Quick Guide to Contact Dermatitis

Jeanne Duus Johansen
Jean-Pierre Lepoittevin
Jacob P. Thyssen
Editors

Springer

Quick Guide to Contact Dermatitis

Jeanne Duus Johansen
Jean-Pierre Lepoittevin • Jacob P. Thyssen
Editors

Quick Guide to Contact Dermatitis

Springer

Editors
Jeanne Duus Johansen
Gentofte Hospital
National Allergy Research Centre
Hellerup, Denmark

Jacob P. Thyssen
Department of Dermato-Allergology
Gentofte Hospital
Hellerup, Denmark

Jean-Pierre Lepoittevin
Laboratoire de Dermatochimie
University of Strasbourg
Strasbourg cedex, France

ISBN 978-3-662-47713-7 ISBN 978-3-662-47714-4 (eBook)
DOI 10.1007/978-3-662-47714-4

Library of Congress Control Number: 2015951817

Springer Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer-Verlag GmbH Berlin Heidelberg is part of Springer Science+Business Media (www.springer.com)

Contents

Contributors

Kristiina Aalto-Korte, MD, PhD Health and Word Ability, Finnish Institute of Occupational Health, Helsinki, Finland

Anne Birgitte Simonsen, MD Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

Klaus Ejner Andersen, MD, DMsc Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Odense, Denmark

Ulrik Fischer-Friis, PhD Department of Derma-Allergology, National Allergy Research Centre, Copenhagen University Hospital Gentofte, Hellerup, Denmark

Kristian Fredløv Mose, MD Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Odense, Denmark

Johannes Geier, MD IVDK, University of Göttingen, Göttingen, Germany

Ana Gimenez-Arnau, MD, PhD Department of Dermatology, Hospital del Mar. Universitat Autònoma de Barcelona, Barcelona, Spain

Margarida Gonçalo, MD Clinic of Dermatology, University Hospital and Faculty of Medicine, University of Coimbra, Coimbra, Portugal

An Goossens, RParm, PhD Contact Allergy Unit, Department of Dermatology, University Hospital K.U.Leuven, Leuven, Belgium

Marléne Isaksson, MD, PhD Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Skåne, Sweden

Jeanne Duus Johansen, MD DMsc Department of Dermato-allergology, National Allergy Research Centre, Copenhagen University Hospital Gentofte, Hellerup, Denmark

Anneli Julander, PhD Unit of Occupational and Environmental Dermatology, Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden

Christophe J. Le Coz, MD Laboratoire de Dermatochimie, University of Strasbourg, ILB, Strasbourg, France

Jean-Pierre Lepoittevin, DSc Laboratoire de Dermatochimie, University of Strasbourg, ILB, Strasbourg, France

Christopher Lovell, MB, ChB, MD, FRCP Department of Dermatology, Royal United Hospital, Bath NHS Trust – RD1, Bath, UK

Bruze Magnus, MD, PhD Department of Occupational and Environmental Dermatology, University Hospital, University of Lund, Malmö, Sweden

Vera Mahler, MD Department of Dermatology, University Hospital of Erlangen, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Bavaria, Germany

Laura Malinauskiene, MD, PhD Department of Occupational and Environmental Dermatology, Lund University, Skåne University Hospital, Malmö, Sweden

Department of Pulmonology and Allergology, Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania

Swen Malte John, MD, PhD Department of Dermatology, Environmental Medicine and Health Theory, Lower Saxonian Institute of Occupational Dermatology (NIB), University of Osnabrueck, Osnabrück, Germany

John McFadden, BM, DM, FRCP Department of Cutaneous Allergy, St John's Institute of Dermatology, St Thomas' Hospital, King's College, London, UK

Kristina Morgardt-Ryberg, MD, PhD Department of Occupational and Environmental Dermatology, Lund University, Skåne University Hospital, Malmö, Sweden

Department of Dermatology, Uddevalla Hospital, Uddevalla, Sweden

Suchismita Paul, BA Harvard Medical School, Boston, MA, USA

Thomas Rustemeyer, MD, PhD Department of Dermatology and Allergology, VU university medical center, Amsterdam, The Netherlands

Peter C. Schalock, MD Department of Dermatology, Massachusetts General Hospital, Harvard Medical School/Dermatology, Boston, MA, USA

Marie-Louise Anna Schuttelaar, MD, PhD Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Vanessa Smith, MRCP Department of Dermatology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Mette Sommerlund, MD, PhD Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

Apra Sood, MD Department of Dermatology and Plastic Surgery, Cleveland Clinic, Cleveland, OH, USA

Meike Strunk Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrueck, Osnabrueck, Germany

Cecilia Svedman, MD, PhD Department of Occupational and Environmental Dermatology, Skane University Hospital, University of Lund, Malmö, Sweden

James S. Taylor, MD Dermatology-Plastic Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

Anja Thielitz, MD Department of Dermatology, Institute for Interdisciplinary Dermatologic Prevention and Rehabilitation (iDerm) of the University of Osnabrück, Dermatologic Centre, Trauma Hospital, Hamburg, Germany

Jacob P. Thyssen, MD, PhD Department of Dermato-Allergology, Allergy Research Centre, Copenhagen University Hospital Gentofte, Hellerup, Denmark

Wolfgang Uter, MD, PhD Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Erlangen, Germany

Niels K. Veien, MD, PhD Honorary professor of Dermatology, University of Aarhus, Aarhus, Denmark

S. Mark Wilkinson, MD, FRCP Department of Dermatology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Britta Wulfhorst Faculty of Human Sciences, Medical School Hamburg, Hamburg, Germany

Sherry H. Yu, BS, BA School of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH, USA

Part I

General Aspects

Immunological Background of Allergic Contact Dermatitis

1

Thomas Rustemeyer

Contents

Abbreviations

APC	Antigen-presenting cells
CCL	C-C chemokine ligand
CCR	C-C chemokine receptor
CD	Classification determinant
IFN-γ	Interferon-γ
IL	Interleukin
MHC	Major histocompatibility complex
TGF-β	Transforming growth factor-β
Th	T-helper cell

T. Rustemeyer, MD, PhD
Department of Dermatology and Allergology, VU University Medical Center,
De Boelelaan 1117, Amsterdam 1081 HV, The Netherlands
e-mail: t.rustemeyer@vumc.nl

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_1

1.1 Introduction

Allergic contact dermatitis is an acquired immunological inflammation in response to contact with specific allergens which are recognized by pro-inflammatory T cells. The majority of contact allergens are small molecules which can penetrate the epidermal barrier. In the skin, dendritic cells can pick up the allergen and present it on their cellular surface in the context of MHC class I and/or class II molecules. The release of unspecific danger signals facilitates the activation of dendritic cells. This allows for the maturation of allergen-presenting dendritic cells in the epidermis and dermis. The activated and fully matured dendritic cells migrate to the draining lymph nodes and present the allergen to T cells. They start to proliferate and form effector cells, which can get activated upon contact to their specific allergen. From now on, allergen contacts can induce allergen-specific T-cell-mediated immune responses with the clinical picture of allergic contact dermatitis. In the following sections, all major immunological events will be discussed (Fig. 1.1).

1.2 Allergens

Most of the contact allergens are small and chemically reactive molecules not exceeding a molecular weight of 800 Dalton. Due to their size, they can penetrate through the epidermal barrier. In the epidermis and dermis, they can react with endogenous peptides and form immunologically relevant allergen-carrier complex. For some allergens, an enzymatic of metabolic activation step is needed to generate the actual allergen.

In principal, all contact allergens have to a certain extent irritant properties. This irritancy can add to the allergenic potency by triggering the release of innate danger signals from immune cells.

1.3 Antigen-Presenting Cells

In the epidermis and dermis are different types of professional antigen-presenting dendritic cells. Their common feature is the capacity to pick up and present antigens to other cells of the immune system. The epidermal antigen-presenting cells are called Langerhans cells, and the dermal types are summarized as dermal dendritic cells. Upon contact with contact allergens, dendritic cells get activated. The release of pro-inflammatory danger signals from surrounding cells or directly from the dendritic cells amplifies this activation. Under the inflammatory pressure, dendritic cells get fully matured and start to emigrate from (epi)dermal structures via the lymphatic vessels toward the draining lymph nodes. Here, they get attracted by chemokines binding to the chemokine receptor CCR7, which is expressed on the cellular surface of matured dendritic cells. This allows antigen-presenting cells to settle in the subcapsular compartments of the draining lymph nodes.

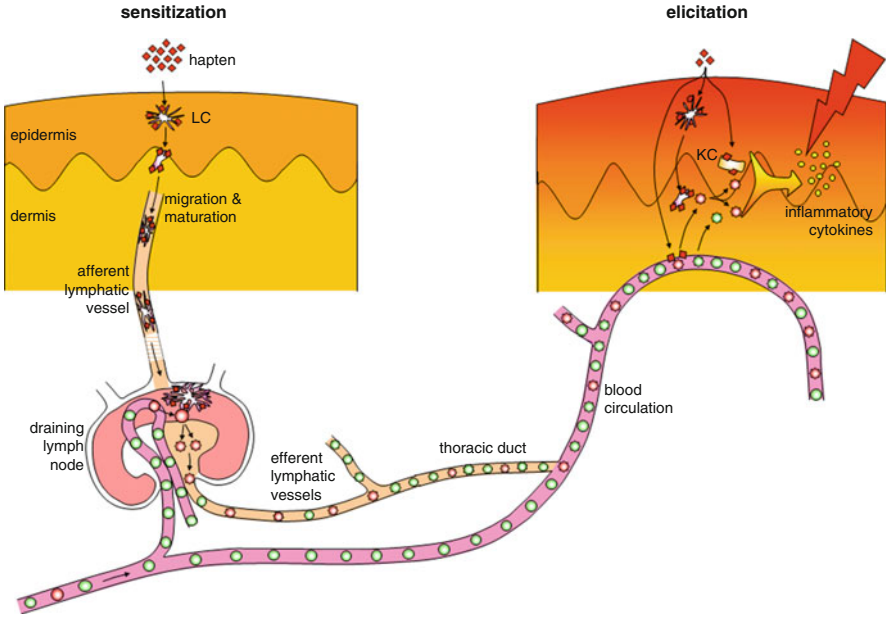


Fig. 1.1 Major immunological events in allergic contact dermatitis. In the induction phase of allergic contact dermatitis (*left side* of the drawing), skin contact with a contact allergen triggers migration and maturation of antigen-presenting cells (*APC*). These cells reach via the afferent lymphatic vessels the regional skin-draining lymph node. Allergen-presenting dendritic cells home into the T-cell-rich paracortical areas. Here, local conditions are optimal for encountering naive T cells that recognize allergen–MHC molecule complexes. During T-cell priming, hapten-specific T cells strongly proliferate and generate effector and memory cells, which are partly released into the circulation. Renewed allergen contact leads to the elicitation reaction (shown at the *right side*). Allergen-specific effector T cells are triggered to produce pro-inflammatory cytokines. Thereby, more inflammatory cells are recruited to the allergen contact site which results in strong local inflammatory mediator release. This leads to a gradually increasing inflammatory reaction, reaching a maximum within one to few days, after which reactivity successively declines (*Kanerva's Occupational Dermatology*, 2012 Editors: Thomas Rustemeyer, Peter Elsner, Swen-Malte John, Howard I. Maibach et al. ©Springer-Verlag Berlin Heidelberg 2012, with Permission of Springer Science+Business Media)

1.4 Priming of Allergen-Specific T Cells

In the draining lymph nodes, naive T cells can extravasate from capillaries and patrol in the subcapsular compartments. If they encounter properly presented antigen which fits in the groves of their specific T-cell receptors, they get the first signal for getting activated ("antigen-specific signal"). If the antigen is presented in the context of MHC class I molecules on the surface of the dendritic cell, then $CD8^+$ T cells do recognize it. In analogy, presentation of antigen by MHC class II molecules results in the recognition by $CD4^+$ T cells. The second signal consists of sufficient interaction of co-stimulatory cell membrane-bound signals of both matured

dendritic cells and naive T cells ("receptor-mediated co-stimulatory signal"). These two signals stimulate the priming of allergen-specific T cells from the naive state into the antigen-experienced state. The primed T cells start to proliferate, which can result in swelling of the lymph node. The presence of soluble immunological mediators in the microenvironment of the T cells can skew developing T cells toward distinct effector subtypes (third signal: "cytokine-driven T-cell skewing"). These local cytokines are generated by antigen-matured dendritic cells and by resident stromal cells of the lymph node. As a consequence, the generating allergen-specific T cells can either become pro-inflammatory cells or immunoregulatory T cells. The first T-cell types can be subdivided into Th1 cells, characterized by the production of IFN-γ in particular; Th2 with a predominant production of IL-4, IL-5, and IL-13; and Th17 with high IL-17 and IL-23 production. The latter T cells have immunoregulatory properties and can either actively suppress pro-inflammatory reactions, then they are called suppressor T cells or cause antigen-specific tolerance. These cells are characterized by the release of immunosuppressive/-regulatory cytokines such as IL-10 and TGF-β. Furthermore, a subset of primed T cells keep homing receptors to settle in the draining lymph node. These cells express CCR7 and bind their ligand CCL19 expressed in the subcapsular compartment. They form the long-term immunological memory and are called central memory T cells. In contrast, $CCR7^-$ T cells have to leave the lymph node and become peripheral effector/memory T cells. These T cells recirculate in the blood and control peripheral tissues. In summary, during the priming of allergen-specific T cells, functionally different subsets can develop. These subsets determine the immunological outcome and clinical appearance of the elicitation reaction in allergic contact dermatitis.

1.5 Elicitation Reaction

In case of repeated contact with the specific allergen, an elicitation reaction can occur. Hereto, less allergen suffices to stimulate the immunological reaction. As during the sensitization reaction, allergen binds to endogenous peptides and proteins and gets presented by antigen-presenting cells. In contrast to the sensitization reaction, also nonprofessional antigen-presenting cells such as keratinocytes and endothelial cells can present the allergen in a sufficient manner to stimulate allergen-specific T cells since these primed T cells are not longer dependent on the allergen presentation by professional antigen-presenting cells. When the allergen gets detected by randomly bypassing allergen-specific T cells, they start to produce and to secrete their specific cytokines. In case of a developing allergic contact dermatitis reaction, pro-inflammatory effector T cells belonging to Th1, Th2, or Th17 subsets secrete pro-inflammatory cytokines. This drives the attraction and subsequent activation of infiltrated immunological cells and resident tissue cells. The massive release of inflammatory mediators causes vasodilatation, edema, spongiosis, and vesiculation. The development of this delayed immunological response can take several days. In later phases of acute allergic contact dermatitis reactions, the allergen is eliminated by either metabolization or taken away by phagocytes. As a

consequence, the inflammatory reaction starts to silence and fades away. In case of longer-lasting allergen exposures, epidermal changes can occur with acanthosis and hyperkeratosis and desquamation of the keratinocytes. Although complete clinical healing can occur, few allergen-specific T cells can reside at sites of former allergen exposure. These T cells form a local skin memory. Upon repeated local allergen exposure, these cells get more easily activated and can already show clinical reactions within several hours. The residing allergen-specific cells cause a local lower activation threshold of allergic contact dermatitis reactions.

1.6 Immunological Tolerance

Under certain conditions, the priming of allergen-specific T cells can result in anti-inflammatory T cells. These T cells are rather immunosuppressive and tolerogenic. In particular, primary allergen contacts via oral mucosa seem to stimulate the generation of tolerogenic allergen-specific T cells. Individuals who are tolerized in this way are protected from developing sensitization and getting allergic contact dermatitis reactions at later allergen contacts.

Further Reading

Rustemeyer T, Ingrid MW, van Hoogstraten B, von Blomberg ME, Gibbs S, Scheper, RJ. Mechanisms of irritant and allergic contact dermatitis. In: Johansen JD, Frosch, PJ, Lepoittevin, J-P, editors. Contact dermatitis. 5th ed; 2011. p. 43–91.

Clinical Features of Contact Dermatitis

2

Niels K. Veien

Contents

2.1 Introduction

A significant proportion of patients referred to a general practice of dermatology have eczema/dermatitis. The two terms will be used interchangeably in the following.

The most common etiological diagnoses of eczema are atopic dermatitis, seborrheic dermatitis, and contact dermatitis. Nummular eczema and stasis dermatitis are less commonly seen.

N.K. Veien, MD, PhD
Honorary professor of Dermatology, University of Aarhus, Aarhus, Denmark
e-mail: veien@dadlnet.dk

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_2

The diagnoses of atopic dermatitis (Fig. 2.1) and seborrheic dermatitis (Figs. 2.2 and 2.3) are made on clinical grounds, based mainly on the history of the patient in combination with a physical examination. For practical purposes, stasis dermatitis is seen only below the knees and in persons with a damaged venous system. Nummular eczema is a morphological diagnosis based on well-circumscribed patches of eczema (Fig. 2.4).

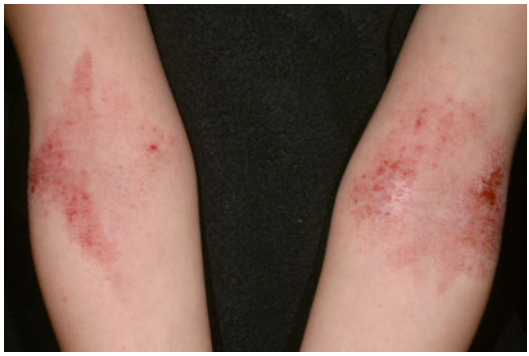


Fig. 2.1 Atopic dermatitis of the antecubital fossa

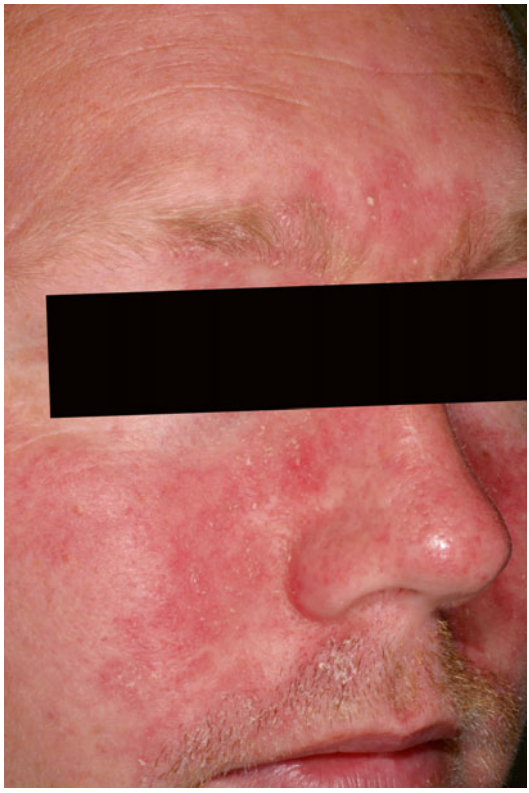


Fig. 2.2 Seborrheic dermatitis of the face

Fig. 2.3 Seborrheic dermatitis of the medial aspect of the eyebrow

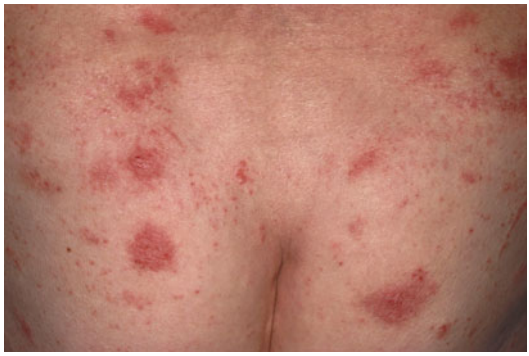


Fig. 2.4 Nummular dermatitis

By definition, contact dermatitis is the result of interaction between the skin and an object in contact with the skin. Contact dermatitis can be irritant or allergic. Protein contact dermatitis is a less common variant (see Chap. 8) as are phototoxic and photoallergic contact dermatitis (see Chap. 7). In sensitized persons, systemic presentation of the hapten may cause systemic contact dermatitis.

In addition to the history of the patient and a physical examination, a diagnosis of allergic contact dermatitis or protein contact dermatitis is based on the results of cutaneous testing. Patch testing is the basic test method in diagnosing allergic contact dermatitis (see Chap. 3). Test batteries are designed to take into account the most common allergens in a specific geographical region (see Chap. 5).

In addition to patch testing, prick tests and prick-prick testing may be indicated in selected cases of suspected protein contact dermatitis (see Chap. 8). In vitro test methods such as lymphocyte proliferation tests have not to date been shown to be useful routine test methods in diagnosing allergic contact dermatitis.

In most cases, it is not possible to distinguish between irritant and allergic contact dermatitis on clinical grounds. The diagnosis of irritant contact dermatitis is based on the history of the patient, the pattern of exposure, the physical findings, and the exclusion of allergic contact dermatitis.

It should be stressed that persons with seborrheic dermatitis, atopic dermatitis, or nummular eczema may develop secondary contact sensitization, thus complicating the fundamental diagnosis [1].

2.2 Clinical Features

Pruritus is the predominant symptom of contact dermatitis. Stinging with few physical signs may be experienced, and phototoxic reactions may be accompanied by a severe burning sensation.

Onset of symptoms is from seconds to minutes in contact urticaria to hours or days in contact dermatitis.

Acute contact dermatitis is characterized by erythema, edema, infiltration, and possibly vesicles (Fig. 2.5) in an area of skin that has been in contact with either an irritant or a substance to which the person has developed contact allergy. Chronic dermatitis is characterized by erythema, infiltration, scaling, and fissures (Fig. 2.6).

A contact pattern is the classic clinical manifestation of contact dermatitis. The most common example of this pattern is nickel dermatitis. Nickel dermatitis develops in areas of the skin in direct contact with nickel-plated objects such as buttons, clasps, buckles (Fig. 2.7), or cell phones with nickel-plated keys (Fig. 2.8).

Exposure patterns to nickel may not be as obvious as in typical allergic nickel contact dermatitis. Nickel dermatitis caused by cell phones with nickel-plated keys may, for example, be seen on the cheeks, on the sternum if the phone is carried in a pouch around the neck, or on the thigh if the phone is carried in a trouser pocket.

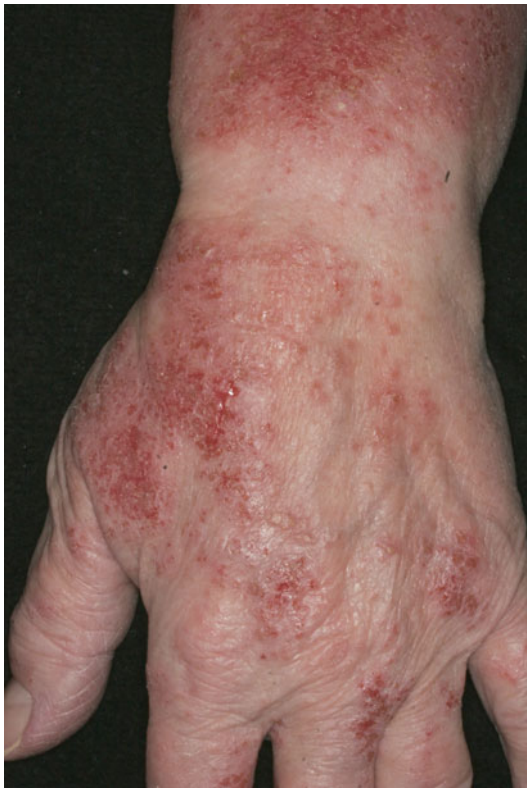


Fig. 2.5 Acute irritant contact dermatitis on the dorsal aspect of a hand

Airborne contact dermatitis is another clinical pattern of contact dermatitis. Dust, vapors, or fibers may cause dermatitis, typically seen on the exposed skin of the face, in particular on the eyelids, the sides and back of the neck, the forearms, and/or the dorsal aspects of the hands (Fig. 2.9) [2].

Connubial dermatitis is a term used to describe secondary exposure from a spouse or from mother to child (Fig. 2.10).

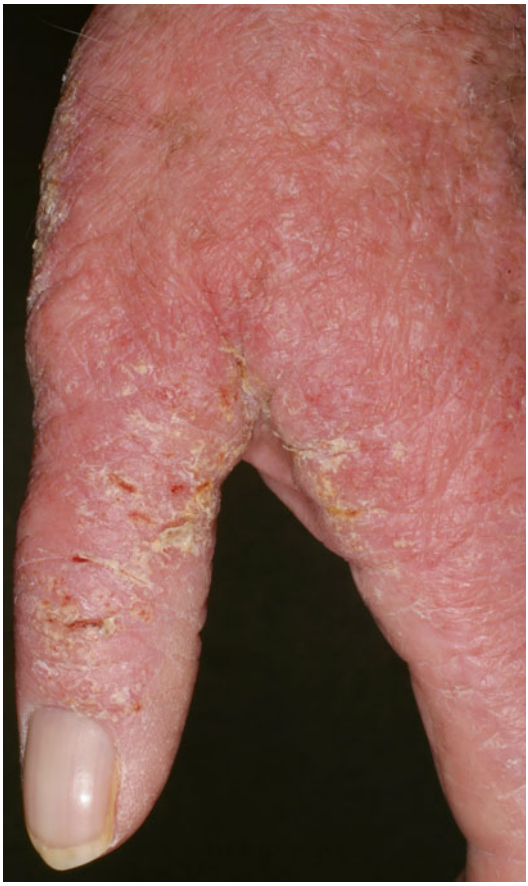


Fig. 2.6 Chronic contact dermatitis on a hand

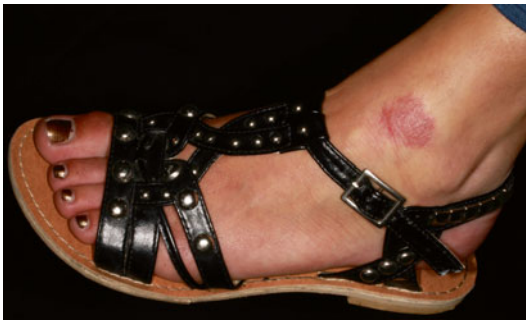


Fig. 2.7 Allergic contact dermatitis caused by nickel in the metal buckle on a sandal

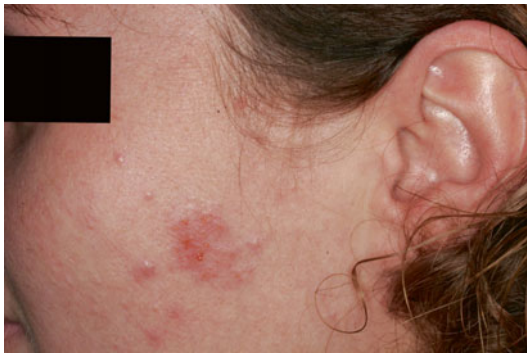


Fig. 2.8 Allergic contact dermatitis caused by nickel in a mobile phone

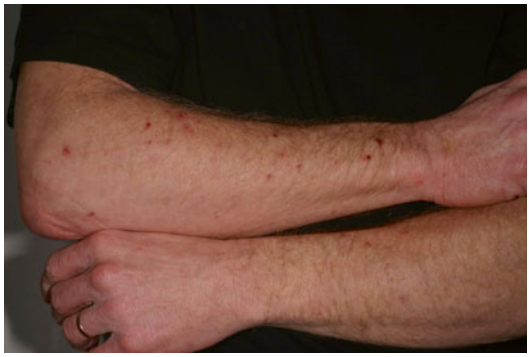


Fig. 2.9 Airborne irritant contact dermatitis caused by glass fiber used in a wind turbine wing factory

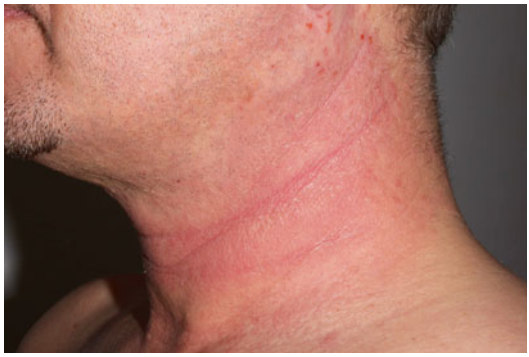


Fig. 2.10 Connubial contact dermatitis caused by contact allergy to para-toluenediamine in a hair dye used by the spouse

A striped pattern of dermatitis can be caused by irritant liquids running down an arm or a leg. A more common cause of a striped pattern of dermatitis is phototoxic contact dermatitis from plants that brush against the skin (Fig. 2.11). Phototoxic dermatitis is often vesicular or bullous and painful. The diagnosis of phototoxic contact dermatitis from plants is usually fairly obvious from the pattern of exposure (see more about plant dermatitis in Chap. 22). Unusual histories include phototoxic contact dermatitis around the mouth caused by repeated sucking on a lime and rashes in children exposed to rue rubbed on the skin to protect against mosquito bites.

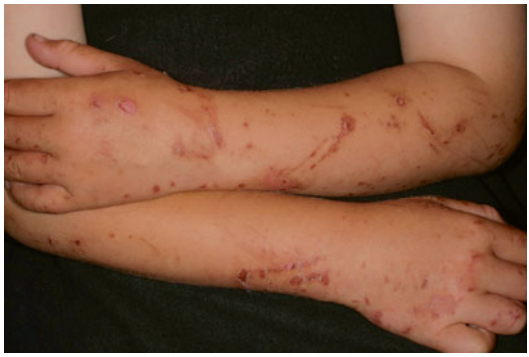


Fig. 2.11 Phototoxic dermatitis caused by contact with wild parsnip

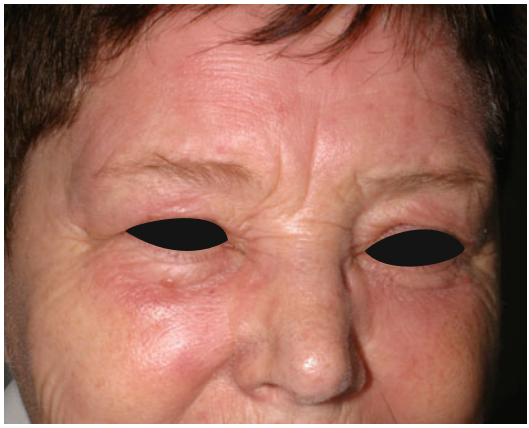


Fig. 2.12 Periorbital edema caused by allergic contact dermatitis to para-toluenediamine in hair dye

Contact dermatitis in areas with loose subcutaneous tissue often becomes edematous. One example is edema of the eyelids following contact dermatitis of the scalp and forehead (Fig. 2.12). Another example is edema of the penis associated with contact dermatitis in the pubic area.

The clinical features of contact dermatitis include less common manifestations [3]. Purpuric contact dermatitis may occur following sensitization to N-isopropyl-N-phenyl-paraphenylenediamine (IPPD) used as an antioxidant in rubber or after sensitization to some textile dyes as well as to balsam of Peru. Irritant contact dermatitis from fiberglass may also induce purpura.

Textile dyes and optical whiteners have also been described as the cause of pigmented contact dermatitis [4]. It is not always possible to identify the cause of pigmented contact dermatitis (Fig. 2.13).

Color developers have caused lichenoid contact dermatitis with lichen planus-like morphology. Hyperpigmentation follows resolution of the dermatitis. While, initially, positive patch tests have the usual morphology, they may later become lichenoid. Contact stomatitis of the oral mucosa may be lichenoid.

Erythema multiforme-like eruptions are occasionally seen, particularly in connection with allergic contact dermatitis caused by strong allergens such as certain

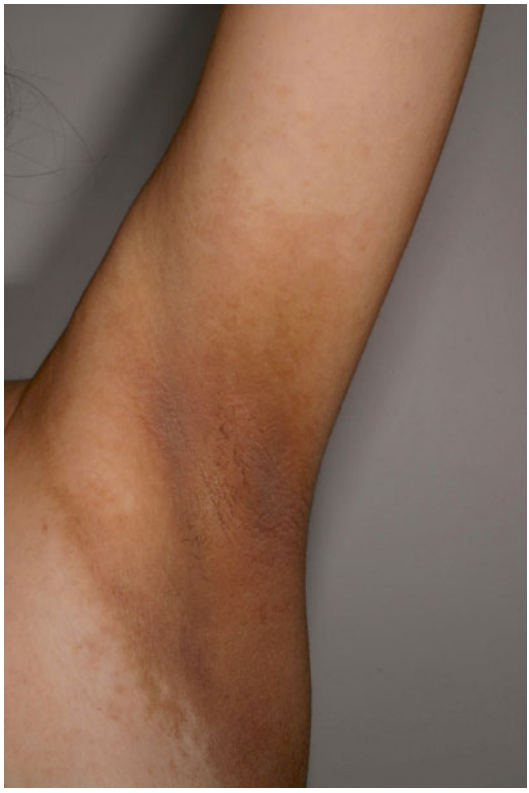


Fig. 2.13 Pigmented contact dermatitis. The specific cause was not identified in spite of extensive patch testing

exotic woods and other plants and para-phenylenediamine. Characteristically, intense contact dermatitis initially appears at the site of contact. After 1–2 weeks, erythema multiforme-like eruptions appear (Fig. 2.14). The eruption fades once the contact allergen is removed. A short course of systemic steroid may be useful in hastening the resolution.

In rare instances, contact dermatitis can present as lymphomatoid tissue reactions with clinical features similar to parapsoriasis en plaques. The most common causes of this clinical manifestation are para-phenylenediamine, gold, and ethylenediamine.

2.3 Regional Contact Dermatitis

In the following, contact dermatitis typically seen in specific areas of the body (the scalp and face, the trunk, the hands, and the feet) will be described in greater detail (see Table 2.1).

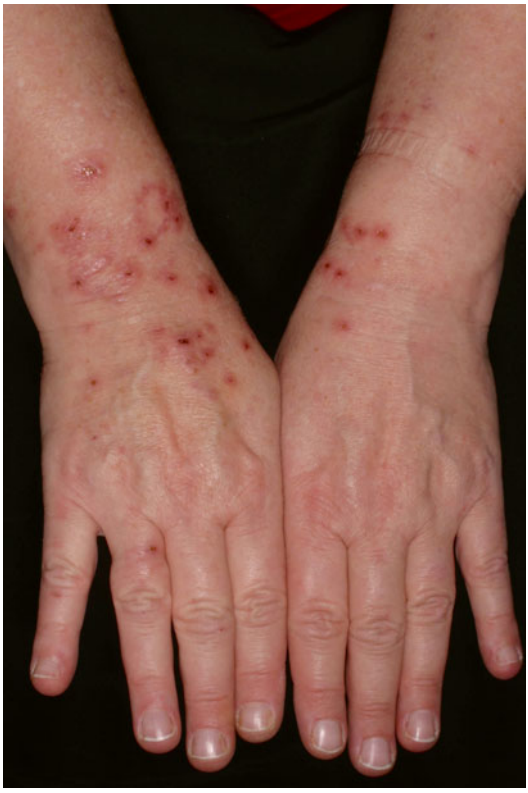


Fig. 2.14 An erythema multiforme-like reaction caused by allergic contact dermatitis

2.3.1 Irritant Contact Dermatitis of the Scalp

Contact dermatitis of the scalp can be either irritant or allergic. There is often more visible dermatitis at the periphery of the scalp, on, for example, the forehead and/or the neck (Fig. 2.15).

Hair care products are the most common cause of contact dermatitis of the scalp. Bleaching the hair or the use of topical drugs such as minoxidil or calcipotriol may cause irritant contact dermatitis Acute, severe irritant dermatitis in the form of chemical burns on the scalp has been described as a result, in particular, of highlighting procedures [5].

2.3.2 Allergic Contact Dermatitis of the Scalp

Hair coloring agents containing para-phenylenediamine or para-toluenediamine are common causes of allergic contact dermatitis of the scalp. Perfumes, preservatives

Table 2.1 Common irritants/allergens

Irritant	Allergic
Face and scalp	
Hair bleaching products	Fragrances
Fibers (rock wool, glass wool, plants)	Hair coloring agents
Topical drugs for treatment of acne	Preservatives
Topical drugs for treatment of actinic keratosis	
Trunk	
Fibers in clothing	Dyes in clothing
Urine and feces (stoma dermatitis and diaper dermatitis)	Nickel in clasps and buckles
Cream soaps (misuse)	Rubber additives in undergarments
Hands	
Detergents	Fragrances
Wet work	Thiurams
Soluble oils	Potassium dichromate
Disinfectants	Preservatives
Cement	
Foods (vegetables, fruit, fish, meat)	
Feet	
Cement	Potassium dichromate
Wood dust	Mercaptobenzothiazole
Wet work	Dimethyl fumarate

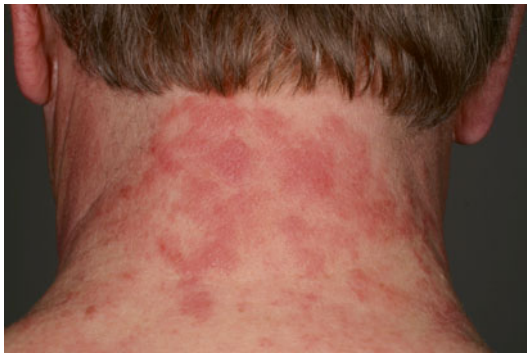


Fig. 2.15 Irritant contact dermatitis caused by a hair care product. The dermatitis was more pronounced on the neck than on the scalp itself

in hair care products, and bleaching products containing ammonium persulfate are other common causes of allergic contact dermatitis of the scalp [6].

