a]	1 % pet
	Zinc dibutyldithiocarbamate (ZDBC)	1 % pet.
	Zinc dibenzyldithiocarbamate	1 % pet.
	Zinc dimethyldithiocarbamate (Ziram)	1 % pet.
Thiazoles	N-cyclohexyl-2-benzothiazylsulfenamide (CBS)	1 % pet.
	Dibenzothiazyl disulfide (MBTS)	1 % pet.
	2-(4-Morpholinylmercapto) benzothiazole (MOR, MBS; MMBT)	0.5 % pet.
Guanidines	1,3-Diphenylguanidin (DPG)	1 % pet.
Thioureas	Diphenylthiourea (DPTU)	1 % pet.
	Dibutylthiourea (DBTU)	1 % pet.
Antidegradants		
Antioxidant/antiozonant	N,N′-diphenyl-4-phenylenediamine (DPPD)	0.25 % pet. (or 1 % pet.)
Antioxidant/antiozonant	N-cyclohexyl-N-phenyl-4-phenylenediamine (CPPD)	1 % pet.
Antioxidant/antiozonant	N,N-di-2-naphtyl-4-phenylenediamine (DBNPD)	1 % pet.
Antioxidant	Hydroquinone monobenzyl ether (monobenzone)	1 % pet.
Antioxidant	4,4′-Dihydroxydiphenyl	0.1 % pet.
Antioxidant	N-phenyl-2-naphtylamine (PBN)	1 % pet.
Antioxidant	2,2,4-Trimethyl-1,2-dihydroquinoline	1 % pet.
Antioxidant	4,4′-Diaminodiphenylmethane (DADPM)	0.5 % pet.
	(syn. 4,4′-methylenedianiline (MDA))	
Other additives		
Bonding agent	Methenamine (hexamethylenetetramine)	1 % pet. (or 2 % pet.)
Stabilizer	Ethylenediamine dihydrochloride	1 % pet.
Stabilizer	4-tert-Butylcatechol	0.25 % pet.
Retarder	Cyclohexylthiophthalimide	0.5 % pet. (or 1 % pet.)
Retarder	Dodecyl mercaptan	0.1 % pet.
Plasticizer	Dibutyl phthalate	5 % pet.

[a]ZDEC may instead be tested in the baseline series

with pollinosis who have no history of clinical reactivity to latex, commercially available latex-specific IgE assays are often positive, but may not be clinically relevant [29].

It is important to keep in mind that the outcome of in vivo as well as in vitro tests is related to the quality of allergen extracts [33]. The composition of natural rubber extracts is highly dependent on the raw material which may vary in allergen composition even depending on the hour of harvest of rubber sap. Standardization of test material is therefore required [33]. Due to exhaustive and costly standardization procedures, skin test allergen preparations for occupational allergens (e.g., latex) may have never been licensed for in vivo use, or already licensed skin test products may have been voluntarily withdrawn by allergen-producing companies in some countries (e.g., since 2014, no commercial skin prick test solutions for natural rubber latex are any longer available in Germany).

In contrast, in vitro test systems have been improved: the diagnostic sensitivity increased 10 % by spiking the NRL extract used for ImmunoCAP™, while the diagnostic specificity remained the same [19, 28]. Component resolved approaches have been successfully used to diagnose different groups at risk [28]: a combination of rHev b 1 and 3 was able to recognize 87 % of all spina bifida patients with latex sIgE. This included 95 % of SB patients with latex-related symptoms and 83 % who were asymptomatic. However, only 30 % of the latex-allergic MS patients and 17.6 % of latex-allergic HCW could be detected with Hev b 1 and Hev b 3 alone on the allergosorbent. In contrast, a combination of rHev b 5 and 6.01 was able to detect IgE in 92.2 % of all HCW, 71 % of the SB patients with latex sIgE, and 70 % of the MS patients. Combining rHev b 5, 6.01, and nHev b 2 on the allergosorbent permitted identification of 98 % of NRL-allergic HCW and 77 % of SB patients (89 % of SB with and 58 % without latex-related symptoms). A mix of rHev b 5, 6.01, and nHev b 13 on the allergosorbent would result in the correct identification of 100 % of the latex-allergic HCW and an enhanced detection rate of SB patients (80.1 % in the total group, 89 % in the symptomatic, and 67 % in the asymptomatic group) [28].