Less commonly, topical medications such as steroids, minoxidil, diphenylcyclopropenone, or glues used to attach wigs cause contact allergy.

2.3.3 Irritant Contact Dermatitis of the Face

Airborne irritants such as fibers from fiberglass used, for example, for insulation or in the production of wind turbine wings or plant products such as grain dust may cause facial irritant contact dermatitis [7].

Caustic substances such as sodium hydroxide may inadvertently splash onto the face and cause a severe irritant reaction (Fig. 2.16). Seepage of sputum into folds at the corners of the mouth commonly causes irritant contact dermatitis in older persons with deep folds (Fig. 2.17).

If used too vigorously, topical acne drugs like retinoids and benzoyl peroxide may cause irritant contact dermatitis at the sites of contact. Similarly, preparations used to treat actinic keratosis commonly cause irritant contact dermatitis (Fig. 2.18).

Irritant contact dermatitis from cosmetics is rare, as manufacturers are careful to limit the use of irritant compounds in facial preparations.

2.3.4 Allergic Contact Dermatitis of the Face

Allergic contact dermatitis of the face, on the other hand, is common and is commonly caused by cosmetic products [8]. Fragrances and preservatives are the most common causes, although emulsifiers and other ingredients may also induce allergic contact dermatitis.

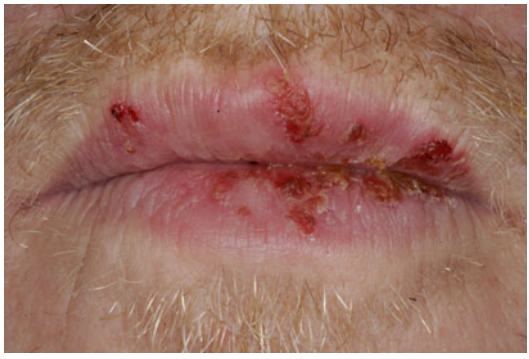


Fig. 2.16 A caustic reaction caused by a sodium hydroxide solution inadvertently splashed onto the face

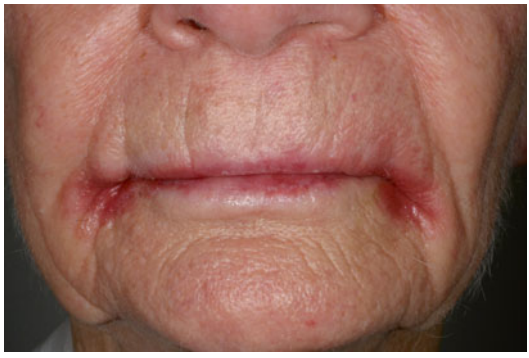


Fig. 2.17 Irritant contact dermatitis caused by sputum that had seeped into folds on the lateral aspects of the mouth

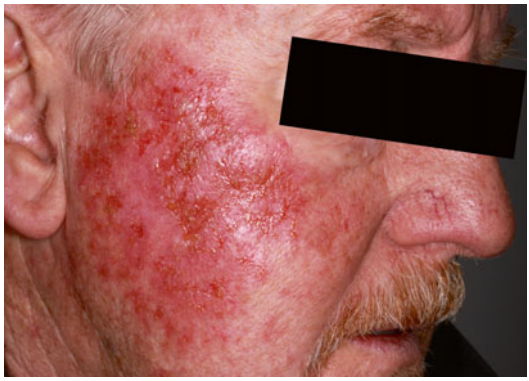


Fig. 2.18 Irritant contact dermatitis caused by diclofenac gel used to treat actinic keratoses of the face

Airborne patterns of allergic contact dermatitis in the face may be caused by dust from plants, particularly of *Composita* species (see Chap. 22), from methylisothiazolinone used in paint, and from epoxy products used in the wind turbine industry.

In a large study of periorbital dermatitis, younger persons were shown to be more likely to have positive patch tests to cosmetic ingredients, while older persons had more reactions to ingredients in topical medications used to treat eye conditions [9].

Ingredients in lipstick and components of musical instruments and orthodontic appliances may cause facial dermatitis and allergic cheilitis.

Photoallergic contact dermatitis of the face is rare. Causative agents may be sunscreen chemicals and cosmetics. Phototoxic contact dermatitis of the face may follow contact with Umbelliferae plants, figs, or citrus fruits in drinks.

2.3.5 Irritant Contact Dermatitis of the Trunk

Dermatitis caused by clothing is most often seen where clothing is in close contact with the skin, e.g., the axillary folds, the sides of the trunk, and the abdomen.

Stoma dermatitis is commonly caused by irritants in feces or urine [10].

Diaper dermatitis is usually irritant and typically located at the top of the folds of skin in the diaper area. Irritants from urine and feces and mechanical trauma are the most common causes. Modern diaper materials are less likely to cause diaper rash than older types of diapers [11]. It is worrying that wet wipes used in the perianal area caused sensitization to methylisothiazolinone in children.

2.3.6 Allergic Contact Dermatitis of the Trunk

Classic allergic contact dermatitis of the trunk is allergic contact dermatitis caused by nickel and presents as periumbilical dermatitis. This type of dermatitis is less

common after the adoption of a nickel regulation by European Union countries [12]. However, the legislation is not fully protective and items such as belt buckles may still cause allergic contact dermatitis to nickel (Fig. 2.7).

Rubber additives may cause allergic contact dermatitis where elastic is in contact with the skin. This includes sites of contact with brassieres and other undergarments.

Disperse blue 106 and 124 and disperse yellow-3 and para-phenylenediamine were the most common causes of allergic textile dermatitis in a recent large study in Italy [13].

Allergic contact dermatitis from dimethyl fumarate became known as Chinese sofa dermatitis and is often seen as severely inflamed dermatitis of the trunk and extremities from prolonged contact with furniture [14] (Fig. 2.19). Dimethyl fumarate in footwear and wallets has also caused dermatitis at sites of contract.

Allergic stoma contact dermatitis is rare.

2.3.7 Irritant Contact Dermatitis of the Hands

The hands are the most common site of contact dermatitis. One-third of patch-tested persons in Denmark have hand eczema.

Irritant hand eczema is more common than allergic contact dermatitis [15], but the two may occur in combination [16]. Acute irritant contact dermatitis on the hands in a person who has not previously had hand eczema can often be linked to a specific exposure, and the dermatitis is typically seen where exposure was most intense.

It is rarely possible to distinguish between chronic irritant and chronic allergic contact dermatitis based on the morphology of the dermatitis. Allergy testing, primarily patch testing, must be carried out. As a minimum, the patient should be patch tested with a baseline series from the relevant geographical area. More extensive testing may be necessary, and prick tests and/or use tests may be called for (see Chap. 5).

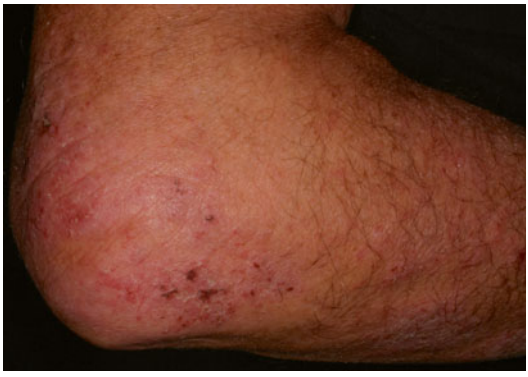


Fig. 2.19 Allergic contact dermatitis caused by dimethyl fumarate used as an anti-molding agent in furniture. The patient also had dermatitis on the trunk

In order to make a diagnosis of irritant hand eczema, it is very important to take a detailed history of the exposure pattern, and it may be necessary to analyze the substances to which the patient has been exposed. This is particularly important in occupational hand eczema.

Location of the dermatitis on the dorsal sides of the fingers and hands proved more common among those with irritant contact dermatitis than among those with allergic contact dermatitis (Fig. 2.20) [15].

Endogenous factors such as previous or current atopic dermatitis lower the threshold for the development of irritant contact dermatitis, particularly in patients prone to hand eczema.

2.3.8 Allergic Contact Dermatitis of the Hands

A diagnosis of contact dermatitis of the hands can be made when patch testing has detected a contact allergen of current relevance. Ideally, allergen avoidance should result in resolution of the dermatitis. This is, however, not always the case. One explanation is exposure to hidden sources of the contact allergen and another is that the hands are invariably exposed to irritants from everyday activities such as cooking, cleaning, and home maintenance.

Common examples of allergic contact dermatitis of the hands are often occupationally induced and include thiuram allergy from exposure to latex gloves, fingerstalls, and rubber bands (Figs. 2.21 and 2.22).

Perfume in shampoo, soap, creams, and other cosmetic products is another frequent cause of allergic contact dermatitis of the hands. Exposure may occur in the workplace or in the home.

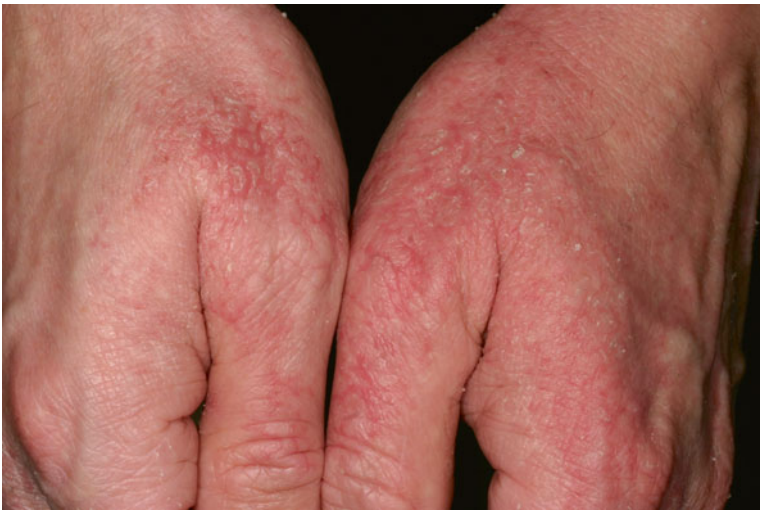


Fig. 2.20 Irritant contact dermatitis of the hands caused by wet work

Preservatives in cosmetic products and in industrial products such as paint, cooling fluids, and lubricants may also cause allergic contact dermatitis of the hands. It can prove difficult to trace the exposure, and the diagnosis is easily missed if patch testing is not carried out.

It is often difficult to link a positive patch test to nickel to hand eczema. One reason for this is that exposure to a ubiquitous contact allergen such as nickel can be almost impossible to trace in persons with a multitude of daily exposures.

Some handheld tools, coins, and other metal items containing nickel may cause hand eczema with an exposure pattern of dermatitis at sites of contact.

The ability of nickel to penetrate the skin may be increased in persons with filaggrin mutations.

Allergic contact dermatitis on the hands caused by chromate is often the result of contact with leather items such as protective gloves. The exposure can be both occupational and non-occupational.

A positive patch test to cobalt may be related to work with the metal itself in various hard metals or to animal feed containing cobalt. In most cases, it is difficult to link a positive patch test to cobalt to hand eczema.

In order to make an etiological diagnosis of hand eczema, it may be necessary to carry out a prick test or a prick-prick test with selected allergens. This will enable the

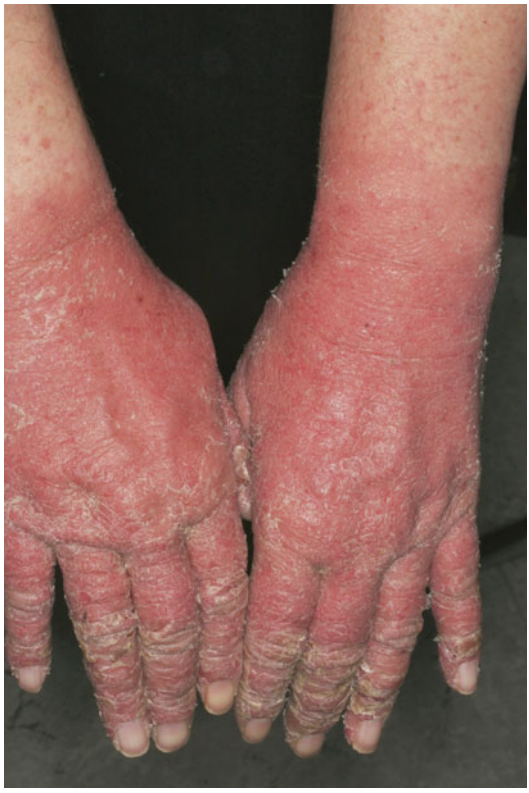


Fig. 2.21 Allergic contact dermatitis of the hands caused by thiurams in rubber gloves

Fig. 2.22 Allergic contact dermatitis caused by thiurams in rubber on a ballpoint pen

clinician to detect immediate-type sensitization. Prick-prick testing is particularly useful in diagnosing protein contact dermatitis/contact urticaria caused by food items (see Chap. 8). This type of dermatitis is a significant problem among women with hand eczema, possibly due to the ease of penetration through damaged skin of proteins from uncooked fruits and vegetables as well as from meat and fish [17].

Allergic contact urticaria to latex protein in gloves, rubber tubing, and other rubber items has been shown to cause severe hand eczema and contact urticaria as well as respiratory symptoms among hospital personnel and among patients whose care required the use of rubber tubing (Fig. 2.23).

2.3.9 Irritant Contact Dermatitis of the Feet

Irritant contact dermatitis of the feet is rare if the feet are protected by adequate footwear. Acute irritant contact dermatitis has been seen after spillage of toxic substances such as sodium hydroxide intended for the cleaning of kitchen drains and used in dairy farming and the dairy industry.

Cement dust in socks and footwear can cause chronic irritant contact dermatitis (Fig. 2.24). In addition to irritant contact dermatitis from cement, the patient in question also had a relevant positive patch test to mercaptobenzothiazole in the work boots. The importance of patch testing cannot be overestimated.

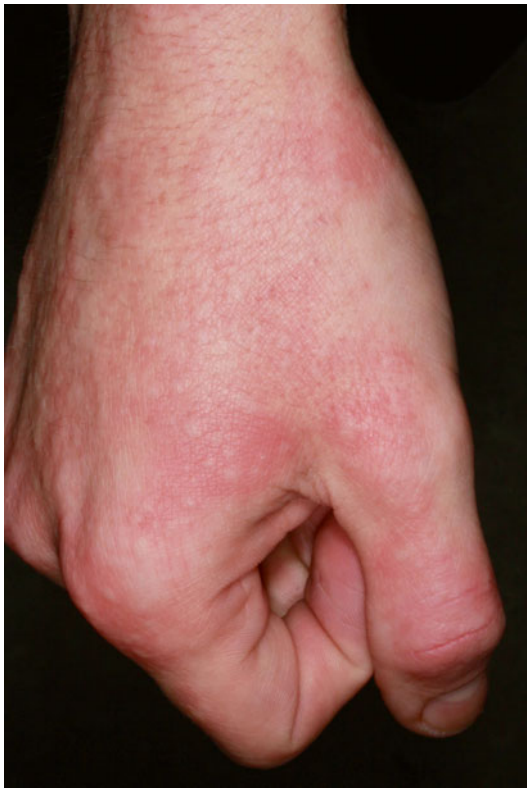


Fig. 2.23 Allergic contact urticaria caused by latex protein in a rubber glove

2.3.10 Allergic Contact Dermatitis of the Feet

Contact allergy to hexavalent chromate is the most common cause of allergic contact dermatitis on the feet (Fig. 2.25).

Another important contact allergen in footwear is mercaptobenzothiazole. The sites of dermatitis often do not reveal an obvious pattern of exposure to rubber components of the footwear (Fig. 2.26). This is also true for colophonium and para-tertiary-butylphenol-formaldehyde used as glue in footwear [18].

An obvious contact pattern can be seen in nickel-sensitive patients with dermatitis on the dorsal aspects of the feet caused by metal in footwear (Fig. 2.7).

2.3.11 Systemic Allergic Contact Dermatitis

Persons who are contact-sensitized usually develop dermatitis after cutaneous or mucous membrane contact with the substance in question.

In rare instances, the substance to which the person is sensitized may elicit a reaction if introduced to the immune system orally, by inhalation, by injection, or by rectal application [19].

The clinical features of systemic allergic contact dermatitis can be seen 1–3 days after exposure. Acute reactions with pruritus, erythema, and edema may occur at sites of previous allergic contact dermatitis caused by the same allergen (Figs. 2.27 and 2.28). A flare-up at the site of a previously positive patch test to the allergen is commonly seen in experimental oral challenge but is uncommon in clinical situations. The term "baboon syndrome" was coined to describe an edematous dermatitis as an expression of systemic contact dermatitis in the anogenital region.

Prior to the adoption by EU countries of the nickel regulation, recurrent vesicular hand dermatitis – in its severe variant called pompholyx – was often seen in patients with contact allergy to ubiquitous allergens such as nickel, cobalt, chromate, and food flavorings. Experimentally, a relatively high oral dose of the allergen reproduced such vesicular reactions.

In contact-sensitized persons, it can be difficult to explain sharply demarcated vesicular eruptions located solely on palmar skin as the result of external contact with the allergen (Fig. 2.29). In such cases, systemic exposure could be considered.

General malaise and/or gastrointestinal symptoms are rarely seen in connection with systemic allergic contact dermatitis.

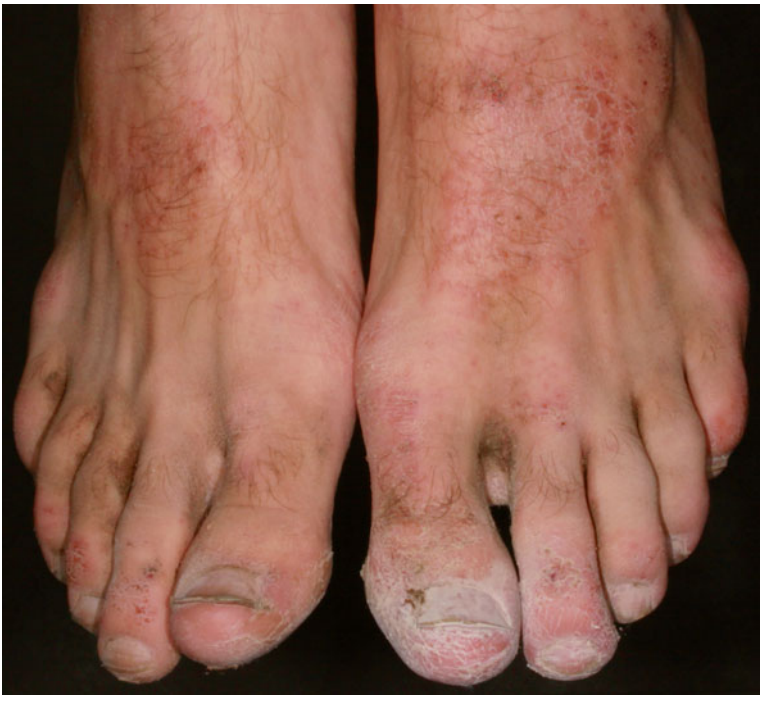


Fig. 2.24 Irritant contact dermatitis caused by cement

2.4 Differential Diagnoses

It is important to note that even though a clinical diagnosis such as atopic dermatitis (Fig. 2.1), nummular dermatitis (Fig. 2.4), or stasis dermatitis appears to be obvious, one cannot rely on clinical appearance alone.

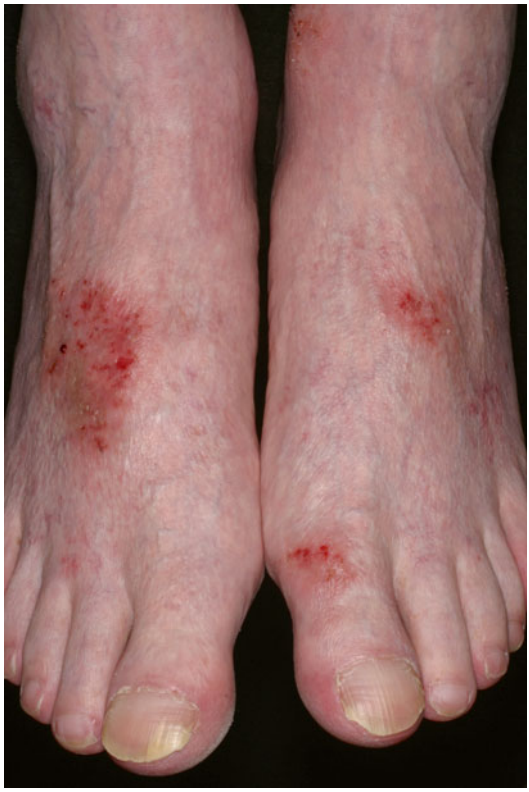


Fig. 2.25 Allergic contact dermatitis cause by potassium dichromate in leather footwear

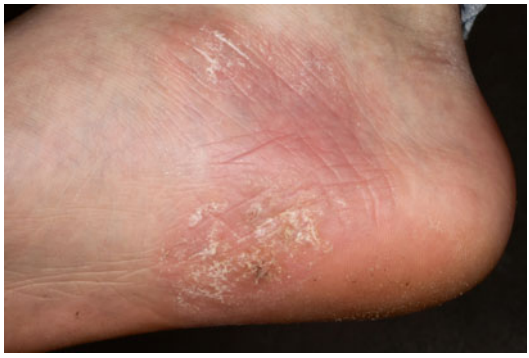


Fig. 2.26 Allergic contact dermatitis caused by mercaptobenzothiazole in shoes

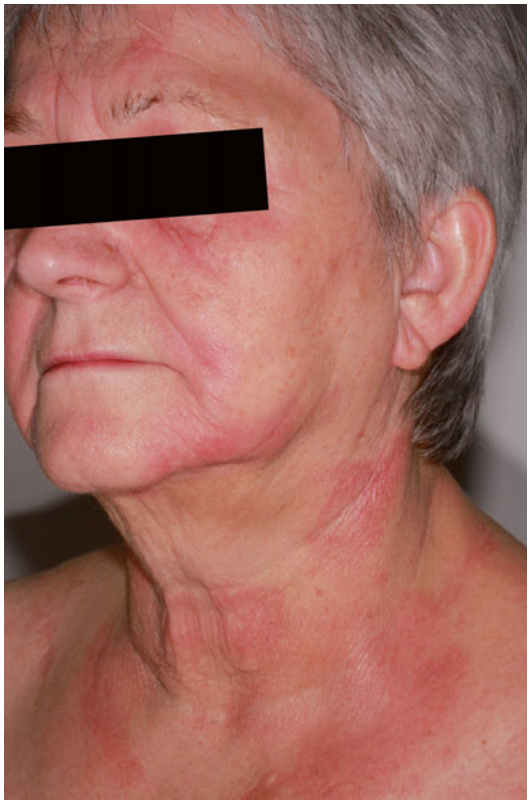


Fig. 2.27 Systemic allergic contact dermatitis caused by balsam of Peru

If such dermatitis does not fade after adequate prophylactic measures and proper treatment, the possibility of allergic contact dermatitis should be considered, and patch testing should be carried out. This consideration is true of all eczematous dermatoses. A prerequisite for the diagnosis of irritant contact dermatitis is that contact allergy has been excluded by patch testing.

Eczema of one nipple (Fig. 2.30) should fade after appropriate treatment. If the eczema does not fade, a diagnosis of Paget's disease should be considered. The same is true of Bowen's disease on a finger which clinically can have a striking resemblance to contact dermatitis (Fig. 2.31).

Factitious dermatoses may mimic contact dermatitis. Irritants deliberately applied to the skin may produce irritant contact dermatitis.

Bullous pemphigoid may imitate vesicular hand eczema. It is difficult to make a correct diagnosis if symptoms of bullous pemphigoid occur only on the palms and/or the soles.

Fixed drug eruptions characterized by recurrent eruptions of erythema and edema in exactly the same site may have an eczematous variant with the same features.

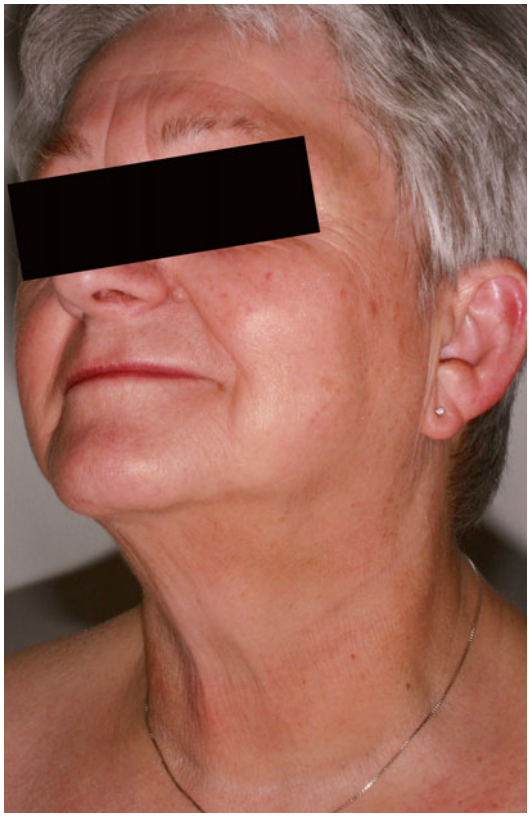


Fig. 2.28 The same patient as shown in Fig. 2.27 after 3 months on a low balsam diet

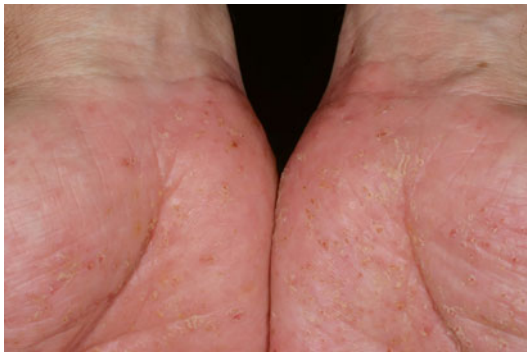


Fig. 2.29 Recurrent vesicular hand eczema. Note that there is no dermatitis on the forearm

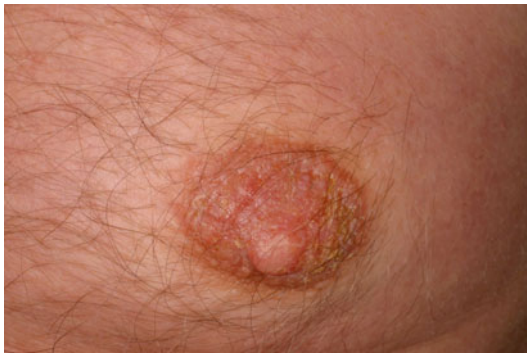


Fig. 2.30 Irritant contact dermatitis of the left nipple

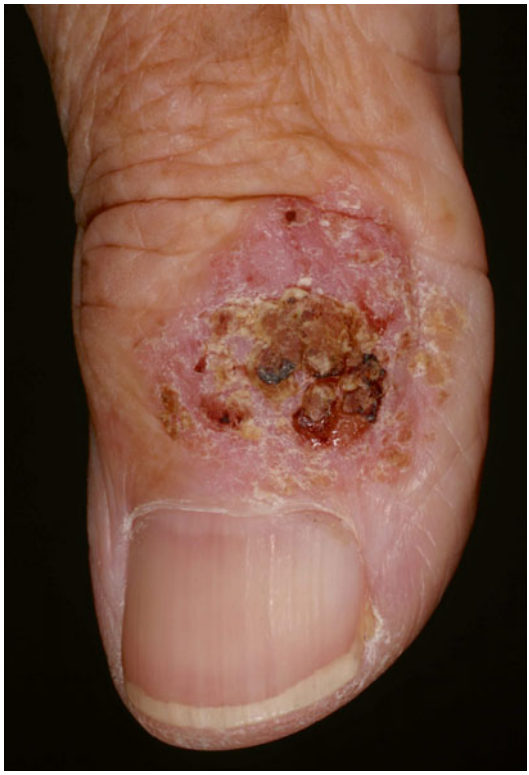


Fig. 2.31 Bowen's disease on the thumb

References

1. Bonamonte D, Foti C, Vestita M, Ranieri LD, Angelini G. Nummular eczema and contact allergy: a retrospective study. Dermatitis. 2012;23:153–7.
2. Sinnen I, Goossens A. An update on airborne contact dermatitis. Contact Dermatitis. 2013;68:232–8.
3. Bonamonte D, Foti C, Vestita M, Angelini G. Noneczematous contact dermatitis. ISRN Allergy. 2013;2013(361746):1–10.

4. Malinauskiene L, Bruze M, Ryberg K, Zimerson E, Isaksson M. Contact allergy from disperse dyes in textiles: a review. Contact Dermatitis. 2013;68:65–75.
5. Chan HP, Maibach HI. Hair highlights and severe acute irritant dermatitis ("burn") of the scalp. Cutan Ocul Toxicol. 2010;29:229–33.
6. Wang MZ, Farmer SA, Richardson DM, Davis MD. Patch-testing with hairdressing chemicals. Dermatitis. 2011;22:16–26.
7. Lundgren L, Moberg C, Lidén C. Do insulation products of man-made vitreous fibres still cause skin discomfort? Contact Dermatitis. 2014;70:351–60.
8. Schnuch A, Szliska C, Utr W, IVDK. Facial allergic contact dermatitis. Data from the IVDK and review of literature. Hautarzt. 2009;60:13–21.
9. Landeck L, John SM, Geier J. Periorbital dermatitis in 4779 patients – patch test results during a 10-year period. Contact Dermatitis. 2013;70:205–12.
10. Al-Niaimi F, Beck M, Almaani N, Samarasinghe V, Williams J, Lyon C. The relevance of patch testing in peristomal dermatitis. Br J Dermatol. 2012;167:103–9.
11. Shin HT. Diagnosis and management of diaper dermatitis. Pediatr Clin N Am. 2014;61: 367–82.
12. Lidén C, Bruze M, Thyssen JP, Menné T. Metals. In: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011.
13. Lisi P, Stingeni L, Cristaudo A, Foti C, Pigatto P, Gola M, Schena D, Corazza M, Bianchi L. Clinical and epidemiological features of textile contact dermatitis: an Italian multicentre study. Contact Dermatitis. 2013;70:344–50.
14. Susitaival P, Winhoven SM, Williams J, Lammintausta K, Hasan T, Beck MH, Gruvberger B, Zimerson E, Bruze M. An outbreak of furniture related dermatitis ('sofa dermatitis') in Finland and the UK: history and clinical cases. J Eur Acad Dermatol Venereol. 2010;24:486–9.
15. Johansen JD, Hald M, Andersen BL, Laurberg G, Danielsen A, Avnstorp C, Kristensen B, Kristensen O, Kaaber K, Thormann J, Menné T, Veien N, Danish Contact Dermatitis Group. Classification of hand eczema: clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. Contact Dermatitis. 2011;65:13–21.
16. Schwensen JF, Menné T, Johansen JD. The combined diagnosis of allergic and irritant contact dermatitis in a retrospective cohort of 1000 consecutive patients with occupational contact dermatitis. Contact Dermatitis. 2014. doi:10.1111/cod. 12288.
17. Vester L, Thyssen JP, Menné T, Johansen JD. Occupational food-related hand dermatoses seen over a 10-year period. Contact Dermatitis. 2012;66:264–70.
18. Landeck L, Uter W, John SM. Patch test characteristics of patients referred for suspected contact allergy of the feet – retrospective 10-year cross-sectional study of the IVDK data. Contact Dermatitis. 2012;66:271–8.
19. Kaae J, Veien NK, Thyssen JP. Systemic allergic (contact) dermatitis. In: Wilhelm K-P, Zhai H, Maibach HI, editors. Dermatotoxicology. 8th ed. Boca Raton: CRC; 2012.

Part II

Patch Testing Basics

Patch Testing Essentials

3

Cecilia Svedman and Bruze Magnus

Contents

3.1 When to Patch Test

In order to patch test the right patients, it is important first to define allergic contact dermatitis.

When defining allergic contact dermatitis (ACD), one must consider that from the clinical picture, it is not possible to differentiate between contact dermatitis based on other etiologies and endogenous eczema.

Furthermore, in reality, often endogenous, irritant, and allergic etiologies coexist and give eczema. To diagnose irritant contact dermatitis, clinically relevant contact allergies have to be excluded. A diagnosis of contact dermatitis and ACD requires

C. Svedman, MD, PhD (✉) • B. Magnus, MD, PhD
Department of Occupational and Environmental Dermatology, Skane University Hospital, University of Lund, Malmö, Sweden
e-mail: Cecilia.Svedman@med.lu.se

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_3

Table 3.1 What patients should be patch tested? Remember that dermatitis does not necessarily only include eczematous conditions!

1. Patients with hand dermatitis, even if suspected endogenous, always be liberal when considering patch testing. The hands are exposed to a multitude of substances both willingly and unknowingly. Hand dermatitis is often also costly both for society and the individual.
2. Patients with dermatitis that has a clear history that connects aggravation/elicitation to a particular exposure.
3. Patients with a dermatitis that does not heal after adequate treatment.
4. When a patient comes with no former history of dermatitis, an exogenous dermatitis should be ruled out .
5. When the diagnostic framework does not fit with the dermatosis investigated, the possibility of contact allergy should be considered [1].

careful consideration of many variables and knowledge of the possible reactions of the skin to different substances.

Eczema is the most common clinical picture seen in an ACD patient, but other manifestations are possible, mainly depending on the allergen, such as allergic contact granuloma, lichenoid eruptions, erythema multiforme, lymphomatoid lesions, and scleroderma-like dermatosis. The exposure will define where the reaction is situated. It is most often found on the hands, arms, and face, areas that most often are unprotected and in contact with many substances. Systemic contact dermatitis, i.e., the allergen has on re-exposure reached the patient systemically, by the mucosae or skin or through injection, often gives a different clinical picture. The clinical features of systemic contact dermatitis include flare-up of previous dermatitis or previously positive patch test sites, vesicular palmar and/or plantar dermatitis, flexural dermatitis, and baboon syndrome.

It is therefore not easy to give general recommendations on when to patch test; however, some general advice is given in Table 3.1.

The diagnosis of allergic contact dermatitis is actually divided in three steps, patch testing, deciding on exposure for the found allergen, and finally deciding on whether the dermatitis under investigation can be explained by the found contact allergy, i.e., deciding on relevance. In this chapter, focus will be on with what to patch test and on how to patch test. It must be emphasized that even if the patch test procedure and patch test reading is performed according to given rules and standards, we will be limited by the fact that we only have information with regard to what we have patch tested with. The first crucial step is then with what to patch test and what to avoid patch testing with.

3.2 What Substances Have the Capacity to Be Contact Allergens?

There are several prerequisites necessary for a substance to become an allergen (Table 3.2).

Many contact allergens are weak allergens that require repeated exposure before they actually cause sensitization, but there are also strong allergens that may sensitize after one exposure. Therefore, with what to patch test is decided both by the

Table 3.2 Prerequisites for a substance to be a contact allergen

Penetration through stratum corneum is determined by:
The size of <1000 Da, usually <500 Da
Sufficient number of molecules, i.e., the dose/cm^2, has to be adequate both for sensitization and elicitation, that dose is however not the same.
Metals have to be in ionic form; for other molecules, these have to be more or less lipophilic.
In the epidermis, several factors are of importance:
The small molecules must conjugate with proteins to enable sensitization or elicitation.
The tertiary structure: there must be sufficient amount of antigenic determinants.
Enantiospecificity: the three-dimensional structure is important; sometimes only one of two isomers will be sensitizers.
Certain allergens act as allergen only after activation, they need to be chemically changed before exposure to the skin and on or in the skin in order to act as haptens, and these are called pre- and prohaptens. They can be activated, for example, by oxidation, light, or metabolization.

possibility for the substance to act as a hapten and by the possible exposure in the individual that is to be tested.

3.3 Pros and Cons with a Baseline Series

In most countries, a baseline series exists based on the most frequent allergens found in the exposed population. When transferring a baseline series to a new population differences in exposure patterns might mean that the results will be misleading, i.e., if we do not patch test with the right substances, we will not get accurate results. In many countries therefore, the baseline series is a tool that changes over time. A general rule is that if an allergen is found in frequencies above 1 % in a population, this is considered a ratio that merits the allergen to be in the baseline series. A weak allergen but with a large exposure such as nickel will thus merit to be included, but also stronger allergens with a smaller exposure will be included due to their tendency to sensitize even if the exposure is less. Sometimes, other factors decide if the allergen should be in the baseline series such as the fact that legal aspects or regulatory measurements have been taken and there is a need to follow a trend as is the case with methyldibromo glutaronitrile that was actually banned in 2008 from cosmetic products on the European market.

The baseline series thus include common allergens that the tested population can meet in daily life activities (see also Chap. 6). It is important to patch test a limited number of substances. Mixes are often used within the baseline series and are necessary in order to shorten the number of allergens to patch test with i.e., the number of chambers put on the back but may be a pitfall in itself. Fragrances are such an example, where the patients to patch test with ie the number of chambers put on the back can be positive to a mix and negative to a separate substance and vice versa [2, 3]. When evaluating the patch test results, one has always to consider relevance and if necessary patch test with the separate ingredients of the mix and the patients' own products. Within the baseline series, the test doses and vehicles should be carefully evaluated, but as our patch test technique improves and the use of substances changes also, how the allergens of the baseline series

are tested must be subjected to change [4, 5]. A baseline series is of course a great advantage due to the fact that it is well standardized with regard to allergen and dose and that it, since it includes common allergens, will result in many positive reactions. It must, however, be emphasized that the series in itself may be a pitfall. You will only have results from what you have patch tested with, i.e., one has always to judge the individual patient and decide if there is a need to patch test also with other series/substances [6].