14.3.3 Pitfalls in Testing

- Consumers feel safe having been using a “hypoallergenic” rubber product and may not take this into consideration as a possible source of contact allergy. However, the product label “hypoallergenic” is not defined. It is frequently used for gloves but also other medical devices (e.g., catheters, stomata, wound dressings, etc.) most often implying that they do not contain natural rubber latex; however, most frequently the content of accelerators is not covered. Most consumers are not aware of the existence of rubber accelerators as potential contact allergens in natural as well as synthetic rubber materials.
- Due to a combined exposure, type I allergy to natural rubber latex and a type IV allergy to a rubber accelerator may coexist which will require to perform both,

patch tests with rubber chemicals and skin prick test/in vitro specific IgE determination for latex allergens.

- Patients are most frequently not aware of the delayed immunologic reaction pattern of type IV allergies to rubber components. When searching for the culprit allergen exposures to decide on the test series and patient's own materials which need to be patch tested, patients most often reflect on their exposures the day when the skin lesions first occurred (which would be helpful to identify elicitors of contact urticaria), but may not spontaneously recall the allergen contact having occurred days before onset of contact dermatitis. To find the relevant exposures, in the interview prior to patch testing, an active request on the patient's skin exposures (Table 14.1) 1–4 days prior to onset of skin lesions is crucial.
- Approximately 20 % of the thiuram-sensitized patients are missed by the mix. Therefore, it is advisable to patch test not only with the baseline series but also with the rubber series in cases of suspected rubber (glove) allergy [17].
- MBT derivatives are metabolized or otherwise converted to MBT in the skin. It could be shown that MBT is the responsible allergen in contact allergy to MBT derivatives [20, 10]. However, by patch testing with MBT only, approximately one quarter of the patients concerned would be missed [17]. Andersen showed that 30 % of sensitized will be missed by patch testing the mercapto mix alone, whereas in contrary, 12 % of the cases negative to MBT will show positive test reactions with the mix [4]. Since a high rate of false-negative results was repeatedly demonstrated when testing with the mix or MBT alone [4, 13, 14, 16, 17], patch testing should be done in parallel with mercapto mix as well as with MBT.
- PPD may only rarely cross-react with IPPD. Therefore, PPD is not a feasible indicator test substance to identify a sensitization against IPPD [31].
- The mix of two thiourea chemicals (DETU and DBTU), also referred to as mixed dialkyl thioureas (MDTU), tested 1 % in pet. will detect 75 % of relevant thiourea reactions [3, 9]. Reactions to other thioureas (diphenylthiourea and ethylene thiourea) will be missed. In case of high suspicions that a thiourea is the cause of dermatitis (e.g., if there is contact to a neoprene product), testing of further thiourea chemicals is recommended to increase the test sensitivity.
- Due to the low diagnostic quality of the test preparation of 1,3-DPG 1 % pet. positive reactions, in particular weak positive reactions, to 1,3-DPG 1 % pet. have to be interpreted very carefully.
  1,3-DPG is sometimes used in rubber glove production, and there are cases of true allergic sensitization [21], but the majority of cases are probably false-positive reactions [15, 17].
- Inconsistent results between patch test results to rubber chemicals and those to pieces of patients' own rubber materials may occur:
  (i) Patch test with patients' own rubber materials may be positive, whereas patch testing with accelerators in the baseline series and rubber series may show negative results. Between 2002 and 2011, $N=292$ patients with suspected contact allergy due to protection gloves were patch tested with their

own gloves in the Allergy Unit of the Department of Dermatology, University Hospital of Erlangen. Forty-eight patients exhibited at least one positive patch test reactions to at least one of their gloves, 46 % ($n=22$) of which exclusively reacted to their own gloves and not to any of the commercial test chemicals contained in the German baseline series and the rubber series or leather series, respectively. Testing patients' own rubber material is a useful element in diagnosing a rubber allergy. Moistening the rubber test piece prior to patch testing with 96 % ethanol instead of water (which was done in parallel in all 292 cases) exhibited 44 % more positive patch test reactions for nitrile gloves (nine positive with alc. versus five with aqua).