3.4 When Not to Patch Test

Even if we have an individual with a dermatitis where we suspect exposure to something in the environment to be the possible cause, there are certain situations where patch testing is contraindicated or at least must be carefully evaluated [6]. The list below is made considering that the clinician patch tests not only the well-defined allergens that are commercially available but also the patients' own material.

Totally unknown substances/products should of course not be put on the skin! Always think of how the patient is exposed to the presumed allergen! Always require data safety sheets and ingredient lists before patch testing new products. Take into careful consideration how the product is actually thought to be in contact with the skin.

- The substance is a well-known strong sensitizer and we cannot test in a well-defined dose. We might actively sensitize the patient.
- We have no knowledge/not full knowledge of the product the patient is exposed to and suspect it to be a strong sensitizer. Get information on the ingredients of the product and try to patch test these separately.
- When a patient product is tested, pH should always be investigated. The indicator should be slightly moistened with water before use. If the product/substance has a pH that may cause a toxic reaction in the patient and we cannot buffer the solution enough, patch testing has to be avoided. *See Chap. 4 for more information*.
- When the patient has when presenting a generalized dermatitis also of the back, this increases the risk for a generalized flare that will make patch test reading difficult. Treat the dermatitis so that the back is healed before patch testing can be performed.
- Corticosteroids or immunosuppressive therapy. Local corticosteroids have been shown to give rise to false-negative patch test results, as well as irradiation (UVB/UVA) which has been shown to modulate reactivity also in shielded areas. Oral corticosteroids have been shown to suppress reactivity. Patients on different immunosuppressive drugs have been patch tested, and positive reactions have been elicited, but the studies are scarce, and further studies are needed. If a patient is patch tested and found negative when on immunosuppressive therapy and a contact allergy is suspected to be the cause, the patient should be retested when not on the therapy [7].

3.5 Overview of Procedures of Patch Testing

Fig. 3.1 Prepared for patch testing

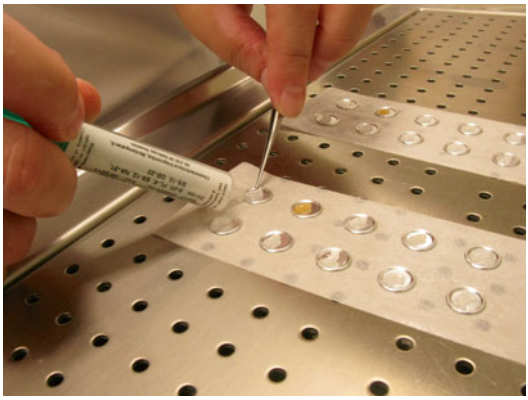


Fig. 3.2 Preparing the test chambers with the test substance just prior to use

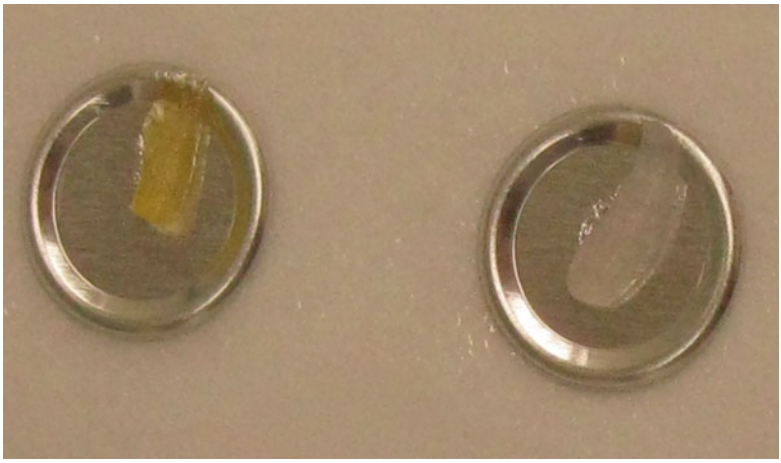


Fig. 3.3 The correct dose is of the utmost importance

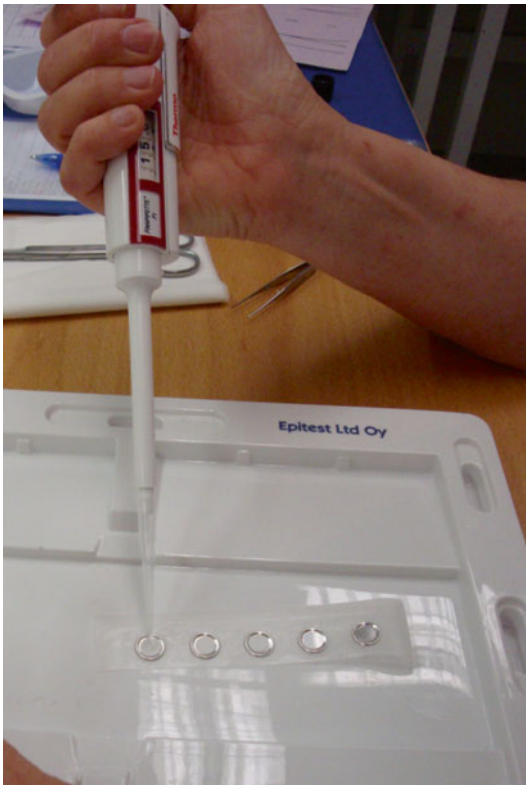


Fig. 3.4 Liquid preparations administered by micropipette for best accuracy and precision

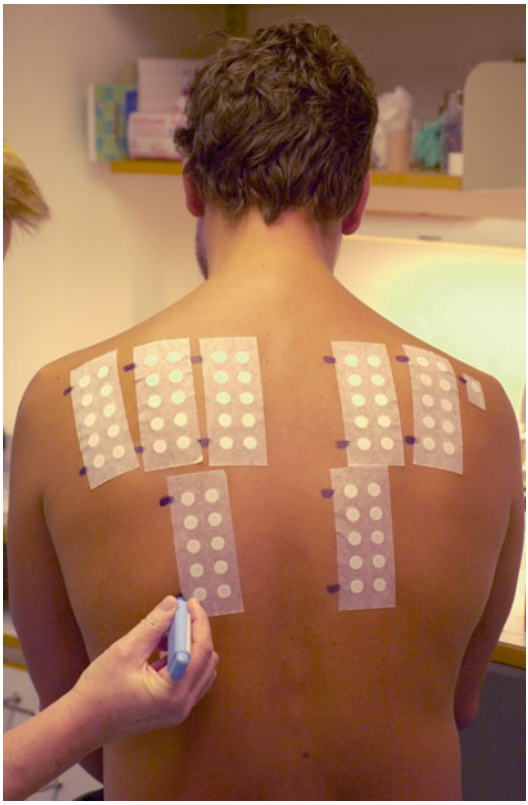


Fig. 3.5 The patch test preparations are fixed to the skin on the upper back and marked with a good water resistant marker pen

3.6 Important Technical Issues to Be Aware of

It is of importance that the patch testing procedure (Figs. 3.1–3.5) and patch test reading are standardized. In the following section, we will be referring to the allergens of the baseline series, but the same general principles adhere to all testing.

3.6.1 Stability of Test Material/How to Store

Patch test material should be stored according to recommendations from the manufacturer. Patch test substances can either be defined as chemically defined substances such as nickel and formaldehyde, compound chemicals such as colophony and para-tertiary butylphenol formaldehyde resin, or mixes. They are as such to be considered defined, but it has happened that they have proved to be unintentionally incorrectly declared or to both contain impurities and/or be degraded/chemically changed so that what is patch tested with is actually not what is declared on the labeling [8–10].

In general, patch test preparations when not used should be stored dark and in refrigerator or freezer when stored for longer periods of time. Once the substance is to be used, it should be applied on the test chamber if possible just before use Fig. 3.2. This is true especially for volatile substances [10, 11].

3.6.2 Types of Chamber

There exist several different test chamber systems, some with circular chamber areas and some with squares. The systems can either be preloaded or can be those in which the allergen is applied manually before patch testing. The preloaded system is of course quick and easy and ensures a standardized (Fig. 3.3 and 3.4) dose. This system is useful especially if there is a limited test experience and or limited work capacity when patch testing. If several series are tested and there are many patient products, there must exist also the possibility to apply the allergen before testing. This also ensures the possibility to quickly change patch test substances or doses according to the last research findings and thereby catch trends [4, 5]. The choice of test chamber is actually often based on tradition. The inert plastic systems should of course be chosen if contact allergy to aluminum is suspected; the chamber alone does very seldom give reaction, but if the patch tested substance is of a pH that facilitates ionization, there can be false-positive reactions [12] or false-negative [13].

3.6.3 Dosing of Chambers

The dose is of the utmost importance (Fig. 3.3 and 3.4). False-positive, false-negative, and adverse reactions are all dose dependent. With sufficiently low concentrations of sensitizers, there will be no false-positive reactions or adverse reactions. In fact, a false-positive reaction is an irritant reaction with the same morphology as and thus indistinguishable from an allergic patch test reaction [6]. However, with a low test concentration, there will be false-negative reactions [14, 15].

The concentration can only be used to define the patch test dose if exactly the same amount is used at each test occasion. It is of the utmost importance to standardize the dose; the amount to mount the test chambers with therefore differs between chambers due to their area. For each chamber size, the right amount must be used (Table 3.3).

Table 3.3 The dose of allergen to use in the most common chamber sizes

	Liquid preparations	Preparations in pet	µl/mg/cm^2
Finn chamber (area 0.5 cm^2)	15 µl	20 mg	30/40/cm^2
Van der Bendt (area 0.64 cm^2)	20 µl	25 mg	31/39/cm^2
IQ Ultra (area 0.68 cm^2)	20 µl	25 mg	29/36/cm^2

3.6.4 Occlusion Time

There is today a consensus on an occlusion time of 48 h [16], some centers, however, still prefer 24 h occlusion [17]. The dose, used at patch testing, and the occlusion time are theoretically the two parameters influencing the possible patch test result and which could be altered [18], but as the doses today are actually standardized for an occlusion time of 48 h, it is important to keep this parameter the same.

3.7 Reading Scale and Time

We know that with regard to patch test reading, it is important to have two readings. Many centers perform the first patch test reading at 48 h [19], in connection to removing the patch test substances. There are few studies performed, but most indicate that the use of patch test reading on day 3/4 and then a late reading usually on day 7 is recommended [20–23]. We know that within the baseline series, we risk missing up to 30 % of positive results if patch test reading is just performed once at 48 h [23]. In 1970, the ICDRG, the International Contact Dermatitis Research Group, suggested a uniform terminology for patch testing [24], even this scoring has however been subjected to some minor changes. The one we nowadays usually refer to is the version of 1981 [16] (Table 3.4). There are weaknesses in the patch test reading qualities due to the fact that it is the individual who actually scores the reactions. It has been shown that what is difficult to interpret is infiltration versus

Table 3.4 How to improve your patch test results

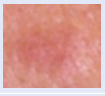
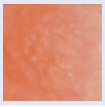
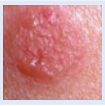
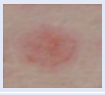
+?	Doubtful reaction; faint erythema only	
+	Weak positive reaction; erythema, infiltration, possibly papules	
++	Strong positive reaction; erythema, infiltration, papules, vesicles	
+++	Extreme positive reaction; intense erythema and infiltration and coalescing vesicles	
–	Negative reaction	
IR	Irritant reaction of different types	
NT	Not tested	

Table 3.5 Morphology criteria typical for patch test reading on day 3/4

Irritation	Doubtful	One plus reaction
Cigarette paper structure Blank skin Petechiae Pustules	Erythema and infiltration not covering the whole patch test area erythema at least 2× "background noise"[a] scattered papules only	Erythema and infiltration covering the whole patch test area possibly few papules

[a]This term indicates how the skin of the patient in general looks on the back. Some patients have more easily irritated skin and will thus have a higher "background noise" [26]

infiltration with a few papules [25]. In studies, it has been found that by education and morphology protocols, this interindividual difference will improve [25].

3.7.1 Irritant Reactions

The irritant reaction has certain typical morphological traits, especially when scored on day 3/4 (Table 3.5). The reaction may however be difficult to differentiate from a one plus reaction and is often misinterpreted as such [14]. Irritant reactions are of course much more common when testing patients' own material or series where the different substances are not that well known. Formaldehyde within the baseline series is however a very good example that the same problem can occur with allergens within the baseline series. With preservatives, these are often irritants in higher concentration. For the allergens in the baseline series, it is of course optimal if there are no false-negative reactions and no false-positive ones, but if there is a steep dose relationship for the substance, as for formaldehyde, a small increase of the dose will increase the reactivity much and finally tip the reaction to an irritant one, and this will be of the utmost importance. Previously, a concentration of 1 % (but not controlled on exact dose) was suggested as the appropriate test dose since 2 % induced irritant reactions; however, it has been shown that provided that the dose is exact and accurate, 2.0 % (0.6 mg/cm^2) [14] does actually catch significantly more allergic reactions and not irritant ones. If there is doubt on a presumed false-positive patch test reaction, dilution series should be performed. For a true allergen, there will be a positive reaction in several dilution steps, whereas this is not the case for the irritant.

3.7.2 Doubtful Reactions

This is perhaps the most difficult reaction to differentiate from the one plus reaction. It it is a reaction that is important to judge correctly. A doubtful reaction may be an allergic reaction but which does not fulfill the criteria due to a too low reactivity in the patient, a too low patch test dose, or a too short occlusion time or that the time when reading is not proper [18]. On the other hand, the dose has to be fixed, and thus

some reactions that are really weak allergic ones will be missed. The reaction has to be judged according to the ICDRG criteria and thus, no allergy is diagnosed in this case. In the clinical situation, if there is a high degree of suspicion, the test dose has to be increased in order to exclude an allergy. With metals also, intracutaneous testing can be performed since one reason for a doubtful reaction may be that not enough allergen penetrates the epidermis in the given time. In the practical clinical situation when patch testing with less defined substances or own material and getting a doubtful reaction, a repeated open application test with the product that has been tested or the product where the test substance is found, may well be tried in order to get clinical support that this is actually a clinically relevant reaction for the patient (even if the ROAT cannot discriminate a contact allergic reaction from an irritant reaction).

Things to remember when patch testing	
Patch test technique	Patch test reading
Standardize your technique	Patch test read twice: day 3/4 and day 7
Diminish the "human factor"	Standardize the reading technique
Dose should be controlled	Read according to the ICDRG
Occlusion time controlled	Remember that it is difficult to differentiate
Occlusion controlled, the chambers must be well fixed	between doubtful/irritant and one plus reaction
Mark the patch test sites with a good marker pen	

References

1. Lönngren V, Young E, Simanaitis M, Svedman C. Neutrophilic and eosinophilic dermatitis caused by contact allergic reaction to paraphenylenediamine in hair dye. Arch Dermatol. 2012;148(11):1299–301.
2. Mann J, McFadden JP, White JM, et al. Baseline series fragrance markers fail to predict contact allergy. Contact Dermatitis. 2014;70:276–81.
3. Nardelli A, Carbonez A, Drieghe J, Goossens A. Results of patch testing with fragrance mix 1, fragrance mix 2, and their ingredients, and Myroxylon pereirae and colophonium, over a 21-year period. Contact Dermatitis. 2013;68:307–13.
4. Bruze M, Engfeldt M, Gonçalo M, Goossens A. Recommendation to include 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. 2013;69:263–70.
5. Pontén A, Goossens A, Bruze M. Recommendation to include formaldehyde 2.0% aqua in the European baseline patch test series. Contact Dermatitis. 2013;69:372–4.
6. Bruze M, Condé-Salazar L, Goossens A, Kanerva L, White IR. Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. Contact Dermatitis. 1999;41:241–50.
7. Wee JS, White JM, McFadden JP, et al. Patch testing in patients treated with systemic immunosuppression and cytokine inhibitors. Contact Dermatitis. 2010;62:165–9.
8. Frick M, Zimerson E, Karlsson D, et al. Poor correlation between stated and found concentrations of diphenylmethane-4,4′-diisocyanate (4,4′-MDI) in petrolatum patch-test preparations. Contact Dermatitis. 2004;51:73–8.

9. Ryberg K, Gruvberger B, Zimerson E, et al. Chemical investigations of disperse dyes in patch test preparations. Contact Dermatitis. 2008;58:199–209.
10. Mose KF, Andersen KE, Christensen LP. Stability of selected volatile contact allergens in different patch test chambers under different storage conditions. Contact Dermatitis. 2012;66:172–9.
11. Mowitz M, Zimerson E, Svedman C, et al. Stability of fragrance patch test preparations applied in test chambers. Br J Dermatol. 2012;167:822–7.
12. Siemund I, Zimerson E, Hindsén M, et al. Establishing aluminium contact allergy. Contact Dermatitis. 2012;67:162–70.
13. Bruze M, Björkner B, Lepoittevin JP. Occupational allergic contact dermatitis from ethyl cyanoacrylate. Contact Dermatitis. 1995;32:156–9.
14. Hauksson I, Pontén A, Gruvberger B, et al. Clinically relevant contact allergy to formaldehyde may be missed by testing with formaldehyde 1.0%. Br J Dermatol. 2011;164:568–72.
15. Bruze M, Frick-Engfeldt M, Gruvberger B, et al. Variation in the amount of petrolatum preparation applied at patch testing. Contact Dermatitis. 2007;56:38–42.
16. Fregert S. Manual of contact dermatitis. 2nd ed. Copenhagen: Munksgaard; 1981.
17. Ale SI, Maibach HI. 24-hour versus 48-hour occlusion in patch testing. Exog Dermatol. 2003;2:270–6.
18. Isaksson M, Bruze M, Goossens A, et al. Patch testing with budesonide in serial dilutions: the significance of dose, occlusion time and reading time. Contact Dermatitis. 1999;40:24–31.
19. Brasch J, Geier J, Henseler T. Evaluation of patch test results by use of the reaction index. An analysis of data recorded by the Information Network of Departments of Dermatology (IVDK). Contact Dermatitis. 1995;33:375–80.
20. Jonker MJ, Bruynzeel DP. The outcome of an additional patch-test reading on day 6 or 7. Contact Dermatitis. 2000;42:330–5.
21. Aw M, Curley R, Graham M, et al. Delayed patch test reactions at days 7 and 9. Contact Dermatitis. 1989;20:127–32.
22. Higgins E, Collins P. The relevance of 7-day patch test reading. Dermatitis. 2013;24:237–40.
23. Mathias CGT, Maibach HI. When to patch test read? Int J Dermatol. 1979;18:127–8.
24. Wilkinson DS, Fregert S, Magnusson B, et al. Terminology of contact dermatitis. Acta Derm Venereol. 1970;50:287–92.
25. Svedman C, Isaksson M, Björk J, et al. 'Calibration' of our patch test reading technique is necessary. Contact Dermatitis. 2012;66:180–7.
26. Bruze M, Isaksson M, Svedman C. A modified reading scale for patch test reactions. In manuscript.

Testing with the Patient's Own Products

4

An Goossens

Contents

4.1 Introduction

The commercially available patch test kits (baseline series and various supplementary series) are the basis for the diagnostic work-up if an allergic contact dermatitis is to be confirmed. However, testing with the products actually used by the patient and if possible also with the ingredients is crucial in order to detect all possible and relevant sensitization sources and/or detect new allergens. Table 4.1 gives the pro's and contra's for testing with the patient's own products.

4.2 Methodology

Guidelines for testing with the patients' own materials have already been extensively described [1]; the materials most frequently tested are usually topical medications, cosmetics of various types, and rubber and leather products. It is very

A. Goossens, RParm, PhD
Contact Allergy Unit, Department of Dermatology,
University Hospital K.U.Leuven, Leuven B-3000, Belgium
e-mail: an.goossens@uzleuven.be

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_4

important though that information on the test material is obtained before skin testing. While the complete composition of pharmaceutical and cosmetic products is known, with regard to industrial products (e.g., metalworking fluids, glues, paints, etc.), the material safety data sheets provide only basic information and do not list all allergy-relevant ingredients. In addition, the producer selling the product is often not aware of contaminants or materials under a different nomenclature.

When a positive test occurs with the patient's own product, further testing with the ingredient is essential.

When a cosmetic product is involved, manufacturers may provide the ingredients at adequate dilutions and vehicles for patch testing; however, some tend to supply the ingredients in dilutions as used in the products, producing false-negative reactions on patch testing. Furthermore, coded material obtained from a manufacturer without knowing the details on the chemical regarding toxicity and appropriate test concentration should never be applied.

The possible methodologies involved in testing with the patient's own products are shown in Table 4.2. Besides patch testing and photopatch testing in case photoallergic contact dermatitis is suspected [2], open and "semi-open or semiocclusive tests" [3] or use tests [4] and repeated open application tests (ROATs) [5] are useful additional methods to identify the culprits.

Table 4.1 Testing with own products: pro's and contra's

Pro's
Practical: products at hand and actually contacted by the patient
Own products: contain other allergens not present in series or commercialized (always incomplete and not updated)
Have physicochemical properties that might be different from the commercial patch test allergens
May contain allergenic impurities or additives
Picks up "compound allergy" (to a product in which the allergen might penetrate better into the skin or in which a new allergen has been formed; indeed, chemical ingredients may interact)
Possibly identifies new allergens
Confirms the relevance of a positive test
Contra's
No "standardized" testing
Requires knowledge of the materials to be tested
Requires a lot of expertise from the examiner
May produce both false-positive and false-negative test results

Table 4.2 Test methodology

Patch tests
Photopatch tests
(Semi-)open or semiocclusive tests
ROATs (repeated open application tests)
Use tests (at original site)
Prick testing (in case of immediate skin reactions or protein contact dermatitis)

4.2.1 Patch Tests and Semi-Open Tests

Patch tests are performed with products that do not contain irritant ingredients such as cosmetic and pharmaceutical creams, lotions, etc., while *open and semi-open* (or semiocclusive) tests are particularly helpful if irritant reactions under occlusion are to be suspected, e.g., in the case of cosmetics such as shampoos, liquid soaps, and nail varnish; medicaments containing irritating constituents, such as benzoyl peroxide, tretinoin, capsaicin, PVP-iodine, or quaternary ammonium compounds; and industrial products such as glues, paints, inks, varnishes, etc. The material is applied to the skin with a cotton swab (about 15 µl) on a small area (2×2 cm), left for drying (possibly dabbing with another Q-tip or tissue) and then covered with acrylic tape (only when completely dried). Sometimes a weak irritant response to a product tested as such semi-open may be observed, but then this method can also be used for diluted products (e.g., shampoos, soaps, paints, etc.).

The golden rule is that when a subject comes directly in skin contact with a product that has irritant properties (either on purpose, e.g., cleansing products, or accidentally, e.g., soluble oils, paints), then the product may be tested in this way.

However, corrosive or other toxic materials (pH <3 or >10) that are normally used in closed systems only or with protection by appropriate clothing are excluded from testing. At pH of 4–9, very few irritant reactions are caused by the acidity or alkalinity itself, and buffering solutions may be used ([6], Table 4.3).

Solid materials can be tested as such placing scrapings or cut pieces in the test chamber or applied on acrylic tape thus avoiding pressure effects. A piece of the suspected material – textiles, gloves, and shoes – (2×2 cm moistened with saline solution), as well as scrapings of (hard) plastic materials, is applied under occlusion for 48 h. However, the reactions may often turn out to be false-negative because the concentration of the sensitizer is too low or the sensitizer is not released. Alternatively, pressure or friction effects of sharp particles may cause some sort of irritant reaction, which should, however, be clearly identifiable as such. Depending on the material, the sensitizer can be extracted with water or solvents ([7], Table 4.4).

Patch testing with pieces of plants is not recommended in general because irritant reactions are frequent and active sensitization may occur, although direct application on acrylic tape and not occluded by a chamber is less apt to do so. Extracts of plants may be used as well (e.g., [8]). Fine wood dust moistened with physiological saline can be patch tested with a Finn chamber or on adhesive acrylic tape. However, exotic woods can be strongly irritating and sensitizing (teak, rosewood,

Table 4.3 Composition of buffer solution, pH 4.7, and alkaline buffer solution, pH 9.9 [6]

Compound	Concentration	% of total volume
Acid buffer, pH 4.7		
Sodium acetate	0.1 N (8.2 g CH_3COONa/L aqua)	50
Acetic acid	0.1 N (6.0 g CH_3COOH/L aqua)	50
Alkaline buffer, pH 9.9		
Sodium carbonate	0.1 M (10.6 g Na_2CO_3/L aqua)	50
Sodium bicarbonate	0.1 M (8.4 g $NaHCO_3$/L aqua)	50

Table 4.4 Materials suitable for extraction and recommended solvents [7]

Material	Solvent
Paper	Ethanol
Plants and wood dusts	Acetone, ether, ethanol, or water
Plastics, e.g., gloves	Acetone
Rubber, e.g., gloves	Acetone or water
Textiles	Ethanol

Macoré) – these should be diluted and tested on acrylic tape (without occlusion) since sensitization might occur even at very low concentrations.

As an additional method, patch testing with thin-layer chromatograms of textiles, gloves, rubber, or any other materials can serve as an elegant adjunct to quickly identify contact allergy to a certain ingredient of a mixture, although the (variable, possibly high) detection limit may yield false-negative results [9].

4.2.2 Use Tests

Use tests at the original site and repeated open application tests (ROATs) are useful additional tests as well. Indeed, patch tests are vastly different from normal use conditions; therefore, tests can be completed by provocative use testing of sensitized subjects. With ROATs, about 0.1 ml of test material is applied twice daily to the flexor aspect of the forearm near the cubital fossa, to an area approximately 5 × 5 cm. The results are read after 1 week, but sometimes ROATs need to be performed up to 21 days, especially with low-concentrated allergens, in order to reveal an allergic reaction.

4.3 Testing for Immediate Reactions to Chemicals and Proteins

As immediate skin reactions are concerned, low molecular chemicals may give rise to contact urticaria (e.g., products containing chlorhexidine, bacitracin, etc.), but also macromolecules can penetrate the skin and are able to induce immunological contact urticaria and/or eczematous clinical pictures, i.e., protein contact dermatitis, most often in an occupational context.

The protein sources are divided into four main groups: group (1) fruits, vegetables, spices, plants, and woods, group (2) animal proteins, group (3) grains, and group (4) enzymes.

To diagnose immediate-type reactions, *skin prick tests* are the gold standard.

Open testing (quite similar to the skin application food test or SAFT), which has only been mentioned in the diagnosis of food allergy in atopic children, can be helpful but is generally negative unless the substance is applied on damaged or eczematous skin (where it even may cause an immediate vesicular reaction). Sometimes a rubbing test (gentle rubbing with the material) on intact or previously damaged skin

might be indicated, if an open test is negative. Scratch and scratch-patch testing carry a higher risk of false-positive reactions, and the latter lacks sensitivity compared to prick testing. Patch tests in protein contact dermatitis are usually negative. If there is a suspicion of any kind of serious extra-cutaneous symptoms, tests should be done with the necessary precautions, and resuscitation facilities should be adequately available [10].

4.4 Product Categories for Skin Testing [1]

Tables 4.5, 4.6, 4.7, 4.8, 4.9, 4.10, 4.11, and 4.12 provide details about testing with different patient's products.

Table 4.13 concerns "products not to test."

Table 4.5 Testing of decorative cosmetics and sunscreens

	Concentration	Comment
Eye makeup		
Eyeliner	As is	
Eye shadow	As is	
Mascara	As is	Semi-open test first, allow to dry (solvents)
Makeup cleanser	As is	Semi-open test first, irritation possible
Facial makeup		
Rouge	As is	
Powder	As is	
Foundation	As is	
Lipstick	As is	Photopatch when sunscreens are incorporated
Moisturizers		
Creams, ointments	As is	Irritation possible; positive patch lotion test reaction should be confirmed by ROAT or use test. Photopatch test when sunscreens are present
Bleaching creams	As is	
Sunscreens	As is	Photopatch test including active ingredients as commercially available
Self-tanning creams	As is	
Perfumed products		
Fine fragrances	As is	Photopatch if clinical findings suggest actinic dermatitis
Eau de toilette	As is	
After shave	As is	
Deodorants		
Spray, roll-on, stick	As is	Irritation possible Often false-negative ROAT!
Shaving products		
Cream	1 % (w)	Semi-open with product as is first. Irritation possible under occlusion
Soap	1 % (w)	Semi-open

Abbreviations for vehicles: *w* water, *MEK* methyl ethyl ketone, *pet* petrolatum, *oo* olive oil, *ac* acetone

Table 4.6 Testing of cleaning products

Product type	Concentration	Comment
Soap bar	1 % (w)	Irritation possible. Use test
Shampoo	1 % (w)	Semi-open
Shower gel	1 % (w)	
Bathing foam	0.1 % (w)	Semi-open
Toothpaste	1 % (w)	Semi-open

Abbreviations for vehicles: *w* water, *MEK* methyl ethyl ketone, *pet* petrolatum, *oo* olive oil, *ac* acetone

Table 4.7 Testing of hairdressing products and nail cosmetics

Product	Concentration	Comment
Hair dyes	2 % (w)	Active sensitization possible! Semi-open test: five drops dye and five drops oxidizing agent. If negative after 48 h, closed patch test with 2 %
Hair spray	As is	Irritation possible
Hair gel	As is	Semi-open test first
Depilatory	As is	Semi-open test first. Irritation possible (do not occlude)
Nail lacquer	As is	Always semi-open test only
Nail lacquer remover		Do not test (highly irritating)
Glues for artificial nails	1 and 0.1 % (MEK)	Semi-open test. Most glues are cured with UV light

Abbreviations for vehicles: *w* water, *MEK* methyl ethyl ketone, *pet* petrolatum, *oo* olive oil, *ac* acetone

Table 4.8 Testing of disinfecting agents

Product	Concentration	Comment
Hand disinfection	As is	Semi-open test first. Closed patch test may be irritating. Use test. Test ingredients!
Disinfecting agents for instruments, floors, etc.	1 %, 0.1 %, 0.01 %	Semi-open test first. Often contain strong irritants

Table 4.9 Testing of paints, lacquers, and solvents. Semi-open test first for all paints or lacquers

Product	Concentration	Comment
One component (water based, e.g., wall paints)	10–100 % (w)	
One component (solvent or oil based, e.g., paints for wood, iron, etc.)	1–10 % (pet)	
Diisocyanate hardeners of polyurethane paints or lacquers	2–5 % (pet)	
Paints containing epoxy, polyesters, or acrylics	0.1–1.0 % (pet)	Obtain detailed information on chemical composition first. Test conc. may be raised to 10 % for some paints
Organic solvents		
Aliphatic, cycloaliphatic	1–10 % (pet)	
Aromatic	1–5 % (pet)	
Chlorinated	0.1–1 % (pet)	
Esters	1–10 % (pet)	

Abbreviations for vehicles: *w* water, *MEK* methyl ethyl ketone, *pet* petrolatum, *oo* olive oil, *ac* acetone

Table 4.10 Testing of technical greases and oils

Product	Concentration	Comment
Lubricating grease	As is and 20 % (pet)	Semi-open test first
Lubricating oils	As is, 50 %, and 10 % (oo)	
Hydraulic oils	1 % (oo)	

Abbreviations for vehicles: *w* water, *MEK* methyl ethyl ketone, *pet* petrolatum, *oo* olive oil, *ac* acetone

Table 4.11 Testing of metalworking fluids (MWF)

Product	Concentration	Comment
Water based	5 % (w)	The usual workplace concentration of fresh MWF is 4–8 %. Test a freshly diluted
		MWF at 5 %, the used one as is (provided the concentration at the workplace is smaller 8 % – otherwise use a dilution of at least 1:1)
Oil based	50 % (oo)	

Abbreviations for vehicles: *w* water, *MEK* methyl ethyl ketone, *pet* petrolatum, *oo* olive oil, *ac* acetone

Table 4.12 Testing of glues and adhesives

Product	Concentration	Comment
Adhesive tapes	As is	
Glues		Semi-open test only
		Allow to dry. See also Table 4.13
Dispersion glues	10–100 % (pet or w)	
Solvent-based contact		
Glues	1–10 % (pet)	
Cyanoacrylate	2 % (pet)	Strong irritant, rare allergen
		Semi-open test first

Abbreviations for vehicles: *w* water, *MEK* methyl ethyl ketone, *pet* petrolatum, *oo* olive oil, *ac* acetone

Table 4.13 Do not test

In general, the following materials should not be tested because they are known as strong irritants but not as contact allergens (with few exceptions)
Patch testing may be performed only if there is high suspicion of contact allergy by history and clinical findings. Then an open and semi-open test should precede closed patch testing (dilution series from 0.1 to 1 %)
Astringents (e.g., $AgNO_3$)
Antifreeze
Car wax
Gasoline
Diesel
Floor wax
Lime
Organic solvents (various types)
Kerosene
Metal chips (coarse)
Rust remover
White spirit
Toluene
Toilet cleaners and other strong caustic cleaning agents
Cement, concrete

All products which have a strong pungent odor and/or contain organic solvents should be tested for pH (see above). If an open and semi-open test is negative, a dilution series starting with a very high dilution can be performed under occlusion (maximum 24 h, locating on the medial aspect of the upper arm, which enables removal by the patient in case pain occurs)

*Be also careful with semi-open testing with undiluted epoxy, acrylic, and other resins (sometimes contacted or contaminating the skin at work): only test if complete ingredient information exists and the concentrations of acrylic or epoxy compounds do not exceed the recommended concentrations for such substances (*see also Chap. 17 and 20*). Only apply a very minute amount with a Q-tip and leave to dry completely before covering with acrylic tape and only when full*

If doubts exist on the nature of the patch test reaction – irritant or allergic – an expert in the field should be consulted before further testing is performed. Active sensitization or ulcerative lesions with scar formation may be the risk of further investigative procedures

References

1. Frosch PJ, Geier J, Uter W, Goossens A. Chapter 57. Patch testing with the patient's own products. In: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. Textbook contact dermatitis. 5th ed. Berlin: Springer; 2011. p. 1107–19.
2. Gonçalo M, Ferguson J, Bonevalle A, et al. Photopatch testing: recommendations for a European photopatch test baseline series. Contact Dermatitis. 2013;68:239–43.
3. Goossens A. Chapter 11. Semi-open (or semi-occlusive) tests. In: Lachapelle JM, Bruze M, Elsner PU, editors. Patch testing tips: recommendations from the ICDRG. Heidelberg: Springer; 2014. p. 123–7.
4. Robinson MK, Stotts J, Danneman PJ, et al. A risk assessment process for allergic contact sensitization. Fed Chem Toxic. 1989;27:479–89.
5. Hannuksela M, Salo H. The repeated open application test (ROAT). Contact Dermatitis. 1986;14:221–7.
6. Bruze M. Use of buffer solutions for patch testing. Contact Dermatitis. 1984;10:267–9.

7. Jolanki R, Estlander T, Alanko K, Kanerva L. Patch testing with a patient's own materials handled at work. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, editors. Handbook of occupational dermatology. Berlin: Springer; 2000. p. 375–83.
8. Le Coz CJ, Ducombs G, Paulsen E. Chapter 46. Plants and plant products. In: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. Textbook contact dermatitis. 5th ed. Berlin: Springer; 2011. p. 873–925.
9. Bruze M, Frick M, Persson L. Patch testing with thin-layer chromatograms. Contact Dermatitis. 2003;48:278–9.
10. Amaro C, Goossens A. Immunological occupational contact urticaria and contact dermatitis from proteins: a review. Contact Dermatitis. 2008;58:67–75.

Basics in Diagnostic Work Up and Assessment of Clinical Relevance

5

Jeanne D. Johansen, Ulrik Fischer Friis, and Jacob P. Thyssen

Contents

5.1 Basics in Diagnostic Work Up

The point of departure for the investigation of allergic contact dermatitis in adults is the available baseline series for the geographical region in question. Advice on testing children can be found in Chap. 10.

As examples Table 5.1 gives the allergens in the European baseline series, Table 5.2 the North American core series and Table 5.3 the Chinese baseline series. Several other baseline series exist and the composition reflects the allergens that are considered to be relevant for exposures in the geographical region. This information can usually be found in the catalogues of the patch test suppliers or in publications from the scientific societies [1, 2].

J.D. Johansen, MD DmSci (✉) • U.F. Friis, PhD • J.P. Thyssen, MD, PhD
National Allergy Research Centre, Department of Dermato-Allergology, Copenhagen University Hospital Gentofte, Kildegårdsvej 28, Hellerup DK-2900, Denmark
e-mail: jeanne.duus.johansen@regionh.dk

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_5

Table 5.1 European baseline series (by January 2015)

Compound	Concentration in investigator filled chambers	Mg per patch in pre-filled patch tests[a]	Type
Potassium dichromate	0.5 % pet	0.019	Metal
p-Phenylenediamine (PPD)	1.0 % pet	0.073	Dye
Thiuram mix	1.0 % pet	0.020	Rubber
Neomycin sulfate	20.0 % pet	0.19	Antibiotic
Cobalt(II)chloride hexahydrate	1.0 % pet	0.016	Metal
Benzocaine	5.0 % pet	NI	Local anesthetic
Nickel(II)sulfate hexahydrate	5.0 % pet	0.16	Metal
Clioquinol	5.0 % pet	Quinolin-mix 0.041	Antibiotic
Colophonium	20.0 % pet	0.69	Resin (glue)
Paraben mix	16.0 % pet	0.80	Biocide
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)	0.1 % pet	Black rubber mix: 0.060	Black rubber
Lanolin alcohol	30.0 % pet	0.81	Wool oil
Mercapto mix	2.0 % pet	0.060	Rubber chemical
Epoxy resin, bisphenol A	1.0 % pet	0.041	Two component glue
Myroxylon pereirae resin	25.0 % pet	0.65	Fragrance/aroma
4-tert-Butylphenolformaldehyde resin (PTBP)	1.0 % pet	0.041	Glue
2-Mercaptobenzothiazole (MBT)	2.0 % pet	0.061	Rubber chemical
Formaldehyde	2.0 % aq	0.15	Biocide
Fragrance mix I	8.0 % pet	0.35	Fragrance
Sesquiterpene lactone mix	0.1 % pet	NI	Plant
Quaternium-15	1.0 % pet	0.081	Biocide
2-Methoxy-6-n-pentyl-4-benzoquinone (primin)	0.01 % pet	NI	Plant
Methylchloroisothiazolinone + methylisothiazolinone 3:1	0.02 % aq	0.0032	Biocide
Budesonide	0.01 % pet	0.0008	Corticosteroid
Tixocortol-21-pivalate	0.1 % pet	0.0024	Corticosteroid
Methyldibromo glutaronitrile	0.5 % pet	NI	Biocide
Fragrance mix II	14.0 % pet	NI	Fragrance
Hydroxyisohexylcyclohexene carboxaldehyde	5.0 % pet	NI	Fragrance
Methylisothiazolinone	0.2 % aq	NI	Biocide
Textile dye mix	6.6 % pet	NI	Dyes

[a]True Test® is the only available system of prefilled chambers
NI not included, *aq* aqua, *pet* petrolatum

Table 5.2 North American core series [1]

Compound	Concentration in %
Benzocaine	5.0 pet
2-Mercaptobenzothiazole (MBT)	1.0 pet
Colophonium	20.0 pet
p-Phenylenediamine (PPD)	1.0 pet

Table 5.2 (continued)

Compound	Concentration in %
Imidazolidinyl urea	2.0 pet
Cinnamal	1.0 pet
Amerchol L-101	50.0 pet
Carba mix	3.0 pet
Neomycin sulfate	20.0 pet
Thiuram mix	1.0 pet
Formaldehyde	2.0 aq
Ethylenediamine dihydrochloride	1.0 pet
Epoxy resin, bisphenol A	1.0 pet
Quaternium-15	2.0 pet
4-tert-Butylphenolformaldehyde resin (PTBP)	1.0 pet
Mercapto mix	1.0 pet
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)	0.1 pet
Potassium dichromate	0.25 pet
Myroxylon pereirae resin	25.0 pet
Nickel(II)sulfate hexahydrate	2.5 pet
Diazolidinyl urea	1.0 pet
DMDM hydantoin	1.0 pet
Bacitracin	20.0 pet
Mixed dialkyl thiourea	1.0 pet
Methylisothiazolinone + methylchloroisothiazolinone	0.02 aq
Paraben mix	12.0 pet
Methyldibromo glutaronitrile	0.5 pet
Fragrance mix I	8.0 pet
Glutaral	0.5 pet
2-Bromo-2-nitropropane-1,3-diol	0.5 pet
Sesquiterpene lactone mix	0.1 pet
Fragrance mix II	14.0 pet
Propylene glycol	30.0 aq
Benzophenone-3	10.0 pet
Chloroxylenol (pcmx)	1.0 pet
Ethyleneurea, melamine formaldehyde mix	5.0 pet
Iodopropynyl butylcarbamate	0.2 pet
Disperse Blue mix 106/124	1.0 pet
Ethyl acrylate	0.1 pet
Glyceryl thioglycolate	1.0 pet
Toluenesulfonamide formaldehyde resin	10.0 pet
Methyl methacrylate	2.0 pet
Cobalt(II)chloride hexahydrate	1.0 pet
Tixocortol-21-pivalate	0.1 pet
Budesonide	0.01 pet
Compositae mix II	5.0 pet
Hydrocortisone-17-butyrate	1.0 pet
Dimethylol dihydroxy ethylene urea	4.5 aq
Cocamidopropyl betaine	1.0 aq
Methylisothiazolinone	0.2 % aq

pet petrolatum, *aq* aqua

Table 5.3 Chinese baseline series (January 2015) [1]

Compound in Chinese	Compound in English
巯基苯丙噻唑	2-Mercaptobenzothiazole (MBT) 1 % pet
松香	Colophonium 20 % pet
对苯二胺	P-Phenylenediamine (PPD) 1 % pet
咪唑烷基脲	Imidazolidinyl urea 2 % pet
肉桂醛	Cinnamal 1 % pet
阿莫醇	Amerchol L 101 50 % pet
卡巴混合物	Carba mix pet 3 % pet
秋兰姆混合物	Thiuram mix 1 % pet
乙二胺二盐酸盐	Ethylenediamine dihydrochloride 1 % pet
双酚A型环氧树脂	Epoxy resin, bisphenol A 1 % pet
夸特15	Quaternium-15 2 % pet
4-叔丁基酚甲醛树脂	4-tert-Butylphenolformaldehyde resin (PTBP) 1 % pet
巯基混合物(硫氢基混合物)	Mercapto mix 1 % pet
氮-异丙基-氮-苯-4-苯二胺	N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD) 0.25 % pet
重铬酸钾	Potassium dichromate 0.25 % pet
秘鲁香脂	Myroxylon pereirae resin 25 % pet
硫酸镍	Nickel(II)sulfate hexahydrate 5 % pet
双咪唑烷基脲	Diazolidinyl urea 1 % pet
二烷基脲混合物	Mixed dialkyl thiourea 1 % pet
分散橙3	Disperse orange 3 1 % pet
尼泊金混合物(对苯类)	Paraben mix 12 % pet
甲基二溴戊二腈	Methyldibromo glutaronitrile 0.5 % pet
芳香混合物	Fragrance mix I 8 % pet
戊二醛	Glutaral 0.5 % pet
溴硝丙醇	2-Bromo-2-nitropropane-1,3-diol 0.5 % pet
倍半萜烯内酯混合物	Sesquiterpene lactone mix 0.1 % pet
蜂胶	Propolis 10 % pet
二苯酮-3	Benzophenone-3 10 % pet
4-氯3,5-二甲苯酚	Chloroxylenol (pcmx) 1 % pet
乙烯脲、密胺甲醛混合物	Ethyleneurea, melamine formaldehyde mix 5 % pet
2-叔丁基-4-甲氧基酚	2-tert-Butyl-4-methoxyphenol (BHA) 2 % pet
金硫代硫酸钠	Gold(I)sodium thiosulfate dihydrate 0.5 % pet
丙烯酸乙酯	Ethyl acrylate 0.1 % pet
甘油基单硫甘醇酸酯	Glyceryl thioglycolate 1 % pet
甲苯磺酰胺甲醛树脂	Toluenesulfonamide formaldehyde resin 10 % pet
甲基丙烯酸甲酯	Methyl methacrylate 2 % pet
氯化钴	Cobalt(II)chloride hexahydrate 1 % pet
椰子二乙醇胺	Cocamide DEA 0.5 % pet
茶树油	Tea tree oil oxidized 5 % pet
芳香混合物	Fragrance mix II 14 % pet
分散黄3	Disperse yellow 3 1 % pet
水杨酸苄酯	Benzyl salicylate 10 % pet
十二烷基葡糖苷	Decyl glucoside 5 % pet
2-羟乙基甲基丙烯酸酯	2-Hydroxyethyl methacrylate 2 % pet
乙内酰脲	DMDM hydantoin 1 % pet

Table 5.3 (continued)

Compound in Chinese	Compound in English
依兰油	Cananga odorata oil 2 % pet
异丙基豆蔻酸酯	Isopropyl myristate 20 % pet
吐温80	Polysorbate 80 5 % pet
2-正辛基-4-异噻唑啉-3-酮	2-n-Octyl-4-isothiazolin-3-one 0.1 % pet
分散蓝106/124	Disperse Blue mix 106/124 1 % pet
苯基过氧化物	Benzoylperoxide 1 % pet
对甲氧基肉桂酸异戊酯	Isoamyl p-methoxycinnamate 10 % pet
新铃兰醛	Hydroxyisohexyl 3-cyclohexene (Lyral) 5 % pet
辛基水杨酸盐	Ethylhexyl salicylate 5 % pet
甲醛	Formaldehyde 1 % aq
甲基氯异噻唑(原名:CL+ME异噻唑)	Methylisothiazolinone + methylchloroisothiazolinone 0.01 % pet
芳樟醇氢过氧化物	Hydroperoxides of linalool 1 % pet
柠檬烯氢过氧化物	Hydroperoxides of limonene 0.3 % pet
纺织燃料混合物	Textile dye mix 6.6 % pet
甲基异噻唑啉酮	Methylisothiazolinone 0.2 % aq,

Personal correspondence with Dr. Ling-Feng Li
pet petrolatum, *aq* aqua

The baseline patch test series contains allergens, which are frequent (give positive reactions in more than 1 % of those tested), or which are difficult to suspect from the clinical presentation e.g. corticosteroids.

It is called 'baseline series' or 'core series' to indicate that other allergens should be included in the patch test depending on the patient's exposures [3].

The patient should be asked to bring the products used for personal hygiene, skin care and other kinds of cosmetics. This should also include soaps, skin cleansers and skin care products from the work place. These products should also be considered for inclusion in the patch test (see Chap. 4). In case a specific product is suspected to have caused or contributed to the dermatitis, its composition should be reviewed to make sure that the relevant potential causative allergens are included in the patch test. In case the product under suspicion is intended for skin contact, a use test can be made with the product simultaneously with the patch test (see Chap. 3).

The use test (repeated open application test) is more sensitive than the patch test and thus more likely to reveal an allergic reaction [4].

The occupation of the patient, if suspected to cause the dermatitis, will also influence the diagnostic work up. For some occupations or exposures special series are available e.g. metal working fluid series or dental personnel series. Most such series varies between different patch test suppliers, and there is no consensus regarding the exact composition of these. Nevertheless such series are usually helpful, as relevant allergens may otherwise be overlooked. The use of patch test series does not replace an exposure assessment, which should always be performed.

5.2 Tools in Exposure Assessment

5.2.1 Patient's Characteristics and History

The medical history is crucial as it provides an overview of all the possible contact allergens the patient may have been exposed to, and therefore makes the basis for correct allergen selection.

It can sometimes be very difficult to get a good understanding of complex occupational cases, but with patience, imagination and perhaps the use of drawings [5], it is often possible to reliably determine significant exposures. However, sometimes work place visits are necessary to better understand work procedures and allergen exposures. Important clues can be retrieved from the clinical presentation (see Chap. 2). The history should cover exposure both at leisure and work. It is important to ask about use of protective equipment at work, as e.g. gloves are frequent causes of allergy. The history should also cover topical treatments as secondary allergies to e.g. corticosteroids and antiseptics can develop. Remission during times off work supports an occupational aetiology of dermatitis, but is not obligatory as the dermatitis may have become chronic.

It can be helpful to ask about rashes to specific product types e.g. perfumes, creams, gloves, shoes, tools, jewellery etc. depending on the localisation of eczema and the allergy under investigation.

5.2.2 Ingredient Labelling

The ingredient labels are valuable sources of information concerning exposures to allergens.

In many countries, cosmetics carry full information about ingredients on the label except for the composition of the fragrance formula. In the European Union, 26 individual fragrance ingredients have to be mentioned on the label if present in certain concentrations (see Chap. 12).

It should be remembered that the names on the patch test preparations often are chemical names (e.g. INN) and it can be necessary to look up synonyms to do an effective exposure assessment. Labelling on medicinal products follows INN. Household detergents label preservatives and fragrances according to the requirements of cosmetic products in the European Union.

5.2.3 Safety Data Sheets

In case of a complex work environment, safety data sheets may be available for certain products.

The Safety Data Sheets (also called Material Safety Data Sheets) only provide limited information concerning allergens. As a general rule, an allergen should be present in a product in a concentration of least 1 % to prompt labelling and warnings with H317: 'May cause an allergic skin reaction', while it is required that the name of the allergen is mentioned down to the concentration of 0.1 %. For certain allergens lower limits apply. The naming of the allergens is not standardized, so e.g. colophony could be called rosin. Current investigations have shown that around one out of five safety data sheets do not contain information about specific allergens in spite of their presence in the product [6]. It is important to be critical about the information given in safety data sheets and ask the producer for the full recipe, if in doubt about the completeness of the information.

5.2.4 Spot Tests and Chemical Analysis

Commercially available spot tests exist for nickel and cobalt, which are quick and easy ways to assess exposures. The nickel spot test is the best validated and has a high specificity and moderate sensitivity in detecting a level of nickel ion release, which may cause dermatitis [7]. In case of suspected occupational exposures, the nickel spot test can be used directly on the hands [8] (see Chap. 11). The cobalt test is based on similar principles, but is more difficult to read and there is less experience with the test (see Chap. 11). The formaldehyde spot test requires laboratory facilities, but can detect small levels of formaldehyde of clinical relevance in those sensitized. More advanced chemical analysis can also be performed, but this is usually only done in highly specialized departments.

5.3 Assessment of Clinical Relevance

The assessment of clinical relevance is, together with many other steps in patch testing, an essential part of the patient work-up [2]. Here, the physician synthesizes the medical history and the outcome of patch testing. This means that all the information that has been gathered so far needs to be carefully reviewed for missing parts and then integrated in the clinical decision process (Box 5.1). Thus, if some information has not come to the attention of the physician, this is the last opportunity to do something about it. Obviously, the clinical relevance of positive patch test reactions can only be sufficiently determined if the physician is aware of all exposures, their magnitude and frequency. Collectively, before the assessment of clinical relevance of positive patch test reactions, the physician is granted a final chance to collect information on missed allergen exposure.

Box 5.1 Assessment of Relevance of Positive Patch Test Reactions

Perform a standardized and thorough medical history
Atopic dermatitis (past or present)
Where did dermatitis begin (was it at a site with contact to an item or product)
How did dermatitis present in the beginning and how did it develop (vesicles increase suspicion of allergic etiology)
Does dermatitis improve or clear during e.g. holidays
Domestic exposures (consider cosmetics, jewellery, wet tissues, plants etc.)
Occupational exposures (detailed, consider work place visits)
Perform a detailed physical examination
Determine distribution of dermatitis and consider specific locations (e.g. textile dermatitis is located to sites of contact with tight clothing; nail lacquer dermatitis may be seen on the neck and around the eyes)
Identify sources of allergenic exposure
Product information (e.g. ingredient labeling, contact manufacturer or supplier, review material safety data sheets and product databases)
Chemical analysis of suspected products, e.g. by use of spot tests
Skin deposition tests (e.g. acid wipe sampling following normal work procedures with metal contact)
If possible, identify allergen concentrations in suspected products
Repeat the patch test and/or perform use test (ROAT)
Consider retesting a suspected allergen in a different vehicle, or use higher test concentration
Perform repeated open application test

Assessment of the clinical relevance of positive patch test reactions should not be mixed with patch test reading. These are two separate entities. Thus, begin by reading the patch test reactions (see Chap. 3), and once positive and doubtful positive reactions have been identified, the evaluation of clinical relevance can then begin. Importantly, positive patch test reactions only indicate that the patient has been previously exposed and sensitized to a chemical, but does not prove that the allergen is responsible for the patient's current problem of contact dermatitis.

Overall, positive test reactions should be categorized into three entities based on the medical history [2]:

- Current clinical relevance
- Past clinical relevance
- Unknown clinical relevance

'Current' or 'present' relevance is applied if an existing exposure to the sensitizer in question can be demonstrated, and this exposure fully or partly can explain the localization and course of the dermatitis. This means that the diagnosis allergic contact dermatitis can be made.

'Past relevance' signifies a past clinical disease explained by the sensitizer, but not directly related to the current symptoms. Positive patch test reactions that are considered to be of 'current clinical relevance' should furthermore be linked to the dermatitis as a primary cause or an aggravating cause.

In case no clinical relevance can be demonstrated, the term 'unknown clinical relevance' is used, as the overall assessment of clinical relevance is complex.

The physician should attempt to carefully integrate all the pieces of information and synthesize a conclusion. Expertise comes with experience, especially for uncommon allergens, as the physician needs to suspect that allergens categorized as being of 'no clinical relevance' might indeed be relevant to the patient's current dermatitis. Thus, a clear limitation in clinical decision making is gaps in the knowledge of allergen exposure. Here, good text books as well as case reports on uncommon allergen exposures may be useful. Also, communication with more experienced colleagues can be valuable. Thus, in some cases, a positive reaction is incorrectly judged as 'nonrelevant' owing to insufficient environmental information.

Doubtful patch test reactions means that the morphology is not clear-cut 'irritant' or 'allergic'. Patch test reactivity can vary for many reasons, including internal and external factors; so a doubtful reaction might become positive if retesting is done, or the concentration slightly increased or the vehicle changed. This means that further investigations may have to be done (see Chap. 2). The weak patch test reaction may also be due to cross-reactivity to another substance, which is the true cause of sensitization and thus be clinically relevant.

A shortcut to assessment of clinical relevance is to test the patients with their own products [9].

In case of a positive patch test reaction to a product used by the patient and an ingredient in the product, it is likely that the patch test reaction is clinically relevant.

5.4 Overview of Diagnostic Work-Up

The flow of an investigation can be as in Fig. 5.1. First based on the patient's characteristics, history and the exposure analysis, a patch and possibly skin prick test is planned. If the outcome of the skin tests are negative, the exposures are reviewed to make sure that an allergen has not been overlooked. In case of a significant exposure to irritants, the diagnosis of irritant contact dermatitis can be considered (see Chap. 6).

In case of unexpected positive reactions at patch or skin prick testing, the environment is examined for the presence of the allergen; this includes reviewing the history of the patient again, ingredient labels and safety data sheets, if available. In case of a positive patch test reaction to nickel or cobalt, spot tests can be used to detect exposure in the home or work environment from metal objects. The assessment should lead to a decision on clinical relevance and thus the diagnosis (Fig. 5.1).

Such systematic step-wise exposure assessment has proven valuable in detecting additional relevant allergies [10].

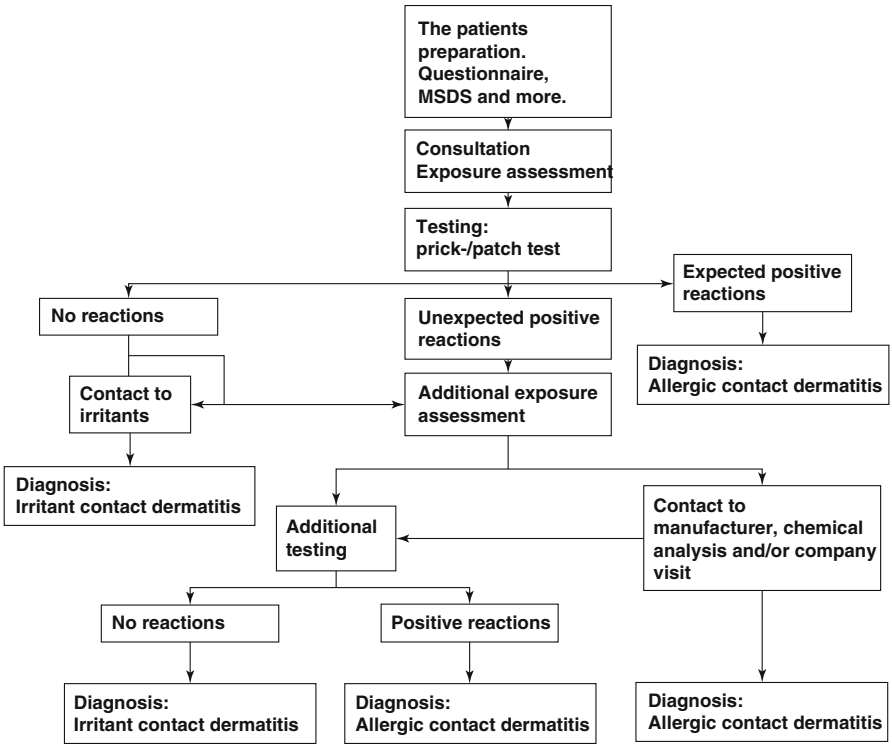


Fig. 5.1 Flow diagram of the investigation of patients with suspected allergic contact dermatitis

References

1. Chemotechnique Diagnostics. http://www.chemotechnique.se/products/national-series/north-american-series. Last accessed 31 Jan 2015.
2. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, Cannavó A, Giménez Arnau A, Gonçalo M, Goossens A, John SM, Lidén C, Lindberg M, Mahler V, Matura M, Rustemeyer T, Serup J, Spiewak R, Thyssen JP, Vigan M, White I, Wilkinson M, Uter W. European Society of Contact Dermatitis guideline for diagnostic patch testing. Recommendations of best practice. Contact Dermatitis. 2015. doi: 10.1111/cod.12432. [Epub ahead of print]
3. Bruze M, Condé-Salazar L, Goossens A, Kanerva L, White IR. Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. Contact Dermatitis. 1999;41(5):241–50.
4. Fischer LA, Voelund A, Andersen KE, Menné T, Johansen JD. The dose-response relationship between the patch test and ROAT and the potential use for regulatory purposes. Contact Dermatitis. 2009;61(4):201–8.
5. Friis UF, Menné T, Thyssen JP, Johansen JD. A patient's drawing helped the physician to make the correct diagnosis: occupational contact allergy to isothiazolinone. Contact Dermatitis. 2012;67(3):174–6.
6. Friis UF, Menné T, Flyvholm MA, Bonde JP, Johansen JD. Difficulties in using Material Safety Data Sheets to analyse occupational exposures to contact allergens. Contact Dermatitis. 2015;72(3):147–53.

7. Thyssen JP, Skare L, Lundgren L, Menné T, Johansen JD, Maibach HI, Lidén C. Sensitivity and specificity of the nickel spot (dimethylglyoxime) test. Contact Dermatitis. 2010;62(5): 279–88.
8. Julander A, Skare L, Vahter M, Lidén C. Nickel deposited on the skin-visualization by DMG test. Contact Dermatitis. 2011;64(3):151–7. Erratum in: Contact Dermatitis. 2012;66(1):53.
9. Bruze M. What is a relevant contact allergy? Contact Dermatitis. 1990;23:224–5.
10. Friis UF, Menné T, Flyvholm MA, Bonde JP, Johansen JD. Occupational allergic contact dermatitis diagnosed by a systematic stepwise exposure assessment of allergens in the work environment. Contact Dermatitis. 2013;69(3):153–63.

Part III

Special Groups

Irritant Contact Dermatitis: Diagnosis and Risk Factors

6

Marie-Louise Anna Schuttelaar

Contents

6.1 Introduction

Irritant contact dermatitis (ICD) occurs after exposure of the skin to irritants from outside. Irritating agents or factors induce a disruption of the skin barrier and lead to an inflammatory reaction mainly mediated by the innate immunity. Any agent that causes damage to the skin is an irritant. The damage to the skin is determined by the chemical, physical or mechanical properties of the agent but also by the extent and duration of exposure. There are two variants: acute ICD and chronic ICD. Acute ICD is mostly due to one toxic event, usually caused by an accidental, short contact with a strong irritant. The chronic variant of ICD develops as a result of prolonged or repeated exposure to primary irritants and depends on the duration and intensity of exposure to the potentially responsible agent(s) [1]. Malten described in 1981 chronic ICD as a result of a sequence of a variety of skin irritating events, each being not strong enough to induce overt dermatitis, but when events taking place before the skin could recover from the previous event, the effect

M.-L.A. Schuttelaar, MD, PhD
Department of Dermatology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, Groningen 9700 RB, The Netherlands
e-mail: m.l.a.schuttelaar@umcg.nl

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_6

becomes clinically discernable [2]. Example of such skin damage incidents assigns its exposure to detergents, shampoos, abrasives, solvents and physical factors such as dry air, moisture and occlusion (by wearing gloves) but also water. At the moment that eczema has developed, even a minimal skin irritation, like a trivial exposure to water and soaps in normal personal care, can cause or maintain eczema.

6.2 Clinical Features

Clinical signs are dependent on the location and duration of exposure to the irritant as well as its chemical structure. Moreover, the clinical signs may vary with the susceptibility of the exposed individual. The morphology of the skin lesions depends greatly on the stage of the dermatitis at which the patient is first examined. In general, skin changes appear quite sharply defined and are located at places where the skin is exposed to aggressive substances. Acute ICD presents with erythema, oedema, infiltration and erosions. Subsequently, scaling and pustules may arise. In case of exposure to strong irritants, the skin changes may include blisters up to necrosis. Chronic ICD develops after repetitive exposure to a variety of damaging factors, such as water, soaps and detergents. Dry skin and mild erythema are often the first clinical signs. Proceeding the exposure leads to an obvious chronic ICD.

In the early phases of ICD, the web spaces, the dorsal surfaces of the fingers and backs of the hands are often affected, since these surfaces are more sensitive to irritant influences than the palm (Fig. 6.1). Subsequently the palmar surfaces are involved. Although vesicles usually do not occur in ICD, the clinical picture may be identical to that of allergic contact dermatitis (ACD).

6.3 Main Groups of Irritants

ICD is induced by direct contact of the skin with liquids, pastes and solids, including contact between aerosols, gases and vapors and the skin. Exposures to irritants that give rise to hand eczema are listed in Table 6.1.

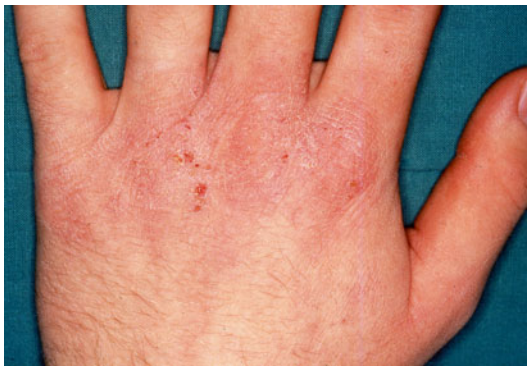


Fig. 6.1 Irritant contact dermatitis in the web spaces, the dorsal surfaces of the fingers and back of the hand

Table 6.1 Main groups of irritants

Chemical irritants	Physical irritants	Other
Acids (also from fruit)	Mechanical	Water
Alkaline substances	Friction	Climate: cold
Cement/lime	Pressure	Environmental condition: low relative humidity
Cooling lubricants	Heat	
Oil products, including cutting oils	Dusts	
Organic solvents (benzene, acetone)	Occlusion (gloves)	
Detergents	Mineral and glass fibers	
	Sand	
	UV radiation	
	Ionizing radiation	
	Wool	

Wet work is an important stressor for the skin and plays a prominent role in the majority of ICD cases. Activities during which workers spend a considerable portion of their working time in a wet work environment or wear liquid-tight gloves or wash their hands frequently or intensively count as wet work. Although gloves protect the skin from contact with allergens and irritants, the occlusion of the skin caused by the glove itself is a risk factor for hand eczema [3, 4]. The liquid-tight effect of protective gloves prevents the dissipation of perspiration to the outside; subsequently, the skin swells up as the time the gloves are worn increases, which reduces the barrier effect. Fartasch et al. investigated the differences between water exposure and occlusion by gloves in an experimental setting on forearm skin [3]. They demonstrated that short occlusion seems to harm the skin less than water exposure for the same time. However, their experiments were performed on forearm skin which indicates that the results may have been different when performed on the hands, in which occlusion of gloves may cause more perspiration due to abundant eccrine sweat glands on the palmar surfaces.

When the skin is pre-damaged by irritants or liquid-tight gloves, it becomes easier for irritants, potentially allergenic substances or infectious agents to penetrate [5]. In the case of combinations of irritative conditions, the damage to the skin is more than the separate effects, e.g., the harmful effect of soap is increased if it is followed by the use of liquid-tight gloves. Fartasch et al. demonstrated that previous occlusion and water exposure were capable of inducing higher susceptibility to sodium lauryl sulfate (SLS) irritation [3].

6.4 Risk Factors and Skin Barrier Dysfunction

The cause of hand eczema is often multifactorial. In addition to exogenous risk factors, there are endogenous risk factors that influence the development of ICD. A current or previous history of atopic dermatitis (AD) increases the risk for ICD [6, 7]. However, among individuals with atopic dermatitis who are exposed to

irritants, it is difficult to distinguish between atopic hand eczema and hand eczema as a manifestation of ICD. Patients with AD have an impaired skin barrier, also in uninvolved skin, which was demonstrated by a higher penetration of SLS [8]. However, individuals without a history of atopic dermatitis may also have an increased susceptibility to irritants. Tupker et al. [9] investigated the susceptibility of the skin to various irritants, among other SLS, in individuals with a history of AD, individuals with a dry skin, and in individuals with clinically normal skin. In those with a previous history of AD, the transepidermal water loss values were both preexposure and throughout the entire period of exposure, higher than in the other groups. Though also individuals with clinically dry skin, without a history of AD, appeared to be more susceptible to irritants than those with normal skin, there was no difference noted in the preexposure barrier function.

The uppermost layer of the skin, the stratum corneum, acts as a barrier that prevents the entry of external irritants, microbes and allergens and controls the transcutaneous movement of water. An impaired skin barrier function in AD can partly be explained by a reduction or absence of the protein filaggrin in the skin. The filaggrin gene *(FLG)* encodes the protein profilaggrine, a major component of the keratohyalin granules in the stratum granulosum of the epidermis. During the later stages of epidermal differentiation, profilaggrine is dephosphorylated and cleaved to form filaggrin monomers, which contribute to the cornified cell envelope [10]. The filaggrin monomers are further proteolyzed, contributing to the natural moisturizing factor of the stratum corneum, and playing a central role in the hydration of the stratum corneum. Loss-of-function mutations in the *FLG* result in either a reduction or complete absence of epidermal filaggrin and its degradation products [11]. These mutations are predisposing factors for AD and are carried by 15–55 % of the patients with AD in European populations [12–14]. However, epidermal filaggrin and its degradation products are influenced not only by the filaggrin genotype but also by inflammation and exogenous stressors [11]. Filaggrin deficiency is observed in patients with AD regardless of filaggrin mutation status [11].

De Jongh et al. [7] demonstrated an increased risk for the development of ICD in individuals with *FLG* mutations. However, this association appeared to be dependent on the presence of a history of AD. In one study, a small, but significant association between ICD and *FLG* mutations persisted after adjustment for the history AD [11]. Both a history of AD and *FLG* mutations contribute to the development of ICD. More research into the skin barrier function in patients with AD and patients with *FLG* mutations is warranted to investigate the role of the different predisposing stimuli in the development of ICD.

6.5 How to Make the Diagnosis

The morphology and distribution of eczema are of limited help in making the diagnosis, and specific tests for ICD are not available. Allergic contact dermatitis and contact urticaria/protein contact dermatitis should be excluded as contributory causes, since combinations of irritant and allergic cases are common. Therefore, diagnostic patch testing should be performed in all patients with hand eczema with

duration of more than 3 months and/or relapse, to identify the role of contact allergens [1]. Hand eczema patients reporting immediate skin reactions may have protein contact dermatitis. This is a distinct form of allergic or irritant hand eczema in which IgE-mediated mechanisms or nonimmunological mechanisms give rise to clinical manifestations characterized by an initial urticarial phase followed by eczema [1]. Triggers are natural rubber latex, food allergens or certain animal proteins. Skin prick testing or serum radioallergosorbent (RAST) testing should be performed to assess these reactions. However, nonimmunological types also exist [1]. See also Chap. 8 on protein contact dermatitis.

A history of hand eczema or AD provides important information on risk factors to develop ICD. Determination of allergen-specific IgE levels can help to establish the atopy status, though is not routinely recommended.

The diagnosis of ICD is based on a documented exposure to an irritant that is quantitatively likely to cause contact dermatitis [1]. A careful history about occupational and nonoccupational exposure to irritants is necessary. Occupational information should be obtained about accidents, new products or defective machinery. Environmental conditions such as changes in season, temperature and humidity and the influence on the contact dermatitis should be obtained. Questioning about the conditions of exposure is crucial to find the offending agents. Information about preceding or concomitant exposure is important if more than one product is involved. Detailed information on chemicals, products and materials should be traced. In case there are suspected materials or products from patient's work environment, material data safety sheets and lists of ingredients should be examined carefully for information about the product, the ingredients, concentrations, etc. [15].

It is important to estimate the duration of the exposures to irritants at the workplace, at home and during leisure activities. In addition, it is important to have insight into the frequency of exposure, whether it is a single exposure or a repeated exposure. Working procedures should be reviewed in order to quantify exposure to irritants. A well-defined exposure to irritants likely to cause ICD is wet work. TRGS 401 is the only existing guideline to regulate exposure to wet work [5]. Criteria for wet work include wet hands or wearing of liquid-proof gloves for 2 h or more per day or more than 20 handwashes daily. This limit of 2 h should be included in the quantification of exposure to irritants to make the diagnosis of ICD. The only correct method to measure wet work seems to be observation since questionnaires appeared not reliable in a study [16]. In Table 6.2, a work-up for a consultation of a patient with ICD is presented. Actually, the work-up is suitable for hand eczema in general. However, some parts such as the extensive, detailed history regarding exposure are important if ICD is suspected.

6.6 Management of Irritant Contact Dermatitis

The first and most important measure in ICD is to eliminate or reduce exposure to irritants and wet work. Healthcare workers should use alcohol-based skin disinfectants instead of water and soap. However, healthcare workers often experience the disinfectants as burning because of the damaged skin, though such a damaged skin

Table 6.2 Work-up consultation of a patient with hand eczema in general, with specific focus on exposure to irritants and recommendation on various gloves

History of hand eczema	Duration, primary site and type of skin changes, work related
Endogenous risk factors	History of atopic dermatitis, dry skin
Exposure	Frequency, duration, combination of irritative conditions
	Cleaning activities, detergents
	Handwashing, usage of soap, alcohol-based skin disinfectants
	Physical irritants (Table 6.1), cold air, low relative humidity
	Leisure activities (e.g., garden work)
	Types of gloves, plastic or rubber (e.g., natural rubber latex, nitrile, PVC)
	Chemicals, products, materials: concentration, dose, frequency, materials safety data sheets
	Wet work environment
Absenteeism	Duration, frequency, influence on hand eczema
Skin care	Usage of emollients and frequency
Impact on quality of life	E.g., hand eczema specific: QOLHEQ [17]
Examination of the skin	Anatomical distribution of skin changes on the hands, assessment of severity
	Skin changes on other sites of the body (e.g., feet)
	Other skin diseases (e.g., psoriasis, mycosis)
Assessment of severity	E.g., Physician Global Assessment (PGA), photographic guide or hand eczema severity index (HECSI) [18, 19]
Diagnostics	Patch testing (to exclude contact allergy)
	Prick testing or sIgE (to exclude protein contact dermatitis, if suspected)
Treatment, advice, education	
Reduction of exposure	Reduce exposure to irritants, wet work, allergens
Protective measures	Usage of gloves adjusted to the irritants and type of work
	Wet work environment: fluid-tight gloves with cotton lining or inner gloves underneath fluid-tight gloves when gloves are worn for longer than 10 min
Gloves: good chemical resistance to various materials [4]	Latex: biologic materials and water-based materials
	Nitrile: solvents, oils, greases, selected acids and bases
	Vinyl: acids, bases, oils, greases, peroxides and amines
	Polychloroprene: acids, bases, alcohols, fuels, peroxides, hydrocarbons, oils, greases and phenols
	Polyvinyl alcohol: aromatic and chlorinated, solvents, ketones, esters, methacrylate (expensive)
	Butyl: ketones, aldehydes, esters (expensive)
	Multilayer laminates gloves (laminated glove of ethylene-vinylalcohol-polyethylene 4H®): almost all substances (poor fit)
Handwashing	Reduce frequency
	Wash only if visibly dirty: lukewarm water with fragrance-free soap without well-known sensitizers such as MCI/MI, dry thoroughly, alcohol-based disinfectants instead of water and soap for hand hygiene
Hand hygiene (e.g. healthcare workers)	Alcohol-based skin disinfectants (instead of water and soap), dry thoroughly before putting on gloves

Table 6.2 (continued)

Daily skin care	Emollients several times per day
Medical treatment	Topical steroids, calcineurin inhibitors (efficacy limited), (tar), UV therapy, systemic therapy (only recommended in severe hand eczema)
Education	Nature of ICD, role of triggering factors like scratching, contact with water and soap, climate
	Use of topical steroids, guidance on the potency, duration and reducing steroid use, instruction on application of emollients/skin care
Support	Strengthening of self-efficacy and self-management

condition should always be avoided. Gloves protect the skin from contact with irritants. Different gloves protect for various exposures making it important to find out the right glove. A recommendation on various gloves [4] is made in Table 6.2. However, the occlusion of the skin caused by the glove itself is a risk factor for hand eczema. As the skin of the hands will sweat after about 10 min in liquid-tight gloves, it is recommended to wear it no more than 10 min continuously. When gloves are worn for longer than 10 min, cotton linings or inner gloves underneath occlusive gloves are recommended. See also Chap. 24 on workers' protection.