(ii) In contrast, a negative test result to the glove piece tested does not exclude an allergy to accelerators having been used during its manufacture according to available information. Patients should not wear gloves to which they had negative patch test results if they had positive results to a chemical listed as present in the glove [9].

- Some patients with positive in vitro tests to the natural latex rubber extract (containing CCDs) are not originally sensitized to latex allergen but exhibit positive test results due to cross-reactivity with other CCD-containing allergen sources (e.g., pollen or insect venom allergens) [25]. Specific IgE binding to carbohydrate determinants is frequently clinically irrelevant. However, except for this IgE binding to clinically irrelevant CCD epitopes, there may be a concomitant IgE binding to glycosylated or non-glycosylated genuine latex proteins. A combined evaluation of patient's clinical history on NRL exposure, in vitro tests (specific IgE against NRL-crude extract, recombinant allergens (non-glycosylated) from *Hevea brasiliensis* and CCD marker allergens (bromelain, horseradish peroxidase; MUXF3)), and in vivo (skin prick and provocation) tests is necessary to diagnose or to rule out a type I allergy to NRL [18, 25].
- Currently, most medical gloves are produced with a low content of natural rubber latex (NRL) protein. Due to their low latex allergen content, a provocation test (glove use test) may be negative, despite clinically relevant latex allergy. A use test may be performed with a latex balloon instead. Gloves with low latex allergen content may have been substituted by unlabeled proteins of foreign origin (e.g., casein from cow's milk) to maintain specific properties of the material, which may induce glove-derived type I sensitization to unexpected allergens [8, 38].

14.4 What to Tell the Patient if They Have a Positive Test?

14.4.1 In General

- If a patch test reaction to a rubber compound is positive, it is mandatory to clarify whether this test reaction is of actual clinical relevance and there is an exposure of the patient to it in the occupational or private environment. This may be challenging since usually rubber products are not or not fully labeled.

Information may be difficult to obtain from the manufacturer due to multiple production sites outside Europe and changing rubber composition of the product from lot to lot.

- If a relevant exposure could be found, further exposure has to be avoided. The patient needs to be informed about possible exposures to rubber chemical contained in rubber as well as in non-rubber materials (Table 14.2). Substitute materials have to be checked. Combined type IV allergies to several rubber additives may have further occupational implications (see below).
- In case neither a substitution of the contact allergen containing rubber material nor implementation of a protective gear to avoid skin contact is possible, it might be necessary that a sensitized individual leaves the respective occupational field (Table 14.2).

14.4.2 Patients Allergic to Dithiocarbamates and/or Thiurams

- Almost all patients with a contact allergy against dithiocarbamates are also allergic against thiurams: vice versa, however, this ratio was only one fifths [15, 21]. This confirms the clinical observation that thiuram-allergic patients will tolerate dithiocarbamate-containing rubber products for a while, before developing also a hypersensitivity toward those [15].
- For patients sensitized against thiurams and dithiocarbamates at the same time, it may be difficult to find adequate elastic protective gloves for specific exposures (e.g., solvents) in cleaning or construction or chemical industries.
- In the individual case, the following occupational areas may be excluded from the job options in a patient if no alternative glove material can be found:
  - Rubber production and processing
  - Handling of cable insulation, sealing, tubes, and tires
  - Farming and floristry
  - Construction
  - Cleaning
  - Chemical industries

14.4.3 In the Medical Field and Hairdressing, Finding Alternative Glove Materials Is More Likely [12]

- For the medical field, several entirely accelerator-free gloves have been developed (e.g., a non-sterile nitrile examination glove (micro-touch™ nitrile accelerator-free) and sterile neoprene surgical gloves (Encore™ Ultra; Gammex™ PF DermaPrene® (Ansell Healthcare Europe N.V.; Brussels, Belgium)) which may be useful for polysensitized individuals.