Acute hand eczema should be treated quickly and consequently to avoid the development of chronic hand eczema [1]. Often the patient has a certain work routine or routine in daily life in which one is accustomed over the years. However, without a thoroughly adjustment of skin damaging behavior, a medical treatment is unsuccessful. Table 6.2 provides detailed information on the treatment of hand eczema. Education is necessary on the nature of ICD, the role of triggering factors like scratching, contact with water and soap, skin protection and daily skin care. Nurses can have an important role in the education, instruction and guidance of patients with hand eczema. Most emollients improve the hydration state of normal skin/stratum corneum and are effective for treatment of contact dermatitis [1]. Besides treatment with emollients, the first line local treatment is a topical corticosteroid, in which once-daily application seems sufficient.

6.7 Prognosis and Personal Prevention

Hand eczema is often a long-lasting disease with a poor prognosis. Meding et al. reported the negative effect of the extensiveness of symptoms on the prognosis. Petersen et al. recently reported a 7-year follow-up study in which they evaluated the clinical course of patients with hand eczema [20]. Patients with a greater risk of a poor outcome were characterized by frequent eruptions, severe hand eczema and more widespread eczema [20]. A poorer prognosis of hand eczema is also associated with longer delay before medical attention [21]. Early accurate medical intervention is recommended to improve the prognosis.

The aim of primary prevention is to decrease the incidence of ICD by limiting exposure to its risk factors. Previous or current AD is a significant endogenous risk

factor for development of ICD, counselling about avoiding wet and soiled occupations should be given to adolescents with AD. Clear risk occupations (hairdressers, healthcare workers, construction staff, cleaning staff, metal workers) should be discouraged. Nevertheless, if patients insist on these jobs, personal protective measures should be started immediately.

In patients with ICD, secondary prevention strategies are indicated. The objective of secondary prevention is to spot early skin changes in order to rapidly implement corrective measures [1]. The first and most important measure is to eliminate or reduce risk factors. Exposure to irritants and work-related skin burden should be avoided. Wearing gloves is often the first option to protect the skin from irritants. However, gloves may contribute to persistent damage by occlusion. In Table 6.2, a recommendation is made on the treatment and advises which are important in secondary prevention.

Conflicts of Interest There was no funding and the author has no conflicts either actual or perceived.

References

1. Diepgen TL, Andersen KE, Chosidow O, Coenraads PJ. Guidelines for diagnosis, prevention and treatment of hand eczema. J Dtsch Dermatol Ges. 2015;13:e1–22.
2. Malten KE. Thoughts on irritant contact dermatitis. Contact Dermatitis. 1981;7:238–47.
3. Fartasch M, Taeger D, Broding HC, et al. Evidence of increased skin irritation after wet work: impact of water exposure and occlusion. Contact Dermatitis. 2012;67:217–28.
4. Kwon S, Campbell LS, Zirwas MJ. Role of protective gloves in the causation and treatment of occupational irritant contact dermatitis. J Am Acad Dermatol. 2006;55:891–6.
5. Federal Institute for occupational Safety and health. TRGS401. Risks resulting from skin contact identification, assessment, measures. [WWW document] (June 2008) URL http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/TRGS-401.pdf. Accessed on 2014.
6. Coenraads PJ, Diepgen TL. Risk for hand eczema in employees with past or present atopic dermatitis. Int Arch Occup Environ Health. 1998;71:7–13.
7. de Jongh CM, Khrenova L, Verberk MM, et al. Loss-of-function polymorphisms in the filaggrin gene are associated with an increased susceptibility to chronic irritant contact dermatitis: a case-control study. Br J Dermatol. 2008;159:621–7.
8. Jakasa I, de Jongh CM, Verberk MM, et al. Percutaneous penetration of sodium lauryl sulphate is increased in uninvolved skin of patients with atopic dermatitis compared with control subjects. Br J Dermatol. 2006;155:104–9.
9. Tupker RA, Pinnagoda J, Coenraads PJ, Nater JP. Susceptibility to irritants: role of barrier function, skin dryness and history of atopic dermatitis. Br J Dermatol. 1990;123:199–205.
10. Osawa R, Akiyama M, Shimizu H. Filaggrin gene defects and the risk of developing allergic disorders. Allergol Int. 2011;60:1–9.
11. Thyssen JP, Kezic S. Causes of epidermal filaggrin reduction and their role in the pathogenesis of atopic dermatitis. J Allergy Clin Immunol. 2014;134:792–9.
12. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet. 2006;38:441–6.

13. Weidinger S, Illig T, Baurecht H, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. J Allergy Clin Immunol. 2006;118:214–9.
14. Sandilands A, Terron-Kwiatkowski A, Hull PR, et al. Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. Nat Genet. 2007;39:650–4.
15. Wahlberg JE. Clinical overview of irritant dermatitis. In: van der Valk P, Maibach H, editors. The irritant contact dermatitis syndrome. Boca Raton: CRC Press; 1996. p. 1–6.
16. Jungbauer FH, Steenstra FB, Groothoff JW, Coenraads PJ. Characteristics of wet work in nurses. Int Arch Occup Environ Health. 2005;78:248–51.
17. Ofenloch RF, Weisshaar E, Dumke AK, et al. The quality of life in hand eczema questionnaire (QOLHEQ): validation of the German version of a new disease-specific measure of quality of life for patients with hand eczema. Br J Dermatol. 2014;171:304–12.
18. Coenraads PJ, Van Der Walle H, Thestrup-Pedersen K, et al. Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. Br J Dermatol. 2005;152:296–301.
19. Held E, Skoet R, Johansen JD, Agner T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. Br J Dermatol. 2005;152:302–7.
20. Petersen AH, Johansen JD, Hald M. Hand eczema – prognosis and consequences: a 7-year follow-up study. Br J Dermatol. 2014;171:1428–33.
21. Hald M, Agner T, Blands J, et al. Delay in medical attention to hand eczema: a follow-up study. Br J Dermatol. 2009;161:1294–300.

Photoreactions and Testing

7

Margarida Gonçalo

Contents

7.1 Definition and Types of Reactions

Photosensitivity represents an abnormal cutaneous reaction to light, usually ultraviolet (UV) light. Photosensitive reactions can occur in individuals who lack the usual UV-defense mechanisms, e.g., vitiligo or xeroderma pigmentosum, who have increased endogenous chromophores in their skin, e.g., porphyrias, or who are exposed to exogenous chemicals that are activated in the skin by UV light, e.g., plants, drugs, and UV filters.

These exogenous chemicals activated by UV light can induce skin inflammation by different mechanisms – phototoxicity, photoallergy, or both. Photoactivation of the exogenous chemical can transfer energy to neighboring molecules and induce aggression of the epidermal cells (lesions on DNA bases, oxidation of lipids of cell membranes, or modification of proteins) or generate reactive oxygen species causing a nonspecific inflammatory reaction – phototoxicity. Also, upon receiving UV

M. Gonçalo, MD, PhD
Clinic of Dermatology, University Hospital and Faculty of Medicine, University of Coimbra, Praceta Mota Pinto, Coimbra P-3000-175, Portugal
e-mail: mgoncalo@fmed.uc.pt

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_7

energy, exogenous chromophores can be modified into stable photoproducts or can bind skin proteins forming antigens that are presented to the immune system and induce a lifelong sensitization dependent on specific memory and effector T cells. A further exposure to the chemical and UV light will cause a delayed hypersensitivity reaction – acute photoallergy – and continuous exposure to the photosensitizer may be associated with chronic photosensitivity. Some few chemicals induce exclusively photoallergy, but many have some phototoxic potential and also induce sensitization in a limited number of individuals [1, 2].

Upon UV exposure, cutaneous photoreactions develop when a significant level of the photoactive chemical reaches the skin after oral/parenteral route (systemic photosensitivity) or when the chemical is applied on the skin (contact photosensitivity). The latter is usually divided into photoallergic contact dermatitis (PhACD) and contact phototoxicity.

7.2 Clinical Aspects and Differential Diagnosis

Cutaneous photoreactions are almost exclusively localized to sun-exposed areas, usually the area where there was concomitant exposure to UV and the chemical applied on the skin. In systemic photosensitivity, they usually involve the face, V of the neck, dorsum of the hands and forearms, and spare shaded areas as the submandibular region, retroauricular folds, upper eyelids and upper lip, deep wrinkles, and areas covered by natural hair or clothing (Figs. 7.1 and 7.2). This pattern needs distinction from airborne contact dermatitis that develops also on exposed areas but needs no sun exposure. Shaded areas are also involved in airborne dermatitis, and body folds can even be preferentially involved. PhACD involving the face can also be difficult to distinguish from contact dermatitis from a facial cosmetic, as the relation with sun exposure is not always very evident due to the delay of 1–2 days for lesion expression. PhACD from products used in the mouth can occur only on the lips and chin [3, 4].

Phototoxicity is more frequent, can occur on first exposure as it needs no previous sensitization, and presents typically as exaggerated sunburn that develops within 24–48 h as erythema, eventually with bullae, usually with sharp limits, and tends to regress with brown hyperpigmentation.

Photoallergy is less frequent than phototoxicity and occurs in a limited number of exposed individuals. Except in a few individuals who are already allergic to a cross-reactive molecule, lesions develop after a longer exposure to the photosensitizer (latency period required for sensitization). Once sensitized, the reaction develops within 24–48 h of exposure and, particularly in PhACD, presents as acute or subacute eczema that begins at the area of application but may extend beyond its limits and, eventually, generalize.

Histopathology shows sunburn cells (apoptotic keratinocytes) and nonspecific inflammation in phototoxicity, whereas in PhACD, an acute eczema with spongiosis and T-cell exocytosis is usually observed, but there is no definite histopathologic distinction between these two patterns (Table 7.1).

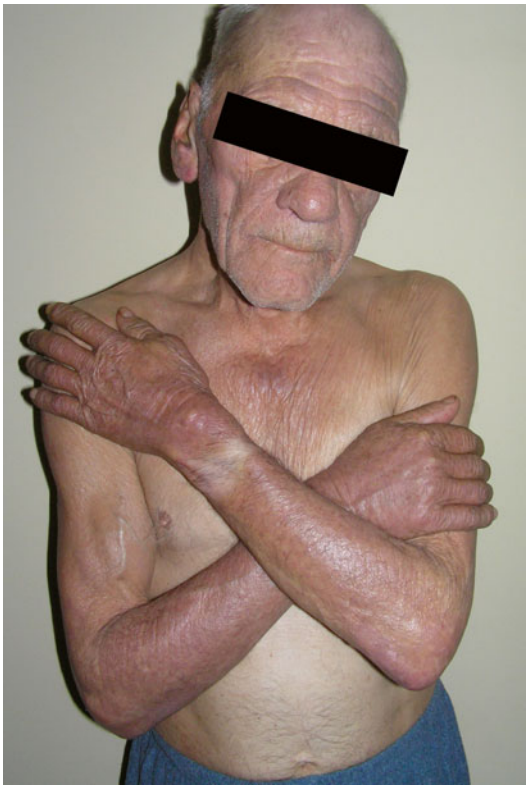


Fig. 7.1 Systemic chronic drug photosensitivity, with symmetrical lesions involving the face and V of the neck and forearms, with protection of the area covered by the wrist watch

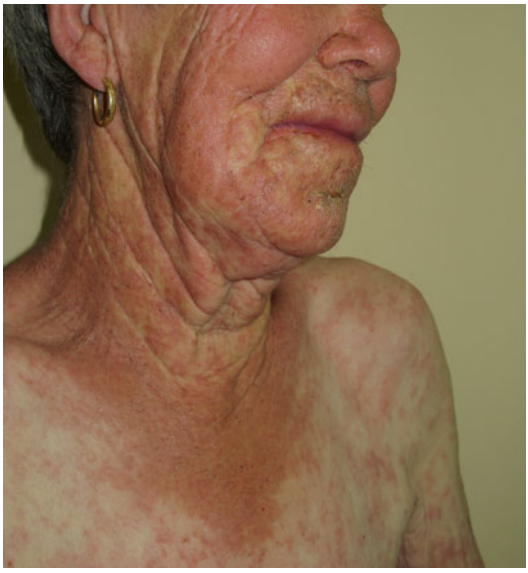


Fig. 7.2 Photoreaction from ingestion of *Hypericum perforatum* infusion with main lesions on photoexposed areas but eczematous and erythema multiforme-like lesions outside the exposed area, suggesting a concomitant photoallergy

Table 7.1 Clinical aspects of photoreactions

Predominant in phototoxicity	Predominant in photoallergy or immune-mediated reactions
Frequent, can occur first exposure	Rare, needs previous sensitization
Lesions with sharp limits	Lesions may extend to covered areas
Exaggerated "sunburn"	Acute vesicular, papular eczema
Pseudoporphyria	Subacute/chronic eczematous lesions
Photoonycholysis	Erythema multiforme-like
Hyperpigmentation	Lichenoid reactions
Hypopigmentation	Cheilitis
Telangiectasia	Urticaria on sun-exposed area
Purpura	Pellagra-like reactions
Histology – sunburn cells	Histology – spongiosis, lymphocyte exocytosis
Quick regression	Possible persistence/recurrence and cross-reactions
Increase in actinic keratosis and nonmelanoma skin cancer in the long term	Possible subacute or chronic cutaneous lupus erythematosus

7.3 Main Causes of Photoreactions

A phototoxic dermatitis occurs frequently after contact with plants rich in furocoumarins (Moracea, e.g., *Ficus carica*, or Rutacea, e.g., *Ruta graveolens*, and citrus fruit peels, particularly lime, *Citrus aurantifolia*). It presents as linear lesions with non-pruritic erythema and bullae, in the acute stage, followed by long-lasting brown hyperpigmentation streaks (Fig. 7.3). Ingestion of infusions of these plants, like *Hypericum perforatum* used as folk medicine to treat depression (Fig. 7.2), can also cause systemic photoreactions [5].

Drugs are the main cause of systemic photosensitivity, mostly dependent on phototoxicity, even though other mechanisms (increased porphyrins levels, as with vemurafenib) [6, 7] and photoallergy also have to be considered (as in photoallergy to the nonsteroidal anti-inflammatory drug (NSAID) piroxicam). Cutaneous lesions in systemic drug photosensitivity involve photoexposed areas mostly in a symmetric distribution and present mainly as eczematous lesions or exaggerated sunburn, or also as pseudoporphyria, simulating porphyria cutanea tarda (naproxen, voriconazole, celecoxib), photoonycholysis (tetracyclines), hyperpigmentation (amiodarone), vitiligo-like lesions (flutamide), telangiectasia (ciprofloxacin), or subacute cutaneous lupus erythematosus (terbinafine, thiazides). Accelerated skin photoaging and an increase in precancerous skin lesions and skin cancers, mostly nonmelanoma skin cancer, are being described as delayed manifestations of exposure to photoactive drugs (voriconazole, fluoroquinolones) [7–11].

Many classic topical photosensitizers have been removed from the European market and now seldom cause PhACD – halogenated salicylanilides used in disinfectant soaps, musk ambrette and bergamot oil used as perfumes, olaquindox an

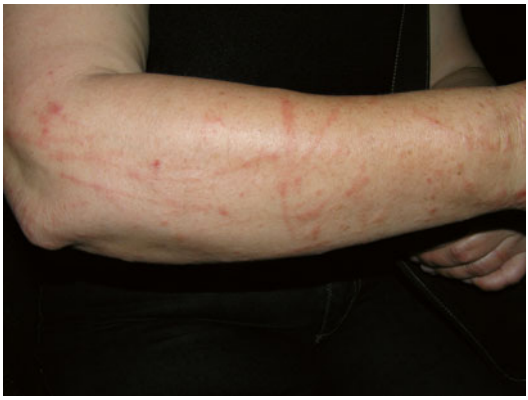


Fig. 7.3 Linear inflammatory and pigmented lesions from phytophotodermatitis from *Ruta graveolens*

antibiotic used as a pig feeder, and PABA (para-aminobenzoic acid) and isopropyl-dibenzoylmethane used in sunscreens. At present, main causes of PhACD are the UV filters and topical NSAID, with predominance for the latter in Southern European countries [12–16]. UV filters are frequently used for individual photoprotection but also to prevent degradation of the products and increase their shelf life. Therefore, apart from sunscreens, where they are present in higher concentrations and number, UV filters are also present in moisturizing, anti-wrinkle, and facial creams and other make-up (e.g., lipstick), nail varnish, shampoos and other cleansing products, and hair products [17]. At present, the main chemicals responsible for PhACD or photoaggravated ACD are oxybenzone or benzophenone 3, octocrylene, butylmethoxydibenzoylmethane, and cinnamates [13, 14, 16, 18]. Newer UV filters, like Mexoryl SX® (terephthalylidene dicamphor sulfonic acid), Tinosorb M® (methylene bis-benzotriazolyl tetramethylbutylphenol or bisoctrizole), and Tinosorb S® (bis-ethylhexyloxyphenol methoxyphenyl triazine), seldom cause PhACD. They are mostly photostable molecules used in mixtures of sunscreens that also photostabilize older photo labile UV filters, like the dibenzoylmethanes. This may explain why, although the use of products containing UV filters is certainly growing, there is no parallel increase in PhACD from these chemicals. Some of them can also cause ACD, particularly Tinosorb M®, due to the surfactant decylglucoside that is used to solubilize the active molecule of bisoctrizole [19, 20].

In most recent studies on photopatch testing, NSAIDs are the main cause of positive photopatch tests, with ketoprofen and related drugs (piketoprofen and dexketoprofen) or cross-reactive substances as the main responsible [16]. Ketoprofen used in gel, and more recently also in transdermal patches, often induces severe forms of PhACD (acute eczema, erysipela-like reactions, erythema multiforme) (Fig. 7.4) that occur very soon after initiating treatment and may persist or recur on sun exposure with no apparent further contact with the drug. This may be explained because, after topical exposure, the drug persists in the epidermis for more than 2 weeks [21]. Also, there are cases of ectopic (at sites distant from the original application), connubial, or "by proxy" contact dermatitis due to contact with the skin/hands

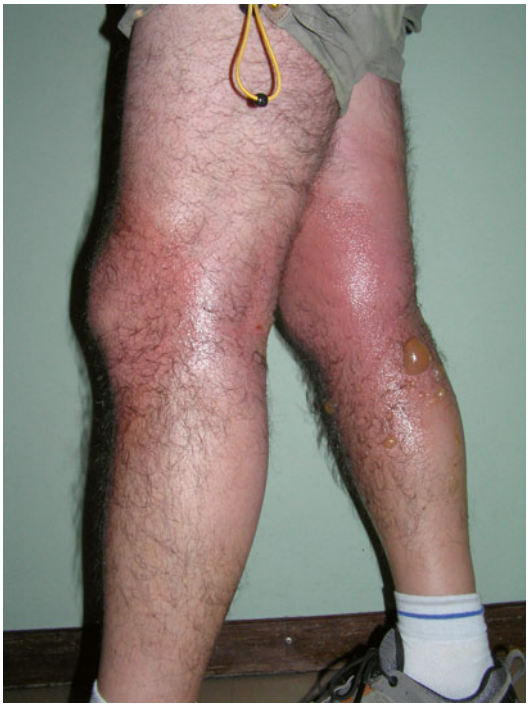


Fig. 7.4 Severe PhACD from a topical NSAID, sparing the thighs under the clothing

contaminated by ketoprofen gel or by contact with contaminated objects, namely, from clothes that retain ketoprofen even after being washed [22–27].

PhACD to ketoprofen is associated with frequent cross-reactive photopatch test reactions to other arylpropionic NSAIDs (tiaprofenic acid and suprofen); benzophenone UV filters, mainly oxybenzone, and the systemic hypolipemic agent, fenofibrate, that induces systemic photosensitivity. Positive photopatch tests to the UV filter octocrylene and patch tests to fragrance mix I and to its constituent cinnamic alcohol are also associated with PhACD to ketoprofen [13, 28–33].

Piroxicam is another NSAID that causes both topical and systemic photoallergy, mostly after previous contact sensitization to thiomersal and its moiety thiosalicylic acid, as photoproducts of piroxicam are chemically similar to these contact allergens [13, 34].

Benzydamine, a topical NSAID used mainly in mouth washes or genital soaps, can cause PhACD, that in the first case presents as cheilitis and chin dermatitis and in the latter involves the dorsum of the hands [3, 35].

Phenothiazine derivatives used in some few European countries as topical antihistamines (promethazine, isothipendyl chlorhydrate) or muscle relaxants (chlorproéthazine) or chlorpromazine whose pills are smashed by caregivers to give disabled patients cause frequent PhACD in countries where they still are available [13, 36–39] (Table 7.2).

Table 7.2 Main exogenous agents causing photoreactions

1. **UV filters**
Benzophenones: oxybenzone, sulizobenzone, mexenone
Dibenzoylmethanes: butyl methoxydibenzoylmethane
Cinnamates: isoamyl-p-methoxycinnamate, ethylhexyl methoxycinnamate, octocrylene, drometrizole trisiloxane
4-methylbenzylidene camphor, phenylbenzimidazole sulfonic acid
2. **Plants** (**main families in Europe**)
Umbelliferae: *Ammi majus*; *Apium graveolens* (celery)
Pastinaca sativa (parsnip); *Petroselinum crispum* (parsley)
Heracleum mantegazzianum (giant hogweed)
Rutacea: Citrus spp., *Citrus aurantica v. bergamia* (bergamot)
Citrus aurantifolia (lime); *Citrus limon* (lemon)
Ruta graveolens (common rue); *Dictamus albus* (burning bush)
Moracea: *Ficus carica* (fig)
3. **Drugs**
a. **Antimicrobials**
Doxycycline, minocycline, sulfamethoxazole
Fluoroquinolones (lomefloxacin[b], ciprofloxacin[b])
Voriconazole, griseofulvin, efavirenz
b. **Nonsteroidal anti-inflammatory drugs** (**NSAIDs**)
Ketoprofen[a], tiaprofenic acid[b], suprofen, carprofen
Piroxicam[c], benzydamine[b], etofenamate[b]
c. **Other drugs**
Chlorpromazine, promethazine[b], chlorproethazine
Amiodarone, furosemide, and thiazide diuretics
Paclitaxel, 5-fluorouracil, dacarbazine, vemurafenib
Fenofibrate, flutamide, sulfonylureas
4. "**Historical**" **photosensitizers**[d]
Perfumes: musk ambrette and bergamot oil
Halogenated salicylanilides
Sunscreens: isopropyl-dibenzoylmethane, PABA
Antibiotics: Olaquindox

Adapted from Gonçalo [2]
[a]Although phototoxic, can induce photoallergic reactions
[b]Induces photoallergic and allergic contact dermatitis
[c]Induces mainly systemic photoallergy
[d]Although "historical" some still induce photoallergic contact dermatitis

7.4 Whom, When, and How to Test Patients

Photopatch testing is indicated to study PhACD and, in selected cases, can be helpful in systemic drug photosensitivity [34, 40), but it is not recommended in typical phototoxic reactions. Therefore, photopatch testing should be performed in all individuals, including children, with dermatitis on photoexposed areas, dermatitis aggravated by UV exposure, sunscreen intolerance, or exposure to NSAID [16, 18]. In patients with chronic photosensitivity (chronic actinic dermatitis, polymorphic

light eruption, cutaneous lupus erythematosus), photopatch testing may be important to exclude a concomitant PhACD, e.g., to a UV filter. In these individuals with a lowered threshold of UV sensitivity, phototesting is usually performed along with photopatch testing, in order to program the adequate UV doses for patch test irradiation [16, 41].

Photopatch testing should be performed, whenever possible, when there are no active lesions or, at least, when the back is clear and when the patient has withdrawn immunosuppressive drugs. If not possible (solid-organ-transplanted patients), interpretation must be cautious, as false-negative results may occur. Photopatch testing should be postponed after sunburn or significant sun exposure on the back, after local use of corticosteroids, and in patients on potential photoactive drugs.

7.5 Photopatch Testing: Technique and Requirements

For performing photopatch testing, apart from material common to contact allergy clinics (allergens and tests chambers), a UV source is necessary. Any broadband UVA source (320–400 nm) with a photometer to quantify UV light delivered to the skin, e.g., a cabin with UVA lamps for PUVA therapy, can be used for UV irradiation.

Recently, ESCD (European Society of Contact Dermatitis and Cutaneous Allergy) and ESP (European Society of Photodermatology) agreed on a recommended European baseline photopatch test series and an extended series including mostly UV filters, NSAIDs, and topical drugs (Table 7.3) to test along with patients' own products (cosmetics, sunscreens, topical drugs). It is recommended whenever possible to perform concomitantly patch testing with the ESCD baseline series of contact allergens and, particularly, with cinnamic alcohol and decyl glucoside that are related, respectively, with PhACD to ketoprofen and ACD to Tinosorb M® [42].

The allergens prepared on the most convenient vehicle are applied in fixed amounts on the chambers as for patch testing (40 mg/cm^2 if in petrolatum) [39, 40]. For photopatch testing, two equal sets of allergens are prepared and applied on symmetrical areas of the back. After a 1 or 2 days occlusion (with no significant variation in test results with these two occlusion times [43]), one set is removed and the skin is irradiated with 5 J/cm^2 of UVA, while the skin under the other set of allergens is shield from light with a UV opaque material [41].

In exceptional cases, UVB irradiation may be necessary to prove photosensitivity, but there is not enough data to recommend regular photopatch testing with this wavelength [44].

When testing a UVA photosensitive patient, e.g., a chronic actinic dermatitis patient, the UVA irradiation dose should be 50–75 % of the MED (minimal erythema dose), preferably calculated on phototests performed concomitantly with photopatch testing [41].

Table 7.3 European photopatch test baseline and extended series, recommended by the ESCD (European Society of Contact Dermatitis and Cutaneous Allergy) and ESP (European Society of Photodermatology)

Series	Type of agent	Name of agent (INCI name for UV absorbers)	Concentration vehicle
Baseline	Classical UV filters	Butyl methoxydibenzoylmethane	10 % pet
		Benzophenone-3	10 % pet
		Benzophenone-4	2 % pet
		Octocrylene	10 % pet
		4-Methylbenzylidene camphor	10 % pet
		Ethylhexyl methoxycinnamate	10 % pet
		Isoamyl-*p*-methoxycinnamate	10 % pet
		PABA	10 % pet
	Newer UV absorbers	Methylene *bis*-benzotriazolyl tetramethylbutylphenol	10 % pet
		Bis-ethylhexyloxyphenol methoxyphenyl triazine	10 % pet
		Drometrizole trisiloxane	10 % pet
		Terephthalylidene dicamphor sulfonic acid	10 % water
		Diethylamino hydroxybenzoyl hexyl benzoate	10 % pet
		Ethylhexyl triazone	10 % pet
		Diethylhexyl butamido triazone	10 % pet
	Topical drugs	Ketoprofen	1 % pet
		Etofenamate	2 % pet
		Piroxicam	1 % pet
		Benzydamine	2 % pet
		Promethazine	0.1 % pet
Extended	UV absorbers	Benzophenone-10	10 % pet
		Phenylbenzimidazole sulfonic acid	10 % pet
		Homosalate	10 % pet
		Ethylhexyl salicylate	10 % pet
		Polysilicone-15	10 % pet
		Disodium phenyl dibenzimidazole tetrasulfonate	10 % pet
	Topical drugs	Dexketoprofen	1 % pet
		Piketoprofen	1%pet
		Ibuprofen	5 % pet
		Diclofenac	5 % pet
	Systemic drugs	Fenofibrate	10 % pet
	Others	Chlorpromazine	0.1 % pet
		Olaquindox	1 % pet
		Triclosan	2 % pet

7.6 Photopatch Testing: Reading and Interpretation of Results

Reactions should be scored according to the guidelines of the International Contact Dermatitis Research Group (ICDRG), as "–" (negative), "+?" (doubtful, only with faint erythema), "+" to "+++" (faint to strongly positive reactions, namely, with erythema, infiltration, and possibly papules for 1+; erythema, infiltration, papules, and vesicles for 2+; and erythema, infiltration, and coalescent vesicles or bulla for 3+), "IR" (irritant), and NT (not tested).

Readings should be performed before and 30–60 min after UV irradiation (D1 or preferably D2) to record reactions present before irradiation (contact allergy) and those that appear immediately thereafter, as in photocontact urticaria. Transient macular erythema that regresses within 24 h, sometimes with residual hyperpigmentation, may occur mostly with phototoxic chemicals, e.g., benoxaprofen, tiaprofenic acid, promethazine, and some UV filters, but this does not represent a positive photopatch test reaction.

For evaluating delayed photoallergic reactions, the most important and obligatory reading should be performed 2 or 3 days after irradiation (D3–D5), the interval necessary for the clinical expression of most T-cell-mediated reactions to the new photoproduct formed during UV irradiation. In this reading, it is important to compare reactions in the irradiated versus the nonirradiated panel of allergens to distinguish a positive patch test reaction or contact allergy (positive reactions in both sets that very often are already present before irradiation) from a positive photopatch test reaction in photoallergy (positive only in the irradiated set) (Fig. 7.5).

A positive patch test in both areas but with a much higher intensity in the irradiated area, usually called a photo-augmented patch test reaction, can occur with contact allergens with some photoactive potential, e.g., etofenamate, ketoprofen, and UV filters [45], and represent the association of allergic and photoallergic contact dermatitis or a photo-augmentation of contact allergy [46].

After patch test reading, evaluation of the relevance of the reactions is mandatory, by going back in detail to the history of recent and past exposure and their possible relation to the site and evolution of the dermatitis. Positive reactions may explain the present dermatitis (current relevance) and can be due to a past exposure, with or without lesions (past relevance or, simply, previous exposure), or be an expression of cross-reactivity [41],

7.7 Advising Patients with Photoreactions

In patients with photoreactions, apart from treating the acute reaction, sun avoidance or use of photoprotective clothing/devices is recommended, as some chemicals can persist in the skin for some days and further UV exposure can aggravate the dermatitis. As UV filters are one of the main causes of photoallergy, a sunscreen

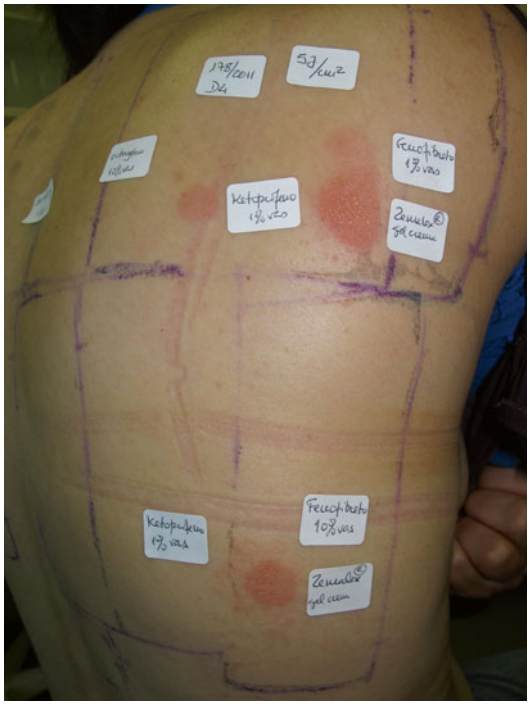


Fig. 7.5 Photopatch test results at D4 (2 days after UVA irradiation with 5 J/cm^2 only in the upper part of the dorsum) with a positive contact allergy to Zemalex cream containing piketoprofen (reactions both in the irradiated and nonirradiated sites) and a positive photopatch test to ketoprofen and fenofibrate (positive only in the irradiated site)

would not be an adequate protective option, unless it is exclusively composed of physical filters (titanium dioxide and zinc oxide), as these have not been reported to induced PhACD or contact dermatitis.

Once a relevant photoallergen is identified during photopatch testing, it has to be further avoided, along with all cross-reactive substances. The list of cross-reactive chemicals is particularly long in patients with PhACD to the benzophenone ring, which includes ketoprofen and some of the other arylpropionic derivatives, UV filters as oxybenzone and octocrylene and oral fenofibrate. Moreover, as patients with reactivity to UV filters often react to more than one chemical [47], particular care should be taken on the choice of future sunscreens, cosmetics, and other products that may contain UV filters [17].

As a preventive measure, it is important to avoid UV exposure or used adequate photoprotection during treatments with known and frequent photosensitizing drugs, as vemurafenib, voriconazole, tetacyclines, amiodarone, or phenothiazines. In some cases, photosensitivity may be so severe as to prevent continuation of a beneficial treatment (vemurafenib) or induce persistent pigmentation of exposed areas with significant cosmetic impairment (minocycline, amiodarone). Moreover, as there is increasing evidence of the relation between photosensitivity and photocarcinogenesis, photoprotection/photo-eviction should be mandatory when exposure to the photosensitizer cannot be avoided.

7.8 Core Message

- Photoreactions due to concomitant skin exposure to an exogenous chromophore and UV light occur due to phototoxicity, photoallergy (T-cell-mediated reaction to a photoproduct), or both.
- Clinical manifestations are polymorphic and occur mainly as exaggerated sunburn with sharp limits that progress to hyperpigmentation (phototoxicity) or eczema on photoexposed areas that may extend beyond.
- Main systemic photosensitizers are drugs, e.g., tetracyclines, fluoroquinolones, voriconazole, NSAID, phenothiazines.
- Main causes of topical photoreactions are plants, UV filters (mainly oxybenzone, octocrylene, butylmethoxydibenzoylmethane), and drugs (ketoprofen, etofenamate).
- Photopatch testing is indicated in all ages in suspected PhACD and dermatitis involving photoexposed areas, namely, to exclude reactivity to a UV filter.
- Use the recommended European baseline photopatch test series, eventually the extended series and patient's own products to diagnose the cause of the photoreations.
- Once identified, the relevant photoallergen and cross-reactive chemicals should be further avoided.
- Careful and adequate photoprotection should follow a diagnosis of a photosensitive reaction.

References

1. Ferguson J. Drug and chemical photosensitivity. 1st ed. New York: Oxford University Press; 1999. p. 155–69.
2. Gonçalo M. Phototoxic and photoallergic reactions. In: Johansen J, Frosch P, Lepoittevin J, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011. p. 361–76.
3. Canelas MM, Cardoso JC, Gonçalo M, Figueiredo A. Photoallergic contact dermatitis from benzydamine presenting mainly as lip dermatitis. Contact Dermatitis. 2010;63(2):85–8.
4. Conti R, Bassi A, Difonzo EM, Moretti S, Francalanci S. A case of photoallergic contact dermatitis caused by unusual exposure to ketoprofen. Dermatitis. 2012;23(6):295–6.
5. Lovell C. Phytophotodermatitis. Boca Raton: CRC Press; 2000. p. 51–65.
6. Dummer R, Rinderknecht J, Goldinger S. Ultraviolet A and photosensitivity during vemurafenib therapy. N Engl J Med. 2012;366(5):480–1.
7. Gelot P, Dutartre H, Khammari A, Boisrobert A, Schmitt C, Deybach J, et al. Vemurafenib: an unusual UVA-induced photosensitivity. Exp Dermatol. 2013;22(4):297–8.
8. McCarthy K, Playforf E, Looke D, Whitby M. Severe photosensitivity causing multifocal squamous cell carcinomas secondary to prolonged voriconazole therapy. Clin Inf Dis. 2007;44:e55–6.
9. Cowen E, Nguyen J, Miller D, Mcshane D, Arron S, Prose N, et al. Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole. J Am Acad Dermatol. 2010;62:31–7.
10. Miller D, Cowen E, Nguyen J, McCalmont T, Fox L. Melanoma associated with long-term voriconazole therapy: a new manifestation of chronic photosensitivity. Arch Dermatol. 2010;146(3):300–4.

11. Rinderknecht JD, Goldinger SM, Rozati S, Kamarashev J, Kerl K, French LE, et al. RASopathic skin eruptions during Vemurafenib therapy. PLoS One. 2013;8(3):e58721.
12. La Cuadra-Oyanguren J, Pérez-Ferriols A, Lecha-Carralero M, Giménez-Arnau A, Fernández-Redondo V, Ortiz de Frutos F, et al. Results and assessment of photopatch testing in Spain: towards a new standard set of photoallergens. Actas Dermosifiliogr. 2007;98:96–101.
13. Cardoso JC, Canelas MM, Gonçalo M, Figueiredo A. Photopatch testing with an extended series of photoallergens: a 5-year study. Contact Dermatitis. 2009;60(6):325–9.
14. Bryden A, Moseley H, Ibbotson S, Chowdhury M, Beck M, Bourke J, et al. Photopatch testing of 1115 patients: results of the U.K. multicentre photopatch study group. Br J Dermatol. 2006;155:737–47.
15. Pigatto P, Guzzi G, Schena D, Guarrera M, Foti C, Francalanci S, et al. Photopatch tests: an Italian multicentre study from 2004 to 2006. Contact Dermatitis. 2008;59(2):103–8.
16. EMCPPTS Taskforce, Kerr A, Ferguson J, Haylett A, Rhodes L, Adamski H, et al. A European multicentre photopatch test study. Br J Dermatol. 2012;166(5):1002–9.
17. Uter W, Gonçalo M, Yazar K, Kratz E-M, Mildau G, Lidén C. Coupled exposure to ingredients of cosmetic products: III. Ultraviolet filters. Contact Dermatitis. 2014;71(3):162–9.
18. Haylett A, Chiang Y, Nie Z, Ling T, Rhodes L. Sunscreen photopatch testing: a series of 157 children. Br J Dermatol. 2014;171(2):370–5.
19. Andersen K, Goossens A. Decyl glucoside contact allergy from a sunscreen product. Contact Dermatitis. 2006;54:349–50.
20. Andrade P, Gonçalo M, Figueiredo A. Allergic contact dermatitis to decyl glucoside in Tinosorb M. Contact Dermatitis. 2010;62(2):119–20.
21. Guy R, Kuma H, Nakanishi M. Serious photocontact dermatitis induced by topical ketoprofen depends on the formulation. Eur J Dermatol. 2014;24(3):365–71.
22. Sugiura M, Hayakawa R, Kato Y, Sugiura K, Ueda H. 4 cases of photocontact dermatitis due to ketoprofen. Contact Dermatitis. 2000;43:16–9.
23. Hindsén M, Isaksson M, Persson L, Zimersson E, Bruze M. Photoallergic contact dermatitis from ketoprofen induced by drug-contaminated personal objects. J Am Acad Dermatol. 2004;50:215–9.
24. Veyrac G, Paulin M, Milpied B, Bourin M, Jolliet P. Bilan de l'enquête nationale sur les effets indésirables cutanés do kétoprofène gel enregistrés entre le 01/09/1996 et le 31/08/2000. Therapie. 2002;57(1):55–64.
25. Devleeschouwer V, Roelandts R, Garmyn M, Goossens A. Allergic and photoallergic contact dermatitis from ketoprofen: results of (photo) patch testing and follow-up of 42 patients. Contact Dermatitis. 2008;58:159–66.
26. Izu K, Hino R, Isoda H, Nakashima D, Kabashima K, Tokura Y. Photocontact dermatitis to ketoprofen presenting with erythema multiforme. Eur J Dermatol. 2008;18:710–3.
27. Béani J. Les photosensibilisations graves. Ann Dermatol Venereol. 2009;136:76–83.
28. LeCoz C, Bottlaender A, Scrivener J-N, Santinelli F, Cribier B, Heidei E, et al. Photocontact dermatitis from ketoprofen and tiaprofenic acid: cross-reactivity study in 12 consecutive patients. Contact Dermatitis. 1998;38:245–52.
29. Pigatto P, Bigardi A, Legori A, Valsecchi R, Picardo M. Cross reactions in patch testing and photopatch testing with ketoprofen, tiaprofenic acid and cinnamic aldehyde. Am J Contact Dermat. 1996;7:220–3.
30. Girardin P, Vigan M, Humbert P, Aubin F. Cross reactions in patch testing with ketoprofem, fragrance mix and cinnamic derivatives. Contact Dermatitis. 2006;55(2):126–8.
31. Avenel-Audrun M, Dulartre H, Goossens A, Jeanmougin M, Comte C, Bernier C, et al. Octocrylene, an emerging photoallergen. Arch Dermatol. 2010;146(7):753–7.
32. Karlsson I, Vanden Broecke K, Martensson J, Goossens A, Borje A. Clinical and experimental studies of octocrylene's allergenic potency. Contact Dermatitis. 2011;64(6):343–52.
33. Infante Hernando L, Serra-Baldrich E, Dordal T, Puig SL. Photoallergic contact dermatitis caused by benzophenones in magazine inks. Contact Dermatitis. 2013;69(2):124–6.
34. Gonçalo M, Figueiredo A, Tavares P, Fontes Ribeiro C, Teixeira F, Poiares BA. Photosensitivity to piroxicam: absence of cross reaction with tenoxicam. Contact Dermatitis. 1992;27:287–90.

35. Lasa Elgezua O, Gorrotxategi P, Gardeazabal Gracia J, Ratón Nieto J, Pérez J. Photoallergic hand eczema due to benzydamine. Eur J Dermatol. 2004;14(1):69–70.
36. Barbaud A, Collet E, Martin S, Granel F, Tréchot P, Lambert D, et al. Contact sensitization to chlorproéthazine can induce persistent light reaction and cross photoreactions to other phenothiazines. Contact Dermatitis. 2001;44:373.
37. Kerr A, Woods J, Ferguson J. Photocontact allergic and phototoxic studies of chlorproethazine. Photodermatol Photoimmunol Photomed. 2008;24:11–5.
38. Bibas N, Sartor V, Bulai Livideanu C, Bagheri H, Nougué J, Giordano-Labadie F, et al. Contact photoallergy to isothipendyl chlorhydrate. Dermatology. 2012;224(4):289–91.
39. Monteagudo-Paz A, Salvador JS, Martinez NL, Granados PA, Martínez PS. Pulpitis as clinical presentation of photoallergic contact dermatitis due to chlorpromazine. Allergy. 2011;66(11):1503–4.
40. Gonçalo M. Explorations dans les photo-allergies médicamenteuses. In: GERDA, editor. Progrès en Dermato-allergologie. Nancy: John Libbey Eurotext; 1998. p. 67–74.
41. Bruynzeel D, Ferguson J, Andersen K, Gonçalo M, English J, Goossens A, et al. Photopatch testing: a consensus methodology for Europe. JEADV. 2004;18:679–82.
42. Gonçalo M, Ferguson J, Bonevalle A, Bruynzeel DP, Giménez-Arnau A, Goossens A, et al. Photopatch testing: recommendations for a European photopatch test baseline series. Contact Dermatitis. 2013;68(4):239–43.
43. Batchelor R, Wilkinson S. Photopatch testing – a retrospective review using the 1 day and 2 day irradiation protocols. Contact Dermatitis. 2006;54:75–8.
44. Avenel-Audrun M. Photopatch testing. Ann Dermatol Venereol. 2009;136:626–9.
45. Goossens A. Photoallergic contact dermatitis. Photodermatol Photoimmunol Photomed. 2004;20:121–5.
46. Beattie P, Traynor N, Woods J, Dawe R, Ferguson J, Ibbotson S. Can a positive photopatch test be elicited by subclinical irritancy or allergy plus suberythemal UV exposure? Contact Dermatitis. 2004;51:235–40.
47. Gonçalo M, Ruas E, Figueiredo A, Gonçalo S. Contact and photocontact sensitivity to sunscreens. Contact Dermatitis. 1995;33(4):278–80.

Protein Contact Dermatitis and Testing

8

Ana Gimenez-Arnau

Contents

8.1 Introduction

Since Maibach [1] and also Hjorth with Roed-Petersen [2] defined in 1976 protein contact dermatitis (PCD) as an immediate eczema induced after contact with proteins, the clinical expression of the hypersensitivity types could be redesigned.

Maibach described a patient with chronic hand eczema, presumably as a manifestation of atopy. But the treatment resistance appeared due to handling foods that produced burning and stinging in the chronically eczematous skin and not otherwise normal skin. The application of pertinent foods over chronically inflamed skin of the arm and back produced a wheal and flare response. On intact skin, scratch tests with foods produced positive results being the intradermal tests with commercial antigens negative. And the most important proof of causality was the consequence

A. Gimenez-Arnau, MD, PhD
Department of Dermatology, Hospital del Mar, Universitat Autònoma de Barcelona, Passeig Maritim 25-29, Barcelona 08003, Spain
e-mail: anamariagimenezarnau@gmail.com

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_8

of avoidance to contact with these foods, the dermatitis being healed. This case it remains within the strictest today for many reasons. PCD continues to be reported as isolated cases or short series of cases. The basis of the diagnosis continues to be the in vivo provocation tests, and finally, the treatment is based in the avoidance of the involved responsible agent.

The study reported by Hjorth with Roed-Petersen included 33 food caterers suffering exacerbation of the itch, immediately after contact with meat, fish, and vegetables followed by erythema and vesicles. Application of the relevant foods to the affected skin resulted in either urticaria or eczema. A new type of immediate contact dermatitis characterized by the clinical findings of eczema was described. This work was important because it was a perfect example of the occupational relevance of most of the cases of PCD.

The association between atopy and PCD is frequent and was demonstrated in approximately 50 % of affected patients [3]. Nevertheless, PCD is not considered one of the diseases defining major criteria of atopy.

PCD and contact urticaria (CoU) are both immediate contact skin reactions induced by environmental triggers and belong to a more general syndrome, the contact urticaria syndrome (CUS). This syndrome comprises a heterogeneous group of immediate contact inflammatory reactions that usually appear within minutes after contact with eliciting substances. Occasionally, systemic involvement can be present. It was defined as an entity in 1975 by Maibach and Johnson [4]. Contact urticaria (CoU) refers to a wheal and flare reaction following external contact with a substance, usually appearing within 30 min and clearing completely within hours, without residual signs [5]. The term was introduced by Fisher (1973), but this phenomenon has long been recognized [6].

This book chapter is focused on how PCD can be recognized and studied. Its inclusion in any contact dermatitis text is crucial as still remains underdiagnosed. PCD break with the traditional immunological pathways. Both trinomial "immediate hypersensitivity (IgE mediated) – protein – wheal" and "delayed hypersensitivity (T lymphocyte mediated)-low molecular weight chemical-eczema" are not applicable to the PCD.

Patients suffering CUS can develop immediately after the contact with the trigger substance, CoU, and/or dermatitis/eczema as PCD. These immediate contact reactions appear on normal or eczematous skin. Wheals are the characteristic symptoms in CoU. Eczema appears rapidly on the hands in PCD. Both cutaneous symptoms and entities can be induced by the same trigger factor and can be suffered by the same patient.

8.2 PCD as Part of the Contact Urticaria Syndrome: How Frequent Is It? Which Is Its Social Relevance?

The global incidence of CUS is not known, but immediate contact reactions are common in dermatological practice [7–12]. There are no available data considering PCD individually. With the exception of latex allergy showing prevalence of

5–10 %, for the rest of trigger factors, just isolated cases or a short series of patients are described [13]. In the occupational setting, CoU and PCD seem to be common although a precise statistical analyses are difficult to obtain in most of the countries because of underreport [14]. In few countries, CoU has been classified as a separate occupational skin disease. This is the case in Finland since 1989. The "Finnish Register of Occupational Diseases" (1990–1994) showed that CoU was the second most frequent cause of occupational dermatosis (29.5 %), after contact allergic dermatitis (70.5 %) [15, 16]. The trigger agents were cow dander (44.4 %), natural rubber latex (23.7 %), and flour, grains, or feed (11.3 %) [16]. Less proportion of occupational CoU was found in a retrospective study done in a tertiary level clinic specializing in occupational dermatology in Melbourne, Australia, showing an 8.3 % CoU prevalence [17]. Hands, arms, and face were the most frequent body area involved. Atopy was a significant risk factor for natural rubber latex, foodstuffs or ammonium persulfate CoU. Health workers, food handlers, and hairdressers were the most common occupations affected. More recently, a survey conducted in 335 restaurant, catering, and fastfood employees in Singapore showed as more common occupational dermatosis irritant contact dermatitis (10 %) being occupational CoU urticaria sporadically reported just in two patients caused by lobster and prawn [18]. If the differential diagnosis in this study included PCD was not reported.

The professional groups with high risk to develop CoU and PCD are food handlers or people involved in agriculture, farming, floriculture, as well as hunters, veterinarians, or biologists. Atopy favors further sensitization in such occupations if protein allergens are concerned [19].

8.3 What Is the Clinical Manifestations of PCD as Part of the Contact Urticaria Syndrome?

Contact dermatitis is an inflammatory skin reaction to direct contact with noxious agents in the environment. Pruritus is the hallmark symptom of contact dermatitis. Spongiosis of the epidermis is the histological hallmark of acute eczematous reactions. Clinically, the confluence of espongiosis leads to vesicles and even bullae. The vesicle is the elemental lesion of eczema. It is preceded by erythema and dermal thickening, and because of scratching, the crusts appear. The vesicular response is associated with acute contact dermatitis. Once contact dermatitis relapses, the skin became acanthotic, and macroscopically, the chronic eczema shows a lichenified skin and characteristic painful fissures. The features of chronic dermatitis are pruritus, lichenification, erythema, scaling, fissures, and excoriation.

The vesicular or bullous reaction may be seen in allergic and irritant contact dermatitis as well as in PCD and cannot be used to distinguish between these types of dermatitis [20]. Protein contact with the skin can induce immunological CoU and PCD. Proteins can be responsible of chronic and recurrent eczema. It may be manifested just as a fingertip dermatitis or extend to hand, wrists, and arms. An urticarial or vesicular exacerbation can be noted in a few minutes after contact of the causal agent, especially on previously affected skin. Some cases of chronic

Table 8.1 Stages of the contact urticaria syndrome

Stage 1	Localized urticaria (redness and swelling) Immediate contact dermatitis (eczema – protein contact dermatitis) Itching, tingling, or burning sensation
Stage 2	Generalized urticaria
Stage 3	Bronchial asthma (wheezing) Rhinitis, conjunctivitis (runny nose, watery eyes) Orolaryngeal symptoms (lip swelling, hoarseness, difficulty swallowing) Gastrointestinal symptoms (nausea, vomiting, diarrhea, cramps)
Stage 4	Anaphylactic or anaphylactoid reaction (shock)

paronychia were considered a variety of PCD, with redness and swelling of the proximal nail fold, e.g., after handling food or natural rubber latex. As for CoU in PCD, extracutaneous symptoms can appear, as rhino-conjuntivitis or asthma and even anaphylaxia. Abdominal pain, diarrhea, and "oral allergy syndrome" may occasionally develop when the allergen comes in contact with the oropharyngeal mucosa [21].

The CUS can be classified in four stages of severity (Table 8.1)

8.4 What Do We Know About the Mechanisms Involved in PCD?

The mechanisms underlying immediate contact skin reactions are partially understood. Each trigger substance has its own mechanism or mechanisms of action. Non-immunologic CoU (NICoU) is due to vasogenic mediators without involvement of immunological processes. The pathogenesis of immunological CoU (ICoU) reflects a type I hypersensitivity reaction, mediated by allergen-specific immunoglobin E (IgE) in a previously sensitized subjects [22]. Skin challenge involves allergen penetration through the epidermis, IgE binding on mast cells, its degranulation, and subsequent release of histamine and other vasoactive substances as prostaglandins, leukotrienes, and kinins.

A combination of type I and type IV allergic skin reactions, the latter supported by positive delayed patch tests, has been suggested as PCD pathogenesis [23, 24]. It has been speculated that PCD is an eczematous IgE-mediated reaction through proteins. PCD shows a similar reaction pattern to aeroallergen-induced atopic eczema or dermatitis [25].

8.5 How to Confirm the Responsible Environmental Agent of PCD

Diagnosis of PCD as of any of the diseases included in the CUS is based on full medical history and skin testing with suspected substances (Fig. 8.1).

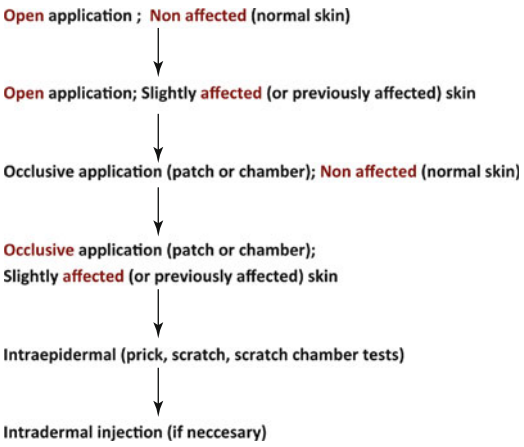


Fig. 8.1 Diagnostic flowchart to test CoU and PCD from the CUS. Proceed to the following suggested provocation test if the test done is negative

In vitro techniques are available for only a few allergens, including latex. The simplest cutaneous provocation test for ICoU, NICoU, and immediate contact dermatitis as PCD is the "open test." The suspected substance studied is applied and gently rubbed on slightly affected skin or on a normal-looking 3 × 3 cm area of the skin, either on the upper back or the extensor side of the upper arm. Often it is desirable to apply contact urticants to skin sites suggested by the patient's history. The suspected substance, commonly foods, is brought by the patient. A positive result is an edema and/or erythema typical of CoU or tiny intraepidermal spongiotic vesicles typical of acute eczema. An immunological and non-immunological contact reaction usually appears within 15–20 min being the non-immunological one lasting within 45–60 min. ICoU can also show a delayed onset, although this is rare.

When the open test results are negative, "prick testing" of suspected allergens using often "prick by prick is the method of choice for immediate contact reactions (Fig. 8.2).

"Scratch test" and "chamber scratch test" (contact with a small aluminum chamber for 15 min) are less standardized than the prick test but are useful when a nonstandard allergen must be studied. For both prick and scratch tests, histamine hydrochloride serves as the positive control and aqueous sodium hydroxide as negative reference. When other than cutaneous organs are involved, it is important to begin ICoU testing with much diluted allergen concentrations and to use serial dilutions to minimize allergen exposure. When testing with poorly or nonstandardized substances, control tests should be assessed on at least 20 people to avoid false-positive interpretation. Nonsteroidal anti-inflammatory drugs and antihistamines should be avoided because of the risk of false-negative results. Following the recommended protocol is important for minimizing the occurrence of hazardous extracutaneous reactions. Life-threatening reactions have been documented during skin tests; therefore, caution is advised, especially when testing certain occupational substances. Skin tests should be performed only if resuscitation equipment and trained personnel are readily available [26–28].

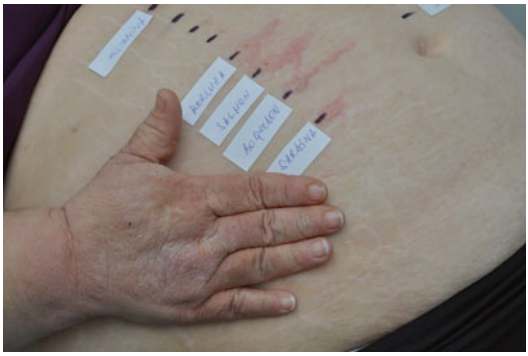


Fig. 8.2 Eczema at the dorsum of hand induced by proteins habitually touched in the daily work of a fisher woman sailor. Positive wheal induced by prick by prick test with hake, salmon, anchovy, and sardine

8.6 Responsible Agents of PCD as Part of the CUS

Proteins (molecular weight 10,000 to several hundred thousands) and also chemicals (molecular weights below 1000) can trigger CUS [29]. Proteins from plants, food, or animals are the main responsible agents of PCD. We know that commonly the same type of protein can be responsible of dermatitis, wheals, or pruritus. Plant or animal proteins, but also chemicals such as drugs and preservatives, or more diverse substances such as metals and industrial chemicals, can induce immunological CoU. Natural rubber latex allergy focused global interest at the end of the twentieth century. Latex sensitization risk factors include atopy and prolonged exposure via damaged epidermis, e.g., glove wearers with hand eczema.

A huge amount of compounds can be responsible of occupational and non-occupational CUS including animal products, plants and plant derivatives, foods, fragrances, cosmetics, flavorings, medications, preservatives, disinfectants, enzymes, metals, and miscellanea of different substances.

8.7 Treatment and Prevention of PCD

CUS clinical symptoms are determined by the route, duration, and extent of exposure, the inherent sensitizing properties of the allergen, and an individual's genetic and/or acquired susceptibility. The best way to treat PCD is based in a correct etiological diagnosis. Identifying the responsible agent is required to avoid correctly the cause. Avoidance of further exposure will improve occupational PCD and CoU. Primary and secondary prevention measures are highly recommended being necessary common guidelines in order to prevent well-known occupational risks as, e.g., latex allergy [30].

Hand and wrist dermatitis is the common location of PCD. For hand dermatitis along with emollients, the local treatment of choice is a topical corticosteroid. These agents are very effective in the short term. The disadvantages of topical corticosteroids include cutaneous adverse effects (skin atrophy), tachyphylaxis, and adrenal suppression after systemic absorption; however, this is rare. Anecdotal experience

suggests that intermittent dosing may reduce the risk of adverse effects. Clinical experience suggests that alternating a topical corticosteroid with a topical calcineurin inhibitor may reduce adverse effects, though randomized clinical trials are missing and the long-term safety of this approach is unknown.

The off-label use of topical calcineurin inhibitors tacrolimus and pimecrolimus licensed for the treatment of atopic dermatitis can be considered. The rationale to use them is based in the suggested pathogenic mechanism of the PCD, similar to the immunological pattern involved in atopic dermatitis. Nevertheless any trial can support this clinical practice. Adverse effects include transient stinging and skin infection; despite concerns about the long-term effects of topical immunomodulators, observational data suggest that these agents are not associated with lymphoma.

Severe cases of PCD in the context of the CUS would need systemic inmunomodulator treatment.

8.8 Challenges and Further Research in PCD

The knowledge of PCD shows some challenges that need further research. Until now, we assume new cases as exceptional findings adding each year new triggers to lists of substances. Still it is an underreported disease. General population-based epidemiological studies are missing. Proteins are responsible of clinical manifestations, urticaria or eczema, consequence of slightly different pathogenic mechanisms. Sometimes the same substance can induce both clinical patterns. This fact opens the door for new insights into immune system response. It would be useful to replace in vivo tests by effective in vitro testing for diagnostic purposes. After symptoms control, an appropriate etiological diagnosis and the development of concrete preventive measures are required. PCD in the context of the CUS is a worldwide health problem.

References

1. Maibach HI. Immediate hypersensitivity in hand dermatitis: role of food contact dermatitis. Arch Dermatol. 1976;112:1289–91.
2. Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. Contact Dermatitis. 1976;2:28–42.
3. Hannuksela M. Atopic contact dermatitis. Contact Dermatitis. 1980;6:30.
4. Maibach HI, Johnson HL. Contact urticaria syndrome: contact urticaria to diethyltoluamide (immediate type hypersensitivity). Arch Dermatol. 1975;111:726–30.
5. Wakelin SH. Contact urticaria. Clin Exp Dermatol. 2001;26:132–6.
6. Fisher AA. Contact dermatitis. 2nd ed. Philadelphia: Lea & Febiger; 1973. p. 283–6.
7. Elpern DJ. The syndrome of immediate reactivities (contact urticaria syndrome). An historical study from a dermatology practice. I. Age, sex, race and putative substances. Hawaii Med J. 1985;44:426–39.
8. Rudzki E, Rebanel P. Occupational contact urticaria from penicillin. Contact Dermatitis. 1985;13:192.

9. Nilsson E. Contact sensitivity and urticaria in “wet” work. Contact Dermatitis. 1985;13: 321–8.
10. Veien NK, Hattel T, Justesen O, Norholm A. Dietary restrictions in the treatment of adult patients with eczema. Contact Dermatitis. 1987;17:223–8.
11. Turjanmaa K. Incidence of immediate allergy to latex gloves in hospital personnel. Contact Dermatitis. 1987;17:270–5.
12. Weissenbach T, Wutrich B, Weihe WH. Allergies to laboratory animals. An epidemiological, allergological study in persons exposed to laboratory animals. Schweiz Med Wochenschr. 1988;118:930–8.
13. Doutre M–S. Occupational contact urticaria and protein contact dermatitis. Eur J Dermatol. 2005;15:419–24.
14. Kanerva L, Jolanki R, Toikkanen J. Frequencies of occupational allergic diseases and gender differences in Finland. Int Arch Occup Environ Health. 1994;66:111–6.
15. Kanerva L, Toikkanen J, Jolanki R, Estlander T. Statistical data on occupational contact urticaria. Contact Dermatitis. 1996;35:229–33.
16. Kanerva L, Jolanki R, Toikkanen J, Estlander T. Statistics on occupational contact urticaria. In: Amin S, Lahti A, Maibach HI, editors. Contact urticaria syndrome. Boca Raton: CRC Press; 1997. p. 57–69.
17. Williams JD, Lee AY, Matheson MC, Frowen KE, Noonan AM, Nixon RL. Occupational contact urticaria: Australian data. Br J Dermatol. 2008;159:125–31.
18. Teo S, Teik-Jin Goon A, Siang LH, Lin GS, Koh D. Occupational dermatoses in restaurant, catering and fast-food outlets in Singapore. Occup Med (Lond). 2009;59:466–71.
19. Bourrain JL. Occupational contact urticaria. Clin Rev Allergy Immunol. 2006;30:39–46.
20. Veien NK. Chapter 15. Clinical features. In: Johanssen JD, Frosch PJ, Lepoittevin J-P, editors. Contact dermatitis. 5th ed. Heidelberg: Springer; 2011. p. 255–303.
21. Goossens A, Amaro C. Chapter 21. Protein contact dermatitis. In: Johanssen JD, Frosch PJ, Lepoittevin J-P, editors. Contact dermatitis. 5th ed. Heidelberg: Springer; 2011. p. 407–13.
22. Amaro C, Goossens A. Immunological occupational contact urticaria and contact dermatitis from proteins: a review. Contact Dermatitis. 2008;58:67–75.
23. Kanerva L, Estlander T. Immediate and delayed skin allergy from cow dander. Am J Contact Dermat. 1997;8:167–9.
24. Conde-Salazar L, Gonzalez MA, Guimaraens D. Type I and Type IV sensitization to Anisakis simplex in 2 patients with hand eczema. Contact Dermatitis. 2002;46:361.
25. Saloga J, Knop J. Does sensitization through skin occur? Allergy review series V: the skin as target for IgE-mediated allergic reactions. Allergy. 2000;55:905–9.
26. Gimenez-Arnau A, Maurer M, de la Cuadra J, Maibach H. Immediate contact skin reactions, an update of contact urticaria, contact urticaria syndrome and protein contact dermatitis – “A Never Ending Story”. Eur J Dermatol. 2010;20:1–11.
27. Haustein UF. Anaphylactic shock and contact urticaria after patch test with professional allergens. Allerg Immunol. 1976;22:349–52.
28. Maucher OM. Anaphylaktische Reaktionen beim Epicutantest. Hautarzt. 1972;23:139–40.
29. Tupasela O, Kanerva L. Chapter 4. Skin tests and specific IgE determinations in the diagnostics of Contact urticaria caused by low-molecular-weight chemicals. In: Amin S, Lahti A, Maibach HI, editors. Contact urticaria syndrome. Boca Raton: CRC Press; 1997. p. 33–44.
30. Nicholson PJ. Evidence-based guidelines: occupational contact dermatitis and urticaria. Occup Med. 2010;60:502–6.

Occupational Contact Dermatitis

9

Anja Thielitz and Swen Malte John

Contents

9.1 Introduction

Occupational skin diseases with an incidence of ~7 per 100,000 constitute up to 30–40 % of all notified occupational diseases in Western industrial countries and account for extensive macroeconomic expenses comprising approximately 1.5 billion € p.a. in Germany, >5 billion € in the EU, and >11 billion $ in the USA.

A. Thielitz, MD
Department of Dermatology, Institute for Interdisciplinary Dermatological Prevention and Rehabilitation (iDerm) of the University of Osnabrück, and Dermatologic Centre, Trauma Hospital, Bergedorfer Str. 10, 21033 Hamburg, Germany

S.M. John, MD, PhD (✉)
Department of Dermatology, Environmental Medicine and Health Theory, Lower Saxonian Institute of Occupational Dermatology (NIB), University of Osnabrueck, Sedanstraße 115, 49069 Osnabrück, Germany
e-mail: johnderm@uos.de

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_9

It is supposed that the real incidence of occupational contact dermatitis is being grossly underestimated because national registries and reporting systems are usually incomplete as a result of underdiagnosis and underreporting of especially the mild cases.

Wet work and atopic predisposition are the most important determinants of risk in classical high-risk professions like hairdressers followed by other occupations in the nutritional sector (cooks/bakers), health-care professionals, metal workers, construction workers, cleaners, painters, and varnishers and occupations handling plants. Most occupational skin diseases (90–95 %) present as eczema or contact dermatitis affecting primarily the hands [4].

Measures of primary, secondary, and tertiary prevention successfully implemented in some countries have been shown to avoid the cessation of occupation in the majority of cases.

9.2 Definition of Occupational Contact Dermatitis

Occupational contact dermatitis results from a complex interaction of exogenous factors (irritant or allergic) and predisposing endogenous factors like atopy or "sensitive skin." While acute irritant dermatitis or chemical burns with severe tissue damage often induced by alkaline or acid materials are mostly seen in occupational injuries, the chronic irritant dermatitis, also denominated "cumulative insult dermatitis" or "traumiterative dermatitis" [7], represents at least a contributory factor in 65–80 % of occupational skin diseases [3, 19]. This diagnosis applies to a persisting (>6 weeks) eczematous condition where an allergic etiology has been ruled out by careful diagnostic procedures ("exclusion diagnosis"). It develops as a consequence of repetitive contact to irritants like water, detergents, organic solvents, or irritant foods which damage the skin barrier slowly in a cumulative way supposing that the time period between different irritant influences is probably too short to allow complete barrier regeneration. Other factors causing or contributing to chronic irritant dermatitis are mechanical pressure, friction, and climatic influences like temperature or humidity.

Occupational skin diseases often have a complex etiology and can also develop from a predisposing chronic relapsing atopic eczema primarily unrelated to the workplace situation (two-phase or "hybrid" eczema) or even in a three-phase process where allergic sensitizations arise in a second (or third) step favored by a chronic irritant dermatitis with persisting skin inflammation and reduced barrier function.

Occupational skin diseases can also be caused by type I hypersensitivity, e.g., latex contact urticaria [1], which is often accompanied by mucosal symptoms and can rarely induce severe anaphylactic symptoms in highly sensitized individuals.

A special form of often occupation-related allergic contact dermatitis represents the so-called protein contact dermatitis, where type I sensitizations can be found that are supposed to induce an eczematous reaction [2]. It is a rare form of contact dermatitis where symptoms are induced by proteins (e.g., plant proteins, fish,

meat, seafood, flour, or enzymes) instead of low molecular haptens. The highest prevalence of 1–4 % can be seen in food-related professions (cooks, bakers, fish processors). The diagnosis is currently based on the combination of a type I sensitization against one of the relevant proteins and a history of relapsing eczema after (re-)exposition. This is described in more detail in Chap. 8.

9.3 Main Clinical Features

The most frequent type of occupational contact dermatitis is the chronic irritant dermatitis, often representing the primary form of an (epi-)dermal intolerance reaction. The prime localization is on the hands and initiates often from the webs (Fig. 9.1) but later spreads to the fingers and backs of the hands (and sometimes the forearms) where it typically appears with redness and infiltration, scaling, and fissuring (Fig. 9.2). The palms and especially the fingertips can also be affected (often presenting with hyperkeratosis), which is often seen in occupations with mechanical pressure or friction. Occasionally, a nummular subtype of eczema on the backs of the hands can be seen, sometimes indicating a microbial (co-)etiology. The volar wrist is, in contrast to allergic or atopic eczema, usually unaffected in irritant contact dermatitis. Vesicles are also not a typical hallmark of chronic irritant dermatitis and can be rather found in allergic or atopic types; however, due to frequent overlaps or "hybrid" types of eczema, the diagnosis cannot be made based only upon clinical morphology.

An acute irritant contact dermatitis has a variable clinical appearance often indistinguishable from an allergic eczema, while acute toxic reactions (chemical burns) resulting mostly from strong acids or alkalis usually present with a sharp demarcation and clinical signs of severe tissue damage, beginning with (sometimes bullous) edema and painful whitening and resulting in deep necrosis and scarring [7].

An acute allergic eczema usually presents 24–48 h after allergen contact with symptoms like redness, edema, vesiculation, and itching in the acute phase, while a chronic allergic contact eczema often resembles a chronic irritant dermatitis with scaling and fissuring. A spreading beyond the borders of the allergen contact can be

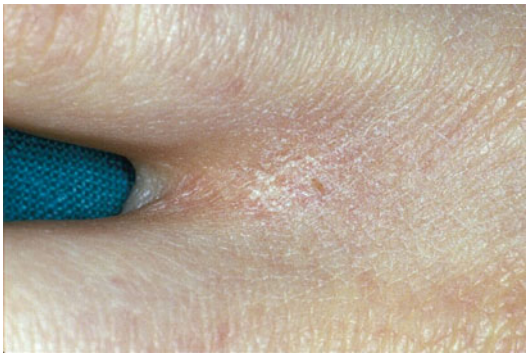


Fig. 9.1 Insidious onset of irritant contact dermatitis in a 17-year-old hairdressing apprentice

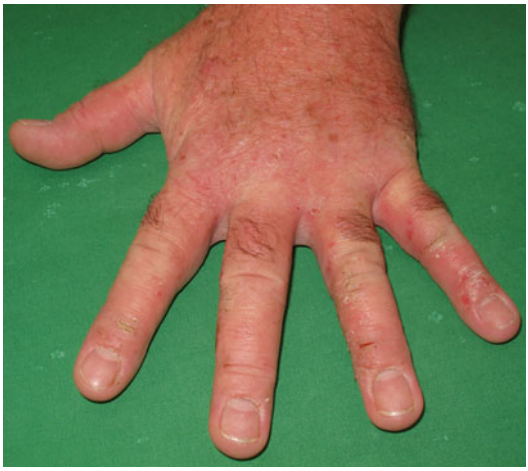


Fig 9.2 Progressing irritant contact dermatitis in a 32-year-old construction worker, showing redness, infiltration, scaling, and fissuring

frequently seen and may also affect other exposed body regions like the face and the forearms especially in airborne contact dermatitis. Frequent occupational allergens causing airborne contact dermatitis are epoxy resins, preserving agents like chloromethylisothiazolinone, or plant components like sesquiterpenlactones deriving from the plant family of Compositae, which may also cause an irritant dermatitis.

Atopic hand eczema is often characterized by vesicles in the palms or lateral fingers but may also affect the back of the hands, sometimes also presenting as nummular type. The volar wrist is often affected including the "tabatière." Atopic individuals are also predisposed to develop hyperkeratotic fingertip eczema ("pulpitis sicca"). Atopic hand eczema flares are often not strictly work related but have their own dynamics.

In addition, a psoriasis vulgaris may sometimes be triggered by occupational factors like friction, heat, mechanical pressure, or occlusion (Koebner phenomenon). In this case, the psoriatic lesions are induced or aggravated in the skin regions affected by occupational irritant and mechanical or allergic influences and usually improve when the occupational "traumiterative factor" is reduced, e.g., by protection measures. The course of the disease should be at least in part work related (i.e., improvement during longer work-free periods) to make the diagnosis of an "occupationally induced psoriasis" [16]. Other differential diagnoses may include pustulosis palmoplantaris, mycosis, palmoplantar keratosis, lichen ruber or herpes simplex, and with regard to airborne contact dermatitis photoallergic/phototoxic reactions and seborrheic dermatitis.

9.4 Main Causes

Irritant factors play a causative role in up to 80 % of occupational skin diseases, primarily determined by "wet work," including frequent contact of the skin with water, soap, detergents, or occlusive gloves. The German guidance TRGS 401

recommends that the duration of wet work (including use of occlusive gloves) should not exceed 2 h per work shift, and also, the frequency of handwashing or hand disinfection should be taken into account (especially when exceeding 20 times per work shift). Usually, several chemical irritants are involved and may cumulate together with mechanical, thermal, or climatic factors to low-grade damage within weeks or months. As a consequence, pH homeostasis is impaired allowing irritant factors like water or detergents to penetrate in the stratum corneum where they induce edema, decreased adhesion of corneocytes, and repetitive washing out of epidermal lipids, the latter constituting the "mortar" of the skin barrier. In addition, dust or dry dirt can induce or contribute to irritant contact dermatitis.

An atopic skin diathesis was significantly associated with hand eczema, and wet work ≥2 h/work shift was positively related to the presence of irritant hand eczema in a long-term follow-up study in the car industry [3]. In several studies, previous or current atopic dermatitis has been determined as significant risk factor for the development of occupational hand eczema in "wet work professions," while in most of these studies, hay fever and/or bronchial asthma without atopic skin disease did not show a markedly increased risk of developing hand eczema [7]. Individuals with atopic dermatitis have often persisting dry skin for the rest of their life showing histological signs of subclinical eczema. Also, subjects without atopy may have dry or sensitive, hyperirritable skin due to a genetic predisposition for an impaired stratum corneum function, e.g., due to altered filaggrin [15] or cytokine expression. In some subjects, secondary (acquired) hyperirritability may persist for months or even years after the eczema has healed [14].

An allergic contact dermatitis often develops in a second step as a consequence of impaired barrier function induced primarily by chronic irritant dermatitis potentially allowing the repetitive penetration of substances acting as haptens (<500 kDa) in the dermis. In addition, persisting inflammation may facilitate the development of an allergic sensitization requiring both signals of innate and acquired immunity (see also the chapter about allergic contact dermatitis). Allergens may also directly stimulate factors of innate immunity which has been shown for nickel activating the expression of toll-like receptor 4 [18].

In contrast to a principally reversible chronic irritant dermatitis, an allergic sensitization persists throughout the whole life. Therefore, after patch testing, it is absolutely essential to assess the identified allergens for their true clinical and occupational relevance and take care of adequate prevention and avoidance strategies whenever possible. Also, cases should be notified as early as possible; there is no innocent irritant skin lesion in wet work occupations.

9.5 Risk Occupations

Table 9.1 summarizes a selection of professions where occupational skin diseases are frequent, including irritant and allergic factors typically present in the specific workplace.