14.4.4 Patients Allergic to Mercaptobenzothiazole (MBT) and Thiurams

- In contrast to thiurams, MBT is also being used in leather processing and shoemaking. Therefore, in patients sensitized against thiurams and MBT at the same time, a wider field of job options ceases to exist. Identifying adequate gloves for specific exposures may be a challenge [12].

14.4.5 Patients Allergic to IPPD and Thiurams

- Generally, IPPD is not included in protective gloves. In patients allergic to IPPD and thiurams at the same time, occupational fields with exposure to thiurams (production or processing of rubber-molded articles, fields with skin contact to fungicides (farming/floristry) or specific protection glove material) and additionally occupational fields with skin contact to black rubber (production and handling) may be not accessible for the allergic individual any longer [12].

14.4.6 Patients Allergic to MBT and IPPD

- In individuals with MBT and IPPD allergy, rubber production and leather processing may be excluded from the job options due to the MBT sensitization as well as occupational fields with skin contact to black rubber (production and handling) due to the sensitization to IPPD. However, occupational fields which require protection gloves are usually not excluded from the job options in general, since most frequently alternative glove materials can be found [12].

14.4.7 Patients Allergic to Thioureas and 1,3 DPG

- Thioureas and 1,3-DPG may occur in glove material [21] and, however, seem to play less frequently a role in rubber glove contact allergies [15].

14.4.8 Patients Allergic to Natural Rubber Latex

- If a type I allergy to natural rubber latex allergens has been diagnosed, the allergic individual needs to be informed about possible exposures to natural rubber latex and the necessary avoidance of skin and airborne contact. At the workplace, the use of powdered gloves needs to be banned for the allergic individual and his/her coworkers to reduce airborne distribution of latex allergens bound to powder particles to allow a latex-allergic individual to continue working [2, 24].

- Preventive prescription of emergency medication (epinephrine autoinjector and further antiallergic add-on medications (H1 receptor antagonists, glucocorticosteroids)) may be advisable for patients at risk for anaphylaxis recurrence in community settings [29] due to accidental contact to natural rubber latex allergens. It is necessary to become familiar with the handling of the autoinjector (ideally by practicing with a dummy autoinjector) and carry it consistently.

14.5 Prognosis

Two years after recognition of occupational disease due to type IV allergy to a rubber chemical or type I allergy to latex, both ubiquitous allergens, only 10 % of cases allergic to rubber chemicals had total clearance of eczema compared to 0 % of those with contact urticaria to natural rubber latex [11]. Sixty percent of those still exposed to the respective allergen at work and 76 % of those not any longer exposed at work reported improvement of skin lesions, whereas 40 % still exposed and 24 % not any longer exposed at work reported no improvement [11]. Improvement was significantly more frequent in those who had changed jobs compared with those who had not changed jobs ($P = 0.010$); this was statistically significant for patients allergic to rubber chemicals and natural rubber latex.

These findings from Denmark are in concordance with recent findings from Germany: whereas primary prevention measures (banning powdered NRL gloves and defining a threshold of 30 µg of leachable protein/gram glove [24]) have proven to successfully lower the incidence of new cases of occupational contact urticaria caused by natural rubber latex [2], 35 % of healthcare workers with latex allergy diagnosed at least 3 years before the follow-up examination still recurrently experienced ongoing work-related (mostly mild) clinical symptoms of the eyes, nose, or airways giving evidence for a need for further secondary preventive measures [26].

14.6 Check List of What to Think About/Action Points

- Identify exposure to rubber materials in the patient's occupational as well as the private environment (see Tables 14.1 and 14.2).
- Patch test baseline and rubber series as well as patient's own materials, eventually according to history: test for specific IgE to NRL in vitro and/or – if possible – in vivo.
- If positive: dig deeper to receive information of contactants and their ingredients.
- Check availability of substitute materials.
- Inform patient about contact allergen avoidance measures.
- If the exposure is occupational: file note to authority in charge (according to national regulations).

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