Table 9.1 Selection of professions where occupational skin diseases are frequent, including main specific irritant and allergic workplace exposures

Occupation	Irritants	Allergic sensitizers (type IV/type I)
Health occupations	Wet work (direct or occlusion), disinfectants, soaps and detergents, pestled pills	Type IV: glove ingredients, drugs (e.g., tetrazepam), disinfectants with aldehydes or quaternary ammonium compounds, fragrances in masseurs and geriatric nurses
		Type I: latex, formaldehyde
Hairdressers	Wet work (direct or glove occlusion), dyes, shampoos, permanent wave liquids, bleaching agents	Type IV: oxidative dyes (para-aminoaryl derivatives), ammonium persulfate, preservatives, fragrances, perming substances (thioglycolate), glove ingredients
		Type I: latex, ammonium persulfate, p-phenylenediamine (rare)
Florists, gardeners, plant growers	Irritant plants, fertilizers, pesticides, manure	Type IV: rubber materials, plant proteins (e.g., Compositae: main allergen sesquiterpenlactones)
		Type I: e.g., pollen proteins
Plastic industry workers	Solvents, acids, ingredients in epoxy resins, oxidizing agents, acrylic monomers	Type IV: epoxy resins and hardeners, phthalates, acrylates, diisocyanates, formaldehyde
		Type I: diisocyanates, formaldehyde
Painters and varnishers	Solvents, emulsion paints, paint removers, organic tin components, hand cleansers, glues, epoxy resins, glove occlusion	Type IV: epoxy resins, preservatives (isothiazolinones), thiurams, colophony, turpentine and substitutes, color pigments (chromate and cobalt)
Construction industry (masons, floor layers, tilers)	Emulsion paints, wet work (direct or glove occlusion), wood preservatives, glue, cement, acids	Type IV: epoxy resins and hardeners, acrylates, diisocyanates, thiurams, chromate and cobalt
		Type I: diisocyanates (asthma)
Metal workers, mechanics, galvanizers	Cooling system fluids, lubricants, detergents, solvents, cleaning solutions, degreasers, antifreeze, battery acid, wet work (direct or occlusion)	Type IV: ingredients of cooling system fluids (formaldehyde releasers or isothiazolinones), anticorrosives (e.g., monoethanolamine), fragrances (as additives), rubber materials, metals
Food professions (bakers and pastry makers, cooks, catering industry, butchers)	Wet work (direct or glove occlusion), soaps, detergents, vegetable and fruit juices, spices, fish, meat, dressing, vinegar, enzymes, acetic, ascorbic, and lactic acid	Type IV: flavors, fragrances, spices, preservatives (e.g., benzoates), food colorants
		Type I: natural latex, proteins from fish, crustaceans, meat, flour, enzymes (also as protein contact dermatitis)
Dentists and dental technicians	Wet work, soaps and detergents, soldering fluxes, adhesives, acrylic monomers, solvents	Type IV: dental metals, acrylic monomers, eugenol
		Type I: latex

9.6 How to Make the Diagnosis

The relationship between clinical type of hand eczema and etiological diagnosis fits with general clinical experience (see main clinical features), but no simple relationship was found to make a clear diagnosis based on morphology and/or distribution alone. Irritant contact dermatitis often appears as chronic, dry fissured hand eczema (44.3 %), pulpitis (41.7 %), and nummular hand eczema (40.9 %) [13]. Furthermore, the lack of itching and slow aggravation after resuming work may be clues indicating chronic irritant dermatitis.

In allergic contact dermatitis, vesicular types with recurrent (35 %) and few (24.2 %) eruptions dominate which, however, are also typical for atopic hand eczema. A careful history of time-dependent development of lesions, patch testing, and exposure analysis is always mandatory to confirm allergic contact dermatitis. The localization may give a clue to an allergic sensitization (e.g., jeans' button dermatitis and nickel sensitization or dermatitis demarcated along the "glove borders" in thiuram sensitization, Fig. 9.3).

Patch tests should be performed as recommended in national [20] or international guidelines [25] and should ideally include the test series recommended for

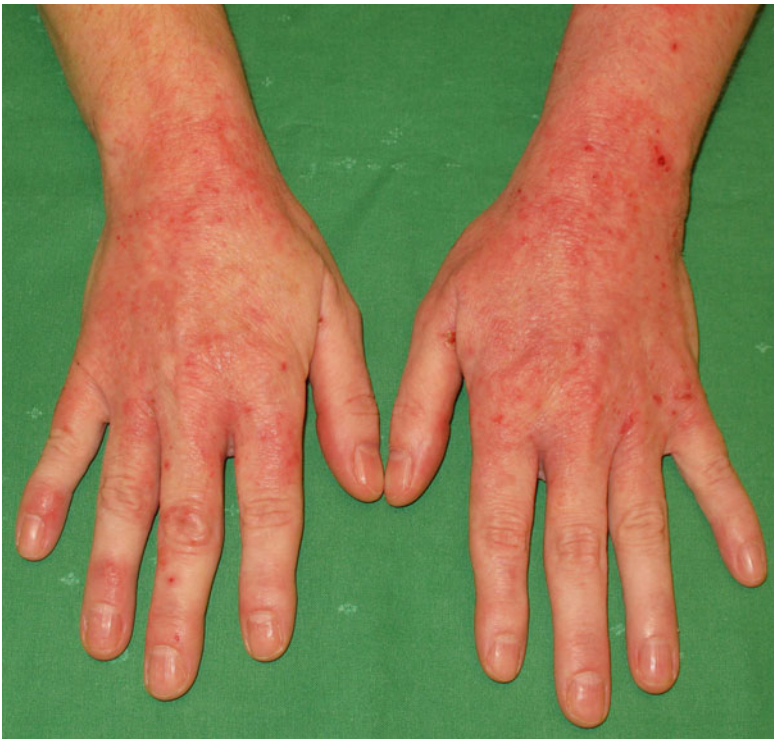


Fig. 9.3 The hands of a floor tiler with allergic contact dermatitis to thiurams in protective gloves in addition to a chronic irritant dermatitis

special occupations and, if necessary, also patients' own products. Substances or mixtures of unknown composition should not be tested because they might contain toxic or corrosive ingredients. Aggressive sanitary cleaners, solvents or toluene, highly alkaline or acidic substances, cement, rust dissolvers, detergents for dishwashers or washing machines, antifreeze materials, or car and floor polish should not be tested. The material safety data sheet should always be obtained when possible because it provides standard information about chemical or physical properties, stability, and personal protection measures. Testing with patients' own products should be performed according to the relevant recommendations for dilution procedures and choice of the appropriate vehicle [8, 10, 25].

A positive patch test reaction always involves assessing the clinical relevance, as a reaction may be also false-positive due to irritant effects. This applies especially in patch tests with patients' own material due to lack of standardized patch test procedures for most materials setting a reliable threshold for irritative vs. true allergic reactions.

For the diagnosis of atopic dermatitis, several minor and major features (history of flexural eczema, rhinoconjunctivitis, allergic asthma, positive atopic family history, and itch when sweating) have been proposed by Hanifin and Rajka [12], and scoring systems may be sometimes helpful to assess atopic predisposition [21]. In addition, standardized differential irritability tests (i.e., performed on the forearm and back of the hands) can identify an impaired barrier function and increased skin sensitivity in atopic or nonatopic individuals [14] and sometimes differentiate between constitutional or acquired skin hyperirritability.

With regard to atopy, hand eczema may be classified as either chronic irritant contact dermatitis with atopic skin disposition or irritant-provoked atopic hand eczema (can also be regarded as hybrid eczema of two etiologies) or atopic hand eczema unrelated to occupational exposures, where the latter has the significance of arbitrary trigger factors like climate, food allergens, or stress.

9.7 Prognosis and Prevention

Past or present atopic dermatitis has been identified as a risk factor for especially the development of irritant contact dermatitis but not contact allergy. It has been estimated that the relative risk of hand eczema in atopy is disproportionally increased by exposure to irritants (from 1.5 in subjects with no atopy to 4 in mild atopic dermatitis and 12 in severe atopic dermatitis) [5].

In a recent study investigating the clinical course of occupational irritant contact dermatitis of the hands in relation to filaggrin (FLG) genotype status and atopy, the carriage of FLG loss-of-function mutations in combination with atopy worsened the course and increased the risk of job loss significantly (odds ratio 3.1) after 3 years when compared with "pure" irritant contact dermatitis [15]. Furthermore, atopic individuals were more resistant to therapy, resulting in lower rates of recovery and job continuation and higher use of topical corticosteroids.

The most important preventive measure is to identify and avoid irritant or allergic trigger factors by the implementation of both workplace-related and worker-related risk reduction strategies. Workplace-related risk reduction focuses on elimination or substitution of harmful exposures or technical measures improving safety at work or exchange of identified allergens as part of individual secondary prevention. Worker-related prevention includes identification of susceptible individuals and continuous health surveillance, educational training programs, and optimizing personal skin protection including gloves, protective creams, and after-work creams (see Chap. 23 on workers' protection).

The selection of suitable gloves should consider the appropriateness for intended use (toxicological and chemical data of contact substances), ergonomic requirements, correct size, and individual sensitizations and usually requires the support of health educationalists or other specialists qualified for this task. Protective gloves selected or worn incorrectly may increase wearers' overall risk due to increased exposure to contaminants or occlusion effects. Protective creams are recommended in conjunction with technical measures and do not replace other personal protection measures. Health education programs ("eczema schools") aim at creating "health literacy" by increasing knowledge about main causes of occupational eczema and implementing changes of routine behavior in the workplace (i.e., correct removal of gloves without contamination, reducing handwashing frequency, correct use of protective or after-work creams, etc.).

Examples for successful primary prevention by substitution of allergens on the workplace are the decrease of chromate sensitization from 43.1 % to 29 % via reduction of hexavalent chromate in cement in construction industry [11], the prevention of new sensitizations to glyceryl monothioglycolate (used in acidic perms) via ban of the substance [22], and the regression of occupationally induced latex sensitizations by reduction of allergen content and compulsory use of powder-free gloves [1].

The target groups of secondary prevention are individuals with initial signs of occupational skin disease focusing on prevention of progress or chronification, while the intensified comprehensive measures of tertiary prevention with 3 weeks inpatient hospitalization are indicated in severe recalcitrant cases threatened by cessation of occupation. A study evaluating the long-term effects of such inpatient tertiary prevention [23] showed that after 1-year follow-up, 87.4 % of patients were able to return to work and remain in the workforce.

The therapy of occupational hand eczema is mainly based on the published guidelines on therapy of hand eczema [6, 17] with the particularity that the use of topical steroids should be avoided or restrained to short-term use in flare-ups to avoid their side effects like skin atrophy and impaired barrier function. Mild forms of hand eczema may be sufficiently controlled by the use of emollients or moisturizers, while in moderate or severe forms, calcineurin inhibitors, UV treatment, and supportive antihidrotic measures like iontophoresis as well as antipruritic and antiseptic external therapy are combined.

9.8 Relevant Legislation of International Character

Recent information on occupational diseases in Europe (incidence, safety, legal aspects) can be obtained from two internet sources: http://www.eurogip.fr/index.php?chlang=en (EUROGIP Enquiry Report 34/E as of Jan 2009: Occupational diseases in Europe. 1990–2006 statistical data and legal news) and from the http://osha.europa.eu/en/publications/reports/TE7007049ENC_skin_diseases (European Agency for Safety and Health at Work – European Risk Observatory report 2008: Occupational skin diseases and dermal exposure in the EU (EU-25). Policy and practice overview) [9, 24].

9.9 Checklist of What to Think About/Action Points

- Every patient presenting with hand eczema should be carefully assessed for occupational trigger factors and endogenous predisposing factors (e.g., atopy, hypersensitive skin).
- The history should comprise the evaluation of the presence and duration of wet work (direct or by glove occlusion), contact to irritant substances or mechanical and climatic influences, and the course of disease in relation to exposure in the workplace.
- Patch testing (if needed, including patients' own products), exposure analysis, and assessment of clinical or occupational relevance are always mandatory to confirm allergic contact dermatitis.
- Notification of cases of occupational skin diseases should be performed according to the national reporting and legislation systems to assure early access to measures of secondary and tertiary prevention and avoid job cessation whenever possible.

References

1. Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. J Allergy Clin Immunol. 2004;114(2):347–51.
2. Amaro C, Goossens A. Immunological occupational contact urticaria and contact dermatitis from proteins: a review. Contact Dermatitis. 2008;58(2):67–75. doi:10.1111/j.1600-0536.2007.01267.x.
3. Apfelbacher CJ, Funke U, Radulescu M, Diepgen TL. Determinants of current hand eczema: results from case-control studies nested in the PACO follow-up study (PACO II). Contact Dermatitis. 2010;62(6):363–70. doi:10.1111/j.1600-0536.2010.01729.x.
4. Diepgen TL. Occupational skin-disease data in Europe. Int Arch Occup Environ Health. 2003;76(5):331–8.
5. Diepgen TL, Coenraads PJ. Occupational contact dermatitis. In: Rustemeyer T, Elsner P, John SM, Maibach HI, editors. Kanerva's occupational dermatology. 2nd ed. Heidelberg: Springer; 2012. p. 51–8.

6. Diepgen TL, Elsner P, Schliemann S, Fartasch M, Köllner A, Skudlik C, John SM, Worm M, Deutsche Dermatologische Gesellschaft. Guideline on the management of hand eczema ICD-10 Code: L20. L23. L24. L25. L30. J Dtsch Dermatol Ges. 2009;7 Suppl 3:S1–16. doi:10.1111/j.1610-0387.2009.07061.x. English, German.
7. Frosch PJ, John SM. Clinical aspects of irritant contact dermatitis. In: Duus Johansen J, Frosch PJ, Lepoittevin JP, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011. p. 305–45.
8. Frosch PJ, Geier J, Uter W, Goossens A. Patch testing with the patients' own products. In: Duus Johansen J, Frosch PJ, Lepoittevin JP, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011. p. 1108–19.
9. Frosch PJ, Aberer W, Agner T, August PJ, Conde-Salazar L, Constandt L, et al. Legal aspects of workers' compensation for occupational contact dermatitis. In: Duus Johansen J, Frosch PJ, Lepoittevin JP, editors. Contact dermatitis. 5th ed. Heidelberg: Springer Berlin; 2011. p. 1029–51.
10. Geier J, Krautheim A, Lessmann H. Allergological diagnostics and current allergens in occupational dermatology. Hautarzt. 2009;60(9):708–17. doi:10.1007/s00105-008-1705-x. Review. German.
11. Geier J, Krautheim A, Uter W, Lessmann H, Schnuch A. Occupational contact allergy in the building trade in Germany: influence of preventive measures and changing exposure. Int Arch Occup Environ Health. 2011;84(4):403–11. doi:10.1007/s00420-010-0581-8.
12. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stock). 1980;(Suppl 92):44–47.
13. Johansen JD, Hald M, Andersen BL, Laurberg G, Danielsen A, Avnstorp C, Kristensen B, Kristensen O, Kaaber K, Thormann J, Menné T, Veien N, Danish Contact Dermatitis Group. Classification of hand eczema: clinical and aetiological types. Based on the guideline of the Danish Contact Dermatitis Group. Contact Dermatitis. 2011;65(1):13–21. doi:10.1111/j.1600-0536.2011.01911.x.
14. John SM. Primary and acquired sensitive skin. In: Berardesca E, Fluhr J, Maibach HI, editors. The sensitive skin syndrome. New York: Taylor & Francis; 2006. p. 129–47.
15. Landeck L, Visser M, Skudlik C, Brans R, Kezic S, John SM. Clinical course of occupational irritant contact dermatitis of the hands in relation to filaggrin genotype status and atopy. Br J Dermatol. 2012;167(6):1302–9. doi:10.1111/bjd.12035.
16. Mahler V, Diepgen T, Skudlik C, Becker D, Dickel H, Fartasch M, Geier J, Häberle M, Hillen U, Krohn S, John SM, Weisshaar E, Werfel T, Zagrodnik F, Work Group "Assessment of allergens in occupational disease (BK) 5101" of the Study Group Occupational and Environmental Dermatology (ABD), German Contact Dermatitis Group (DKG) of the German Dermatological Society. Psoriasis predisposition and occupational triggering factors in the appraisal of occupational medical expertises. J Dtsch Dermatol Ges. 2014;12(6):519–29. doi:10.1111/ddg.12262.
17. Menné T, Johansen JD, Sommerlund M, Veien NK, Danish Contact Dermatitis Group. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. Contact Dermatitis. 2011;65(1):3–12. doi:10.1111/j.1600-0536.2011.01915.x.
18. Schmidt M, Raghavan B, Müller V, Vogl T, Fejer G, Tchaptchet S, et al. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. Nat Immunol. 2010;11(9):814–9.
19. Skudlik C, Weisshaar E, Scheidt R, Elsner P, Wulfhorst B, Schönfeld M, ROQ Study Group, et al. First results from the multicentre study rehabilitation of occupational skin diseases–optimization and quality assurance of inpatient management (ROQ). Contact Dermatitis. 2012;66(3):140–7.
20. Schnuch A, Aberer W, Agathos M, Becker D, Brasch J, Elsner P, German Contact Dermatitis Group (DKG) of the German Dermatological Society – Guidelines of the German Dermatologic Society and German Society of Allergy and Clinical Immunology, et al. Performing patch testing with contact allergens. J Dtsch Dermatol Ges. 2008;6(9):770–5.

21. Uter W, Schwanitz HJ, Pfahlberg A, Gefeller O. Atopic signs and symptoms: assessing the 'atopy score' concept. Dermatology. 2001;202(1):4–8.
22. Uter W, Geier J, Lessmann H, Schnuch A. Is contact allergy to glyceryl monothioglycolate still a problem in Germany? Contact Dermatitis. 2006;55(1):54–6.
23. Weisshaar E, Skudlik C, Scheidt R, Matterne U, Wulfhorst B, Schönfeld M, Elsner P, Diepgen TL, John SM, ROQ Study Group. Multicentre study 'rehabilitation of occupational skin diseases -optimization and quality assurance of inpatient management (ROQ)'-results from 12-month follow-up. Contact Dermatitis. 2013;68(3):169–74.
24. European Agency for Safety and Health at Work. European Risk Observatory Report. Occupational skin diseases and dermal exposure in the European Union (EU-25): policy and practice overview. Available from: http://osha.europa.eu/en/publications/reports/TE7007049ENC_skin_diseases. Last Accessed 5 Jan 2015.
25. Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, Cannavó A, Giménez-Arnau A, Gonçalo M, Goossens A, John SM, Lidén C, Lindberg M, Mahler V, Matura M, Rustemeyer T, Serup J, Spiewak R, Thyssen JP, Vigan M, White IR, Wilkinson M, Uter W. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. Contact dermatitis. 2015.

Contact Dermatitis in Children

10

Anne Birgitte Simonsen and Mette Sommerlund

Contents

10.1 Introduction

Contact allergy and allergic contact dermatitis are common in children and more frequent than previously expected [1]. Several studies have addressed the issue of contact allergy and the reported prevalence rates vary. Most recent studies report frequencies between 25.2 and 95.6 % among children referred for patch testing [1–3]. The large variation is being likely explained by differences in study design, patient selection, and patch test methodology. It is estimated that allergic contact dermatitis accounts for up to 20 % of all forms of dermatitis in children [3].

A. Birgitte Simonsen, MD (✉) • M. Sommerlund, MD, PhD
Department of Dermatology, Aarhus University Hospital,
P.P. Orums Gade 11, Aarhus 8000, Denmark
e-mail: anbsim@rm.dk; mettsomm@rm.dk

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_10

10.2 The Clinical Picture

Although children are not simply a smaller version of adults, the clinical presentation of contact dermatitis is in general the same as in adults. Allergic contact dermatitis can be difficult to distinguish from atopic or irritant dermatitis. Therefore, in any type of persistent dermatitis, allergic contact dermatitis must be considered as a differential diagnosis. The localization of the dermatitis may raise the suspicion of an external cause and provide important clues. Although the localization of the dermatitis generally approximates the site of allergen exposure, it may occur outside the area of initial contact or present as widespread eruptions often referred to as "Id reactions" [4]. One should further keep in mind that a correlation is not always seen between the presenting pattern of dermatitis and the causative allergen. For instance, allergy to methylisothiazolinone may cause airborne allergic contact dermatitis [5, 6] when the child is exposed to painted rooms. Furthermore, children may become sensitized through contact with a product used by their parents [7].

The general belief is that the frequency of contact allergy increases with age because of increased environmental exposure. Although the risk of nonspecific or irritant reactions is thought to be higher among infants [8], even very young children get sensitized to contact allergens [9]. The differences in frequencies of positive reactions to various allergens between age groups reflect the different exposure patterns depending on the age of the child. For example, sucked-on objects may be the cause of perioral dermatitis among infants and very small children, where as nickel, cosmetic ingredients, and occupational allergens are more frequent causes of allergy among older children and adolescents.

10.3 Children with Atopic Dermatitis

Concurrent contact allergy can lead to atopic dermatitis flares, and allergic contact dermatitis may be misdiagnosed as atopic dermatitis [3]. As in children without atopic dermatitis, allergic contact dermatitis should always be suspected, when the dermatitis is not controlled with conventional topical therapies or if the child presents dermatitis in new body areas.

Patients with atopic dermatitis are chronically exposed to a variety of sensitizers in skin care products intended to improve their condition. Many of the common allergens seen in atopic dermatitis are the same as those seen in the general pediatric population. However, certain allergens are especially relevant in children with atopic dermatitis. These include certain topical agents, including topical antibiotics, antiseptics, and topical corticosteroids [10]. Also, Compositae allergy has been reported to be common in this patient group [11] and should be considered, especially if the dermatitis flares during spring or summer, or the history is otherwise indicative of allergy to plants. The children can be sensitized by direct contact to plants, by the popular wet wipes with chamomile and marigold, or by organic emollients with plants.

10.4 Diagnostic Work-Up

A thorough patient history with detailed exposure analysis is crucial for the final outcome of the patch testing. The exposure analysis should include information on all relevant exposures in the child's environment (Table 10.1), hereby guiding the selection of relevant allergens. In this context, a careful clinical examination also provides important clues (Table 10.2).

The most accurate testing is achieved by using standardized series of allergens supplemented by specific allergens based on the patient history as well as the patient's own personal care products. A standardized children's patch test series must be adjusted to the cultural habits, legislation (e.g., regulation on nickel), and special topical medications (bufexamac) used in the country [3, 4].

10.5 Common Allergens

10.5.1 Metals

10.5.1.1 Nickel

As in adults, nickel is the most common allergen in children [1, 4, 12]. Ear piercing and atopic dermatitis are regarded as major risk factors, and the frequency of nickel allergy is higher among girls. Exposure sources in children are numerous. Nickel sensitization

Table 10.1 Useful considerations for the exposure analysis

Where is the dermatitis located? When did it start? Were any events in the child's life related to the debut of the dermatitis? Does the dermatitis worsen in relation to any specific event or season?	
Leisure activities	*Sport* Does the child wear a helmet; use shin guards, gloves, special shoes, resin for handball, rackets (rubber handle), goggles, swimming cap, flippers, wet suit; or feed animals (plants)?
	Music instruments
	Plants Any exposures to plants? Does the child play outside, does the eczema flare during spring or summer, and does the child feed animals?
	Spare time job Does the child wear gloves or any other equipment? Does the child use any skin care products in relation to the job?
Personal care products	Does the child wear makeup? Has the child dyed hair, eyelashes, or eyebrows? Does the child use perfume, oils, deodorant, body lotions, creams, hair products, sunscreen products, or any pharmaceutical topical treatment?
Infants and very small children	Does the mother use perfume, scented skin care products, cosmetics, or jewelry? Diapers: are they scented or contain rubber? Do the parents use wet wipes for the child?
Diffuse distribution	Does the child play or sleep in a freshly painted room? Is there any exposure to plants?

Table 10.2 Localization of dermatitis and possible causative sources

Body site	Possible sources
Face	Topical pharmaceutical products, spectacle frames, cosmetics, cell phone, piercings
Periorbital area	Ophthalmic preparations, cosmetics, eyelash dye, eyebrow dye
Perioral area	Sucked on objects, cosmetics, topical pharmaceutical products, music instruments, orthodontic appliances
Ears	Jewelry, cell phones, cosmetics, fragrances
Neck	Jewelry, cosmetics, fragrances
Trunk	Textile dyes, fragrances, skin care products, topical pharmaceutical products, metal buckles, elastic bands, rubber bands
Arms	Skin care products, henna tattoos, fragrances
Wrists	Jewelry, rubber bands, cosmetics, fragrances
Hands and fingers	Jewelry, gloves, personal care products, rubber handles, resin, sport equipment
Buttocks and thighs	Diapers, toilet seat, vaccines
Diaper area	Diapers, topical pharmaceutical products, wet wipes
Legs	Sport equipment, shin guards, sport socks
Feet	Shoes, socks, topical pharmaceutical products
Diffuse distribution	Airborne exposures, plants, paint

may occur from the contact with jewelry, in particular earrings, metal buttons, zippers, hair clips, snaps, safety pins, jeans and belt buckles, metal accessories on shoes, coins, metal toys, medallions, magnets, keys, door handles, ballet balance bars, school chairs, etc. [4]. Orthodontic appliances containing nickel have occasionally been reported to cause cheilitis, perioral dermatitis, stomatitis [13], and even systemically induced dermatitis or more generalized reactions [14]. Cell phones, computers, and gaming devices have been observed as a new cause of nickel sensitization [15].

When testing infants and very young children with nickel, the risk of false-positive reactions should be kept in mind [16].

10.5.1.2 Cobalt

Cobalt sensitization is often found in association with nickel sensitization; thus, the exposure sources of the two allergens are similar. Other sources that may be relevant to children and especially adolescents are tattoo ink, makeup, nail lacquer, and leather [17].

10.5.1.3 Potassium Dichromate

The most common source of chromium allergy in children seems to be the leather. Especially leather shoes have been observed to cause chromium dermatitis in children.

10.5.1.4 Aluminum

The most important sources of aluminum exposure in children are aluminum-adsorbed vaccines. Aluminum allergy often presents as intensely itchy subcutaneous nodules at the injection site. The nodule may persist for months to years,

whereas the itch normally fades, as does the aluminum allergy. In a Swedish study, the aluminum allergy was no longer detectable in two thirds of the children at follow-up of 5 years or later [18]. In another study of 40 children with aluminum allergy and vaccination granulomas, 25 later received a booster vaccination, and only two developed a new itching nodule [19].

Exposure to aluminum may also occur when children are hyposensitized to type I allergens with aluminum-containing extracts [18], or from treatment with aluminum-containing eardrops, toothpaste, antiperspirants, and other skin care products [20]. Usually, patch testing is performed using aluminum chloride hexahydrate 2 % in pet. and an empty Finn Chamber. However, if contact allergy to aluminum is suspected and the test is negative to 2 %, the aluminum chloride hexahydrate concentration may be increased to 10 % in pet [4].

10.5.2 Skin Care Products and Cosmetics

Cosmetics have become one of the most frequent causes of contact allergy in children and especially in adolescents. Almost every ingredient may be responsible for contact dermatitis [4]. Children may use cosmetic products themselves, although cases of children being sensitized to cosmetic ingredients through products used by their mother have been described.

10.5.2.1 Fragrances

Fragrance contact allergy is increasingly observed among children [1, 3], and even small children are exposed [8]. Exposure is usually due to perfumes, moisturizers, and deodorants. Scented products are ubiquitous, and the threshold for suspecting fragrance allergy as the possible cause of a child's dermatitis should be low. Typical sites of involvement include areas of greatest contact, such as the face, the neck, and the axillae.

10.5.2.2 Preservatives

Preservatives are another common cause of contact allergy in children. In this context, methylisothiazolinone (MI) deserves special mentioning. It is a chemical preservative found in a variety of products used for children such as wet wipes, creams, liquid soaps, and shampoos. MI has recently received increased attention because of an alarming increase in the prevalence of contact allergy [6]. In addition to various cosmetics and skin care products, MI is used in the preservation of paint and can cause airborne dermatitis in individuals sensitized to the allergen [5].

10.5.2.3 Sunscreen Ingredients

Contact allergy to sunscreen ingredients should be considered, especially if a child presents with flares of dermatitis during spring or summer. Several sunscreen agents have been reported to cause contact allergy in children, including octocrylene, butyl methoxydibenzoylmethane,2-ethylhexyl-4-methoxycinnamate,4-methylbenzylidene camphor, and 4-isopropyl-dibenzoylmethane.

10.5.3 Shoes

When encountering a child with a persistent foot eruption, it may be worthwhile considering allergens contained in the child's shoes. Mercaptobenzothiazole, thiocarbamates, and thiuram derivatives are present in rubber as well as certain glues, P-tert-butylphenol formaldehyde resin, and may be the cause of shoe dermatitis. Para-phenylenediamine (PPD) and disperse dyes should also be considered, as it may be dye allergens in socks. Other relevant shoe allergens are potassium dichromate, used in leather, as well as nickel and cobalt. When possible, the patch testing should include a piece of the patient's own shoe [4].

10.5.4 Sport Equipment

Rubber additives or accelerators are common sensitizers in allergic contact dermatitis caused by sport equipment [21]. Although most studies have found shin guard dermatitis to be primarily irritant reactions, allergic contact dermatitis should be considered if a child presents with a characteristic eczema and a relevant history. Rubber components, thiourea derivatives, and textile dyes are the most common sensitizers. Thiourea derivatives, rubber additives, and p-tert-butylphenol formaldehyde resin in neoprene may also cause wet suit dermatitis.

10.5.5 Tattoos and Black Dye

Para-phenylenediamine (PPD) is a strong sensitizer, and extreme positive patch test reactions are frequently observed in children [22]. With a growing popularity of permanent hair dyeing among adolescents, PPD allergy has become increasingly more frequent in this age group. Another important source of PPD exposure in even young children is temporary black henna tattoos, typically made while on vacation. The child may develop severe primary allergic contact dermatitis at the site of the tattoo, but even more concerning is the fact that sensitization through black henna tattoos may cause severe and sometimes life-threatening allergic reactions from hair dyes later in life.

When patch testing with PPD, both concentration and duration of skin exposure are important factors in the elicitation of contact dermatitis. Testing with the standard 1 % pet. often results in unacceptably strong blistering reactions, especially in children. When suspecting allergy to PPD from a child's history, it is therefore recommended to patch test with a 1:100 dilution (0.01 %). If the patch test is negative, the concentration can be increased to 0.1 % pet. or even 1 % to ensure that an allergic contact dermatitis to PPD is not missed. To prevent active sensitization of a child, PPD 1 % should only be tested on clinical suspicion of contact allergy to PPD.

Sensitization to PPD may lead to cross-reactivity to other structurally related compounds, including other hair dyes, azo dyes used in textiles, rubber chemicals, sulfonamides, *p*-aminobenzoic acid (PABA) sunscreens, and local anesthetics such as benzocaine or procaine [23].

10.6 Patch Testing

Patch testing in pediatric patients is considered safe. Although some authors advocate the use of reduced allergen concentrations, the general view is that children tolerate the same patch test concentrations as adults [1]. The risk of actively sensitizing a patient by diagnostic patch testing is considered extremely low [24]. There are no studies addressing this issue in children; however, there seems to be a consensus that the results from adult populations can be applied to children.

Topical corticosteroids or calcineurin inhibitors should not be applied to the back for 2 weeks prior to patch testing. To avoid flare-up of dermatitis elicited by the patch test, all other dermatitis areas may continue to be treated. Patients receiving oral corticosteroid treatment should stop treatment before and during the patch test [3].

Because of the different exposure patterns in children as compared to adults and the inevitable problem of a limited patch test area, it is recommended to use an abbreviated standard series supplemented by additional allergens depending on the child's history of exposure. The challenge is to perform the patch test only with relevant allergens without missing any contact allergies. In very young children where the test area is even more limited, allergen selection should be particularly careful. If a standard series is used, the indication of each allergen should be considered and irrelevant allergens left out. In some cases, it may be necessary to test in more than one session.

Allergen exposure varies throughout the world. Thus, the most common allergens vary, and the pediatric patch test series should be adapted to the different regions. Most studies find nickel, cobalt, and fragrance to be among the most common allergens, but besides this, there are great regional differences [1, 3]. In a large Danish study from 2013, nickel, cobalt, potassium dichromate, PPD, fragrance mix I, fragrance mix II, colophonium, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), balsam of Peru, and mercaptobenzothiazole from the European Baseline Series gave a positive patch test reaction in ≥1 % of the children [2]. In 2007, the German Contact Dermatitis Research Group suggested the use of a pediatric baseline series consisting of 12 allergens. This included the most common allergens from the Danish study but also thiuram mix, bufexamac, methyldibromo glutaronitrile, methyl(chloro)isothiazolinone, neomycin, and Compositae mix and excluding cobalt, balsam of Peru, and HICC [4]. In North America, the ten most commonly positive allergens are nickel, neomycin, cobalt, fragrance, balsam of Peru, gold, formaldehyde, lanolin alcohol, thimerosal, and potassium dichromate [3]. Based on our experience and the current knowledge, we recommend using a pediatric baseline series consisting of 23 allergens (Table 10.3), supplemented with allergens according to the child's history.

As children are very active, special care should be taken to protect the patches with tape.

Patch test readings are analogous to those in adults as outlined by the International Contact Dermatitis Research Group [4]. It is recommended to do two readings at day 3 and days 5–7, as studies in adults have shown that approximately 13 % of contact allergies are missed without a late reading [25]. Not all positive patch test reactions have clinical relevance. The assessment of the relevance of each positive reaction to the child's dermatitis can be extremely challenging but is nevertheless highly important.

10.7 Guidance of the Patient and Their Parents

First-line of treatment is allergen avoidance. Correct identification of the contact allergen and subsequent avoidance can lead to sustained remission of the dermatitis. Allergen avoidance may be difficult, and successful treatment of the contact dermatitis therefore depends on the education of the patient and their families. The information regarding the allergen should be given orally as well as written, and it can be useful to disclose the CAS registry number. It may be useful to remind the patient and their parents of the patch test result. Studies have shown that patients may forget the outcome of the patch test with time, and this is likely to be even more pronounced if the patch testing is carried out at an early age, where information is primarily given to the parents.

10.8 Key Message

Contact allergy and allergic contact dermatitis are common in children and should always be suspected if a child's dermatitis does not respond to standard topical treatment. A thorough patient history and detailed exposure analysis is of utmost importance, and the localization of the dermatitis may provide important clues. Children should be tested with an abbreviated pediatric series of allergens and can be tested with the same allergen concentrations as adults.

Table 10.3 Suggested pediatric baseline series

1. Nickel sulfate (5 % pet.)
2. Cobalt chloride (1 % pet.)
3. Potassium dichromate (0.5 % pet.)
4. Fragrance mix I (8 % pet.)
5. Fragrance mix II (14 % pet.)
6. Balsam of Peru (25 % pet.)
7. Hydroxyisohexyl 3-cyclohexene carboxaldehyde (5 % pet.)
8. Carba mix (3 % pet.)
9. Black rubber mix (0.6 % pet)
10. Mercaptobenzothiazole (2 % pet.)
11. Mercapto mix (1 % pet.)
12. Thiuram mix (1 % pet.)
13. Paraben mix (16 % pet.)
14. Formaldehyde (1 % aq.)
15. Diazolidinyl urea (2 % pet.)
16. Imidazolidinyl urea (2 % pet.)
17. Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (0.01 % aq.)
18. Methylisothiazolinone (0.2 % aq.)
19. Quaternium-15 (1 % pet.)
20. P-tert-butylphenol formaldehyde resin (1 % pet.)
21. Colophonium (20 % pet.)
22. Lanolin alcohol (30 % pet.)
23. Sesquiterpene lactone mix (0.1 % pet.)

References

1. Simonsen AB, Deleuran M, Johansen JD, Sommerlund M. Contact allergy and allergic contact dermatitis in children – a review of current data. Contact Dermatitis. 2011;65(5):254–65.
2. Simonsen AB, Deleuran M, Mortz CG, Johansen JD, Sommerlund M. Allergic contact dermatitis in Danish children referred for patch testing – a nationwide multicentre study. Contact Dermatitis. 2014;70(2):104–11.
3. Admani S, Jacob SE. Allergic contact dermatitis in children: review of the past decade. Curr Allergy Asthma Rep. 2014;14(4):421.
4. Johansen JD, Frosch PJ, Lepoittevin J-P, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011.
5. Lundov MD, Friis UF, Menne T, Johansen JD. Methylisothiazolinone in paint forces a patient out of her apartment. Contact Dermatitis. 2013;69(4):252–3.
6. Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy – growing epidemic. Contact Dermatitis. 2013;69(5):271–5.
7. Nijhawan RI, Jacob SE. Connubial dermatitis revisited: mother-to-child contact dermatitis. Dermatitis. 2009;20(1):55–6.
8. Johnke H, Norberg LA, Vach W, Bindslev-Jensen C, Host A, Andersen KE. Reactivity to patch tests with nickel sulfate and fragrance mix in infants. Contact Dermatitis. 2004;51(3):141–7.
9. Bruckner AL, Weston WL, Morelli JG. Does sensitization to contact allergens begin in infancy? Pediatrics. 2000;105(1), e3.
10. Kwan JM, Jacob SE. Contact dermatitis in the atopic child. Pediatr Ann. 2012;41(10):422–8.
11. Paulsen E, Otkjaer A, Andersen KE. Sesquiterpene lactone dermatitis in the young: is atopy a risk factor? Contact Dermatitis. 2008;59(1):1–6.
12. Bonitsis NG, Tatsioni A, Bassioukas K, Ioannidis JP. Allergens responsible for allergic contact dermatitis among children: a systematic review and meta-analysis. Contact Dermatitis. 2011;64(5):245–57.
13. Veien NK, Borchorst E, Hattel T, Laurberg G. Stomatitis or systemically-induced contact dermatitis from metal wire in orthodontic materials. Contact Dermatitis. 1994;30(4):210–3.
14. Kerosuo H, Kanerva L. Systemic contact dermatitis caused by nickel in a stainless steel orthodontic appliance. Contact Dermatitis. 1997;36(2):112–3.
15. Thyssen JP, Johansen JD, Zachariae C, Menne T. The outcome of dimethylglyoxime testing in a sample of cell phones in Denmark. Contact Dermatitis. 2008;59(1):38–42.
16. Mortz CG, Kjaer HF, Eller E, Osterballe M, Norberg LA, Host A, et al. Positive nickel patch tests in infants are of low clinical relevance and rarely reproducible. Pediatr Allergy Immunol. 2013;24(1):84–7.
17. Thyssen JP. Cobalt sensitization and dermatitis: considerations for the clinician. Dermatitis. 2012;23(5):203–9.
18. Gente Lidholm A, Bergfors E, Inerot A, Blomgren U, Gillstedt M, Trollfors B. Unexpected loss of contact allergy to aluminium induced by vaccine. Contact Dermatitis. 2013;68(5):286–92.
19. Bergfors E, Trollfors B. Sixty-four children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-adsorbed vaccines-prognosis and outcome after booster vaccination. Eur J Pediatr. 2013;172(2):171–7.
20. Beveridge MG, Polcari IC, Burns JL, Adler A, Hendrickson B, Stein SL. Local vaccine site reactions and contact allergy to aluminum. Pediatr Dermatol. 2012;29(1):68–72.
21. Vaswani SK, Collins DD, Pass CJ. Severe allergic contact eyelid dermatitis caused by swimming goggles. Ann Allergy Asthma Immunol. 2003;90(6):672–3.
22. Spornraft-Ragaller P, Schnuch A, Uter W. Extreme patch test reactivity to p-phenylenediamine but not to other allergens in children. Contact Dermatitis. 2011;65(4):220–6.
23. de Groot AC. Side-effects of henna and semi-permanent 'black henna' tattoos: a full review. Contact Dermatitis. 2013;69(1):1–25.
24. Jensen CD, Paulsen E, Andersen KE. Retrospective evaluation of the consequence of alleged patch test sensitization. Contact Dermatitis. 2006;55(1):30–5.
25. Torp Madsen J, Andersen KE. Outcome of a second patch test reading of TRUE Tests(R) on D6/7. Contact Dermatitis. 2013;68(2):94–7.

Part IV

Main Allergen Groups

Metals

11

Anneli Julander

Contents

Abbreviations

Au	Gold
Co	Cobalt
Cr	Chromium

A. Julander, PhD
Unit of Occupational and Environmental Dermatology, Karolinska Institutet, Institute of Environmental Medicine, Box 210, SE-171 77 Stockholm, Sweden
e-mail: Anneli.julander@ki.se

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_11

DMG Dimethylglyoxime
Ni Nickel
Pd Palladium
Pet. Petrolatum

11.1 Introduction

In the earth crust more than 50 metals are present, but from an allergy point of view, we mainly need to focus on nickel, cobalt and chromium, the three most common metals in contact allergy. However, also aluminium, copper, gold, palladium, platinum, rhodium and titanium have been described or discussed to cause skin sensitization. In this chapter a short review of clinically relevant information for nickel, cobalt, chromium and palladium in metallic items, metal compounds and in different types of materials and products is presented.

Metals may in their metallic state (as alloys or pure metal) or as ions act differently. Alloys are mixtures (without chemical bonding) of more than one element in metallic form. Often alloys are produced when you want to have the chemical properties of two or more metals or new unique properties of the alloy itself. Common alloys are, for example, copper-nickel, stainless steel (iron/nickel/chromium) and nickel-silver. Ions are released from a pure metal or an alloy upon contact with different solutions, for example, human sweat. The ions can penetrate the stratum corneum and cause sensitization and allergic contact dermatitis.

11.2 Contact with Metallic Items and Exposure to Metals

It is of great importance to understand that when it comes to contact allergy to metals, it is the surface of the material that is important and not the bulk material. This can be emphasised by thinking of how the skin comes into contact with the metals. For example, the hands are in contact with the surface and rarely the bulk material. On the surface of a metallic item, an oxide is present, and the composition of the oxide depends on which metals are present in the alloy. For example, stainless steel often has a very hard and corrosion-resistant surface due to chromium oxide that protects the bulk material, and to some extent it also prohibits skin deposition of nickel and chromium ions from touching the material. Although, concerning stainless steel, there are lower-grade compositions containing sulphur that may enhance the release of nickel ions [1]. Another example is from coins: nickel-plated coins will have a surface oxide consisting solely of nickel oxide/hydroxide, whereas a copper-nickel coin will have a mixture of copper oxide, nickel oxide/hydroxide and combinations thereof. When handling such coins, the pure nickel oxide will release more nickel ions on the skin than the mixed oxide will, mainly because nickel is present at a higher concentration at the surface. This will result in a higher amount of nickel per surface area on the skin from the nickel-plated coins than from the copper-nickel coins [2].

11.3 Exposure Times: Relevant for Elicitation of Contact Dermatitis

As soon as your hands touch a metallic surface, ions will be transferred to your hands. The skin dose can be assessed using acid wipe sampling. Using the method skin doses after touching work tools and work materials has revealed that already after 30 min to 2 h nickel, cobalt and chromium were present on the skin in doses able to elicit contact dermatitis. Several short and repeated contacts with metallic items will build up a skin dose of metal that is sufficient to elicit contact dermatitis, as explained by Midander et al. [3]. This becomes particularly important for nickel, since so many items in our daily life contain nickel. Well-known examples of such items that may give rise to nickel dermatitis are coins, keys, handles, eyelash curlers, tools, toys and scissors.

Metal release can be measured by immersing items in artificial sweat. Several studies have shown that when metallic items are submerged in artificial sweat, the initial release of metal ions is high. Already after 2 min, high concentrations can be detected in the sweat; for example, copper-nickel coins release nickel between 6 and 25 μg/cm^2/h and nickel-plated coins between 3 and 4 μg/cm^2/h; some dental alloys release cobalt between 1.5 and 4 μg/cm^2/h and chromium between 0.01 and 0.12 μg/cm^2/h, and hard metal discs released cobalt between 6 and 81 μg/cm^2/h. This is important for understanding why metals can be deposited on the skin after only short contact.

The total amount of a substance on the skin is important for developing allergy and reacting to an allergen [4]. This is true for metals as well as for other skin sensitizers. For metals, we often speak of the amount of ions per surface area (μg/cm^2). During the last years, several studies have shown that even a short and repeated contact with metals give rise to high doses of metal on skin. Jensen et al. [5] showed that nickel-allergic patients, performing their normal work tasks during 2 h, had skin doses of nickel varying between 0.05 and 0.3 μg/cm^2 on the volar aspect of the index finger. These patients had on-going vesicular hand eczema, which was significantly improved once the short and frequent occupational exposure had been reduced. At the 3-month follow-up, no eczema was present on the hands of the six patients. This study illustrates that even low doses of nickel on the skin can maintain hand eczema. Occupational exposure and any brief and repeated "private" exposure to metals must always be considered when seeing the patients at the clinic.

11.4 Source of and Exposure to Metals

Sources of metal exposure are present all around us in our daily life. This is particularly true for nickel, which is present in several items, for example, keys, coins, handles, tools, mobile phones, computers, jewellery, belts, buttons and cutlery, that we use every day and therefore are very difficult to avoid [6]. Exposure to nickel through food is most notably found in whole grain products, beans and lentils and from storing acidic food in stainless steel containers. Also dental braces may release

some nickel. Consumer exposure to chromium may occur through leather items such as shoes, belts, gloves, bags and wrist bands. Consumer exposure to cobalt is often considered to be rare, but some items such as computers and mobile phones may contain cobalt at the surface and some high fashion jewellery, cosmetics and even in leather as pigment. Cobalt and chromium are also used in dental alloys as well as palladium and gold. Hence, dental restorations may serve as an exposure to these metals. Also hip implants are often made of cobalt/chromium alloys, which may become a problem for the individual [6].

Occupational exposure to metals is common. Nickel was historically a male allergy in the plating industry. Occupational groups with high exposure to nickel are electroplaters, metal workers, hair dressers, carpenters, cashiers, etc. Occupational exposure to chromium takes place in the construction industry (although it has declined due to the EU limitation of chromium in cement), among tannery workers, electroplaters, dental technicians, welders and metal workers [7]. Cobalt exposure is prominent in hard metal workers, metal workers, construction workers, pottery workers and dental technicians [8]. Few occupational groups are exposed to palladium, most notably jewellers, dental technicians and electroplaters. Occupational gold exposure mainly occurs for electronics workers and jewellers.

11.5 When to Suspect Metal Allergy: Clinical Signs

Regarding consumers, the classic clinical picture for a dermatologist to suspect metal allergy is when the patients present eczema underneath a metallic item that has been worn for a long time, for example, jewellery, spectacles, watches or buttons. But also hand and foot dermatitis should be evaluated for metal allergy. This can be related to nickel, chromium and cobalt exposure. The prevalence of metal allergies is summarised in Table 11.1. Nickel allergy is still the most common allergy both among dermatitis patients and the general population.

11.5.1 Nickel

Occupational nickel dermatitis is often presented as chronic hand eczema. Nickel dermatitis in consumers is often explained by prolonged contact with different personal nickel-releasing items. However, it must be stressed that also consumers develop hand eczema by repetitive contact with a broad range of nickel-releasing items in everyday life (Table 11.2).

11.5.2 Chromium

Patients often have a persistent eczema, sometimes widespread. It can sometimes be missed due to the fact that it resembles atopic dermatitis, due to a marked dryness

Table 11.1 Examples of recent prevalence (%) of allergy to nickel, cobalt, chromium and palladium among dermatitis patients and the general population in Europe and North America (generally adults if not otherwise stated)

Metal	Country/region, period	Dermatitis patients				General population				Ref.
		n	W	M	Total	n	W	M	Total	
Ni	Europe, 1985–2010[a]	180,390	17–32	3–10	12–25					[11]
	Europe 2005–2006	19,793			19–24					[12]
	Denmark 1990/2006					3,460	9	1	5.9	[13]
	Denmark, 1995–1996[b]					1,146	13.7	2.5	8.6	[14]
	Spain, 2000–2005	1,092	26	3	29.3					[15]
	North America, 2009–2010	4,294			15.5					[16]
Co	Europe 2005–2006	19,793			6.2–8.8					[12]
	Denmark 1990/2006					3,460	0.4	0.1	0.2	[13]
	Denmark, 1995–1996[b]					1,146	1.5	0.6	1.0	[14]
	Sweden	3,790	7	9						[17]
	North America, 2009–2010	4,303			6.2					[16]
	Spain 2000–2005	1,092	8.3	2.4	10.8					[15]
Cr	Denmark 1985–2007	16,228	2.5	2.4	2.5					[18]
	Denmark 1990/2006					3,460	0.3	0	0.1	[13]
	Europe 2005–2006	19,793			4.5–5.9					[12]
	Denmark, 1995–1996[b]					1,146	0.2	1.0	0.5	[14]
	North America 2009–2010	4,306			2.3					[16]
	Spain 2000–2005	1,092	4.1	3.4	7.5					[15]
Pd	Spain 2000–2005	1,092	10.5	1.2	11.7					[15]
	Italy 1991–2000	4,446	6.7	2.3	5.3					[19]
	Italy 2006	3,093			13					[20]

[a]Patch test years: Denmark 1985–2010; Italy 1997–2010; Germany 1995–2010; UK 2002–2010
[b]Adolescents 12–16 years

and lichenification. Cement eczema is often initially displayed at the dorsal aspect of the hands, in a nummular pattern. It can in a later stage also involve the rest of the hand. Foot dermatitis is also common due to chromium in leather shoes or boots; hand eczema due to leather gloves and other leather items in contact with the hands is also seen.

Table 11.2 Examples of sources of exposures for consumers and occupational workers

	Sources of exposure – examples	
Metal	Consumer items	Occupational groups
Ni	Belts, buttons, coins, doorknobs, handles, jewellery, keys, laptops, mobile phones, sewing materials, tools, watches	Carpenters, cashiers, dental technicians, electricians, hair dressers, plating industry workers, metal workers, tailors
Co	Body implants, dental implants, jewellery (to some extent), paints, putties	Dental technicians, hard metal workers, metal workers, painters, pottery workers, printing industry
Cr	Cement, dental implants, galvanised metal items, leather items (belts, boots, gloves, shoes, wrist bands)	Construction workers, dental technicians, tannery workers
Pd	Dental implants, jewellery	Analytical chemists, electroplating workers, jewellers
Au	Dental materials, intracoronary stents	Electronics workers, jewellers

11.5.3 Cobalt

It is rare to find cobalt allergy without either nickel and/or chromium allergy in patients. The most prominent finding of solitary cobalt allergy reactions is found among hard metal, glass and pottery workers. It is often difficult for dermatologists to explain the sources of skin exposure to cobalt, because relatively little is known about the uses of cobalt.

11.5.4 Palladium

Regarding palladium allergy, it is rare to find it isolated, due to cross-reactivity with nickel, but concomitant sensitivity or contamination of patch test substances with palladium chloride has also been proposed. Contact stomatitis and oral lichen in patients with dental restorations and granuloma in pierced patients have been attributed to palladium allergy. Palladium allergy among dermatitis patients is often neglected, due to difficulties to find palladium exposure and the cross-reactivity with nickel.

11.5.5 Gold

Gold allergy is still a controversy among scientists and dermatologists. Skin contact with elemental gold has seldom been shown to cause allergic contact dermatitis. However, there are studies indicating that positive patch test results from gold sodium thiosulfate are increasing rapidly, but the clinical relevance of the findings is often not understood. Dental gold and intracoronary stents are of importance for gold sensitization.

11.6 How to Test and Pitfalls in Testing

In Table 11.3 the most common patch test concentrations are summarised and also which regions/countries that uses them. Several countries also have their own patch test series.

11.6.1 Nickel

5 % nickel sulfate in pet is the preferred patch test substance and is part of the European baseline series. 2.5 % is used in the North American baseline series, but this concentration is known to miss cases of nickel allergy.

11.6.2 Chromium

0.5 % potassium dichromate in pet is the preferred patch test substance and is part of the European baseline series. It is known that this concentration will give rise to some irritant reactions, but if using lower concentration, it is also easy to miss allergic patients. When lower concentrations are used, for example, 0.25 % as in the North American base series, fewer irritant reactions are seen but will also miss cases.

Table 11.3 Common patch test systems and concentrations.

Metal	Patch test system	Concentration	Baseline series
Ni	Finn Chamber or other chamber	Nickel sulfate 5 % pet	European
	Finn Chamber or other chamber	Nickel sulfate 2.5 % pet	North American
	T.R.U.E. TEST®	Nickel sulfate 0.2 mg/cm^2	
Co	Finn Chamber or other chamber	Cobalt chloride 1 % pet	European
	Finn Chamber or other chamber	Cobalt chloride 1 % pet	North American
	T.R.U.E. TEST®	Cobalt chloride 0.02 mg/cm^2	
Cr	Finn Chamber or other chamber	Potassium dichromate 0.5 pet	European
	Finn Chamber or other chamber	Potassium dichromate 0.25 pet	North American
	T.R.U.E. TEST®	Potassium dichromate 0.023 mg/cm^2	
Pd	Finn Cambers or other chambers	Palladium chloride 1 % pet	Not in baseline series
Au	Finn Chambers or other chambers	Gold sodium thiosulfate 2 %	Not in baseline series
	T.R.U.E. TEST®	Gold sodium thiosulfate 0.075 mg/cm^2	

11.6.3 Cobalt

1 % cobalt chloride in pet is the preferred patch test substance and is part of the European baseline series. It has been described that 1 % cobalt chloride may cause some false-positive reactions, sometimes described as porous reactions.

11.6.4 Palladium

1 % palladium chloride in pet is usually used to patch test patients. However, within research, there is a discussion about missing cases due to patch testing with the wrong salt for palladium. It has been suggested that by patch testing with sodium tetrachloropalladate might give a higher sensitivity to finding palladium-allergic patients, without the problem of cross-reactivity with nickel [9].

11.6.5 Gold

2 % gold sodium thiosulfate in pet is used for research studies. It is not included in the baseline series of Europe or North America. Although in the extended North America 80 Comprehensive Series and the T.R.U.E. TEST, gold sodium thiosulphate is included. When patch testing with gold compounds, a reading after 1 week must be included, since the reaction occurs late.

11.6.6 Other Test Methods

Contact dermatitis clinics and researchers sometimes patch test with serial dilutions of the metals to assess how sensitive the patient is. This is however not recommended for routine use. For nickel, the ability of the test to diagnose contact allergy is reproducible, while the strength of the patch test reaction may vary over time [10]. Patch testing with metal discs of different metal alloys is also performed in research to investigate the ability of different materials to cause dermatitis [1].

11.7 What to Tell the Patient if They Have a Positive Test

The most important thing is to avoid skin contact with items that can release the metal. Use spot tests (nickel and cobalt) as a quick screening tool for evaluating release (see below). For chromium, be careful with leather products, if possible chose vegetable-tanned leather (although not always safe), and avoid skin contact with wet cement and cement products. If the dermatitis in a nickel-allergic patient is persistent, although skin contact has been significantly reduced, it may benefit the patient to reduce oral nickel intake.

Remember that these metals are often used in coatings on items to give a shiny or mate surface, for example, computers and mobile phones. Sometimes the coating will wear off with using the item. So a computer or phone that was initially spot test positive may not be positive after some time has elapsed.

Regarding gold, tell the patient not to have a gold stent if a coronary operation is planned.

11.8 Quick Screen for Metal Release

To live with a contact allergy to nickel or cobalt can be made easier with the help of spot tests. Spot tests are solutions of chemicals that can be used to quickly evaluate if ions of a specific metal are released from items. The nickel spot test, also known as the dimethylglyoxime (DMG) test based on dimethylglyoxime and ammonia, has been used in dermatology since decades to identify nickel-releasing items. Different tests are commercially available. Using a drop of the test on a white cotton wool tip stick and then rubbing against an item will give a bright pink colour if nickel ions are released from the item. The test procedure takes 1 min (Fig. 11.1). In a similar way, the cobalt spot test will change colour from yellow to orange/red if cobalt ions are released from the item (Fig. 11.2). It is important not to use the two spot tests on the same surface since this might lead to misinterpretations of the colour change.

The DMG test has been validated and found to be highly specific. It correlates well to the nickel limitation in the EU legislation (0.5 μg/cm^2/week, Table 11.4). The DMG test has also been described in a CEN report as a screening test to indicate compliance with the nickel regulation.

To screen for chromium VI, one can use a solution of diphenylcarbazide. The reaction is based on a reduction of chromium VI to chromium III, illustrated by a bright purple colour. The test can be performed by placing an item in a white plastic

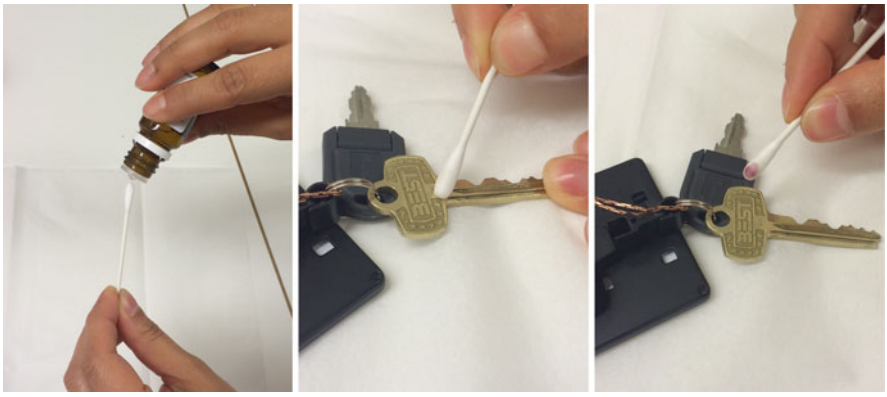


Fig. 11.1 Demonstration of the nickel spot test (dimethylglyoxime test). Put a drop of the solution on a white tipped cotton wool stick, and then rub against the item for 30 s; finally, read the result. A *pink* colour indicates that nickel ions are released from the item (key)

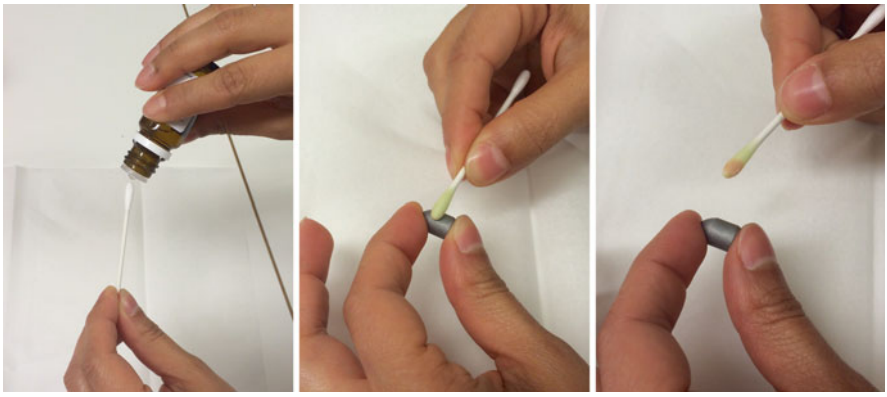


Fig. 11.2 Similar procedure as for nickel but with the cobalt spot test, where the solution is yellow before rubbing the item. An *orange*/*red* colour indicates that cobalt ions are released from the item (hard metal drill bit insert)

Table 11.4 Current legislation regarding nickel and chromium VI within the European Union

Metal	Limit value	Areas of use	Regulation and reference
Ni	0.2 µg/cm^2/week	Assemblies for pierced ears and other pierced parts	REACH; Commission Regulation (EC) No. 552/2009 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0552&from=EN)
Ni	0.5 µg/cm^2/week	Articles intended for direct and prolonged contact with skin Defined as: *Prolonged contact with the skin to articles releasing nickel of potentially more than* *10 min on three or more occasions within 2 weeks or* *30 min on one or more occasions within 2 weeks*The requirement shall be met for at least 2 years of normal use of the article	REACH; Commission Regulation (EC) No. 552/2009 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0552&from=EN) Q&A:s Unique ID 0935 (www.echa.europa.eu)
Ni	Nickel and nickel compounds are prohibited as ingredient in cosmetic products	All cosmetic products intended for human use	Regulation on cosmetic products (Annex II); Commission regulation (EC) No 1223/2009 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:en:PDF)
Cr VI	2 mg/kg (0.0002 %)	Soluble chromium VI in cement	REACH; Commission Regulation (EC) No. 552/2009 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0552&from=EN)

Table 11.4 (continued)

Metal	Limit value	Areas of use	Regulation and reference
CrVI	3 mg/kg (0.0003 % by weight)	Leather articles or articles containing leather coming in contact with skin	REACH; Commission Regulation (EC) No 301/2014 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0301&from=EN)

REACH Registration, Evaluation, Authorisation and Restriction of Chemicals

container or in a test tube and dripping one to five drops of the solution onto the item. The colour change to reddish purple should be present after 1–2 min. It is important to have a blank sample to compare with, that means just the test solution in the same container, but with no item to react with. If iron is present in an item, chromium VI may react with the iron, and no colour change will occur; hence, you will receive a false-negative answer.

When using spot tests, another colour than the anticipated one may occur. For example, the DMG test may react with iron and give a reddish colour; the cobalt spot test may sometime show a green or blue colour, unknown which metals do this. Or sometimes the tip of the cotton wool stick will have a greyish/black colour on the test area. This discolouration will make it difficult to evaluate the spot test result. You cannot say that the test is either positive or negative. Such spot tests should be considered doubtful.

References

1. Lidén C, Menné T, Burrows D. Nickel-containing alloys and platings and their ability to cause dermatitis. Br J Dermatol. 1996;134:193–8.
2. Julander A, Midander K, Herting G, Thyssen JP, White IR, Odnevall Wallinder I, et al. New UK nickel-plated steel coins constitute an increased allergy and eczema risk. Contact Dermatitis. 2013;68(6):323–30.
3. Midander K, Kettelarij JA, Julander A, Lidén C. Nickel release from white gold. Contact Dermatitis. 2014;71:109–11.
4. Fischer LA, Menné T, Johansen JD. Dose per unit area – a study of elicitation of nickel allergy. Contact Dermatitis. 2007;56(5):255–61.
5. Jensen P, Thyssen JP, Johansen JD, Skare L, Lidén C, Menné T. Occupational hand eczema caused by nickel and evaluated by quantitative exposure assessment. Contact Dermatitis. 2011;64(1):32–6.
6. Lidén C, Bruze M, Thyssen JP, Menné T. Metals. In: Johansen JD, Frosch PJ, Lepoittevin J, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011. p. 643–80.
7. Sethi G, Belum B, Burrows D, Maibach HI, Hostynek J. Chromium. In: Rustemeyer T, Elsner P, John S, Maibach HI, editors. Kanerva's occupational dermatology. 2nd ed. Berlin: Springer; 2012. p. 495–504.
8. Lidén C, Julander A. Cobalt. In: Rustemeyer T, Elsner P, John S, Maibach H, editors. Kanerva's occupational dermatology. 2nd ed. Berlin: Springer; 2012. p. 505–10.
9. Muris J, Kleverlaan CJ, Fielzer AJ, Rustenmeyer T. Sodium tetrachloropalladate (Na2[PdCl4]) as an improved test salt for palladium allergy patch testing. Contact Dermatitis. 2008;58(1):42–6.
10. Hindsén M, Bruze M, Christensen OB. Individual variation in nickel patch test reactivity. Am J Contact Dermatitis. 1999;10(2):62–7.

11. Garg S, Thyssen JP, Uter W, Schnuch A, Johansen JD, Menné T, et al. Nickel allergy following European Union regulation in Denmark, Germany, Italy and the U.K. Br J Dermatol. 2013;169:854–8.
12. Uter W, Ramsch C, Aberer W, Ayala F, Balato A, Beliauskiene A, et al. The European baseline series in 10 European countries, 2005/2006–results of the European Surveillance System on Contact Allergies (ESSCA). Contact Dermatitis. 2009;61(1):31–8.
13. Thyssen JP, Linneberg A, Menné T, Nielsen NH, Johansen JD. Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population. Br J Dermatol. 2009;161(5):1124–9.
14. Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema. The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). Acta Derm Venereol. 2002;82(5):359–64.
15. Bordel-Gomez MT, Miranda-Romero A, Castrodeza-Sanz J. Isolated and concurrent prevalence of sensitization to transition metals in a Spanish population. J Eur Acad Dermatol Venereol. 2008;22(12):1452–7.
16. Warshaw EM, Belsito DV, Taylor JS, Sasseville D, DeKoven JG, Zirwas MJ, et al. North American Contact Dermatitis Group patch test results: 2009 to 2010. Dermatitis. 2013;24(2):50–9.
17. Lindberg M, Edman B, Fischer T, Stenberg B. Time trends in Swedish patch test data from 1992 to 2000. A multi-centre study based on age- and sex-adjusted results of the Swedish standard series. Contact Dermatitis. 2007;56(4):205–10.
18. Thyssen JP, Jensen P, Carlsen BC, Engkilde K, Menné T, Johansen JD. The prevalence of chromium allergy in Denmark is currently increasing as a result of leather exposure. Br J Dermatol. 2009;161(6):1288–93.
19. Larese Filon F, Uderzo D, Bagnato E. Sensitization to palladium chloride: a 10-year evaluation. Am J Contact Dermatitis. 2003;14(2):78–81.
20. Cristaudo A, Bordignon V, Petrucci F, Caimi S, De Rocco M, Picardo M, et al. Release of palladium from biomechanical prosthesis in body fluids can induce or support PD-specific INF-gamma T cell responses and the clinical setting of palladium hypersensitivity. Int J Immunopathol Pharmacol. 2009;22(3):605–14.

Fragrances

12

Wolfgang Uter

Contents

12.1 Allergen Characteristics and Exposure

Fragrances are (mixtures of) substances of synthetic or natural origin used for their scent. It should be noted that the effect – pleasant vs. annoying – can be concentration dependent. Skatole (CAS 83-34-1), for instance, is found both in flowers of *Jasminum* spp. and in human faeces. The CosIng database maintained by the EU Commission (http://ec.europa.eu/consumers/cosmetics/cosing/, last accessed 2014-09-03) lists 2747 fragrance substances or natural extracts used for 'perfuming' and 1062 entries for 'masking', with considerable overlap. A few of these ingredients are also used for other purposes, e.g. as biocides/preservatives or antioxidants, and may thus be contained even in 'fragrance-free' products. A comprehensive overview on the problem of fragrance contact allergy due to cosmetics is available by the Scientific Committee on Consumer Safety (SCCS) of the European Commission ([10], http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf, last accessed 2014-04-17), an extract having been published in two reviews [7, 13].

W. Uter, MD, PhD
Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Waldstr. 4-6, Erlangen D-91054, Germany
e-mail: wolfgang.uter@fau.de

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_12

Induction of contact sensitisation to fragrance ingredients and later elicitation of allergic contact dermatitis may develop following skin contact with a sufficient dose/area of fragrance substances, mainly through the use of cosmetic products. Once sensitisation has occurred, e.g. by a deodorant or perfume, elicitation by other product types such as body lotions and hand creams containing much lower levels of fragrances is possible, adding to the clinical problem for the patient. In this context, repetitive exposure, aggregate exposure (to one substance via several different product types) and 'cocktail exposure' (to several potential allergens at the same time [15]) of a skin region apparently facilitate sensitisation [2], possibly further aggravated by host factors such as irritation, occlusion, etc., as in the axilla or in the anogenital region. Most individuals with contact allergy to fragrance ingredients are aware that they cannot tolerate scented products on their skin and are often able to specifically name product categories that initiated their disease. In this context colognes, eau de toilette, deodorants and lotions are named significantly more often by fragrance-allergic eczema patients than by patients without fragrance contact allergy [13].

Besides intentional exposure to own cosmetics, skin contact to fragrances may be due to:

- Cosmetics used by others (e.g. in geriatric nurses applying creams to elderly or hairdressers applying hair cosmetics to clients' hair)
- In terms of 'consort exposure' and subsequent dermatitis via a spouse or child
- Children's toys
- Other scented products such as household cleaners and detergents
- Topical medicaments, aromatherapy or herbal remedies

For some occupations, such as those mentioned above, cosmetics have to be considered a work material. Moreover, in other occupations, fragrances are used for technical purposes, e.g. as re-odorant for cutting fluids, or as degreasing 'natural' citrus terpenes solvent, and may thus also occasionally cause, or contribute to, occupational contact dermatitis.

A number of fragrance substances can act as prehaptens or prohaptens, forming new, often more potent allergens by air oxidation and/or metabolic activation. Such activation processes increase the risk of sensitisation and also the risk for cross-reactivity between fragrance substances when yielding a common metabolite [7, 10].

12.2 Epidemiology

Around 16 % of patients patch tested in the European population are sensitised to fragrance ingredients, with some variation between countries and even departments. Thus, fragrances are the leading group of allergens, at least, in some countries, after the metals. From population-based studies, it can be estimated that the frequency of

contact sensitisation to fragrance ingredients in the general population in Europe is up to 5 %. The overall trend of fragrance sensitisation has largely been stable during the last decades, as some causes have decreased and others increased [10].

Concerning risk factors for fragrance contact allergy, increasing age has been identified as risk factor at least for sensitisation to fragrance mix I in several analyses [4, 14], most likely attributable to the cumulative exposure during lifetime. Only HICC has shown a slightly different pattern, with middle age being at highest risk [12]. Moreover, female gender is associated with a moderately increased risk, as are some occupations (geriatric nurse, masseurs and others) [14]. Consistently, the axillae have been identified as risk factor of outstanding importance but also head/face and hand dermatitis [12, 14]. In conclusion, fragrances may be involved substantially in allergic contact dermatitis of different anatomical sites and need to be considered.

12.3 Clinical Picture

The clinical presentation of allergic contact dermatitis due to fragrances depends on the route of administration of the causative products to the skin, as in the case of other allergens. The spectrum ranges from localised dermatitis clearly attributable to the application of, e.g. perfume, shaving lotion or a deodorant, to appearance or aggravation of dermatitis on body sides exposed to a multitude of products, such as trunk or hands, where exposure to a fragranced product may be less evident. Systemic exposure to fragrances and flavours, e.g. by ingestion or possibly inhalation, may lead to widespread allergic reactions or reactivation of localised allergic contact dermatitis. This has been shown for ingestion of (components of) *Myroxylon pereirae* resin (Balsam of Peru) [8, 9]. In contrast, data on the role of exposure by inhalation is scarce, pointing to a possible risk of elicitation of systemic allergic contact dermatitis [11]. Positive patch test reactions to one or more of the fragrance screening markers (see below) should alert of these more covert exposures and prompt reassessment of the patient's history and the products used on affected body sites and of the possibility of dietary exposures and aggravation of dermatitis, respectively.

Nowadays, phototoxic ingredients are more carefully avoided, so that photodermatitis is a rare phenomenon. However, if the clinical picture and previous use of scented products suggest this, photo (aggravated) dermatitis and subsequent photo patch testing [including the incriminated product(s)] should be considered.

12.4 Diagnostic Considerations

The baseline patch test series contains a number of routinely tested screening allergens: fragrance mix I, fragrance mix II and its single ingredient hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC, also known under the trade name

Lyral™) and *Myroxylon pereirae* resin (Balsam of Peru). Two other allergens can be regarded as fragrance allergy screening agents in wider sense, namely, colophony and oil of turpentine (the latter not part of the European baseline series). A number of additional single substances or natural extracts used as fragrances are available as commercially produced allergen preparations. These are often grouped to special test serious, e.g. the set of ingredients of fragrance mix I and II used for breakdown tests in case of a positive reaction to the respective mix. While the main test allergens have a test concentration which has been well evaluated, the test concentration of single ingredients is often less well established. It has recently been shown, for instance, that the test concentration of 12 allergens not included in the two mixes, among those 26 needing to be labelled, is probably much too low [3]. This puts the common notion that positive reactions mainly to fragrance mix I are often false positive, if none of its ingredients shows a positive patch test reaction subsequently, into perspective: the concentration of single ingredients may need to be higher to achieve a sufficiently sensitive patch test allergen.

However, in view of the vast number of fragrance substances used, the scope of commercially available patch test preparations will always be limited, albeit comprising the most important allergens. Hence, it is important to also include patient's own products, considered to have caused contact dermatitis, into the patch test programme. Perfume products in a strict sense (fine fragrances, Eau de toilette, after shave) can be tested 'as is', allowing the liquid to dry on the patch before its application. Deodorants can also be applied 'as is', allowing to dry; however, mild irritation under the occlusion may occur. Other leave-on products can usually be applied 'as is', while rinse-off products including shaving creams or soaps should be diluted 1 % in water [5]. Such dilation will usually prevent stronger irritant reactions; however, the necessary dilution may dilute product ingredients, including fragrances, to a level which is insufficient to elicit an allergic reaction under the single, occlusive application conditions in patch testing.

Therefore, the gold standard for diagnosing contact sensitisation, also as validation in case of doubtful patch test reactions with a strongly suspected allergen, or clearly positive patch test reactions with unclear relevance, is a repeated open application test (ROAT) or provocative use test (PUT) [6]. These tests, while being standardised, closely mimic actual application of allergen-containing products, i.e. the repetitive open application over a period of several weeks (see Chap. 5). Thereby, if the concentrations used in the ROAT are in a realistic range, as it normally should be, positive reactions prove current relevance of the contact sensitisation by definition. The material used for the ROAT may be (1) the patch test preparation, (2) the suspected allergen in a matrix resembling actual products, e.g. hydroalcoholics, and (3) a finished product. The latter may pose a certain problem, as a finished product usually includes several ingredients, and it may be difficult to relate a positive ROAT reaction to the product to a certain ingredient. It has been pointed out that in case of fragrances particularly, a ROAT needs to be performed for at least 3 weeks, unless a positive reaction occurs earlier. The diagnostic work-up is shown in Table 12.1.

Table 12.1 Steps of the diagnostic work-up in fragrance contact allergy

All (consecutive) patients	Baseline series with fragrance screening markers
Patients with history of fragrance intolerance	PT selected own products
	PT additional fragrance series from the start
Patients with positive PT reaction to fragrances/fragranced products	PT 2nd round supplementary to above
	PT single ingredients (obtained from manufacturer) of positive product; fragrance mixture in creams, etc., often provided as mixture; may need additional breakdown testing
	ROAT, if PT reaction is doubtful (equivocal) or to verify and establish current relevance of a positive PT reaction
Outcome	Discuss and evaluate relevance based on labelling information
	Counsel patient regarding avoidance (also if mixes were positive without mix breakdown having been tested or remaining negative)[1]

[1]Conservatively, sensitisation to all ingredients of the mix may be assumed. However, pragmatically, the patient can be advised to make a self-test (similar to ROAT) with a desired product before buying and actually using it. *PT*: patch test

12.5 Prevention

Primary prevention means, in this context, the avoidance of new cases of sensitisation to a fragrance substance, that is, healthy persons should not get sensitised. Secondary prevention basically means that persons who already got sensitised avoid future contact to their allergen(s) to prevent relapses of allergic contact dermatitis. Tertiary prevention, which implies limiting the severity of an existing disease by intensive and often continuous or repeated care (also called rehabilitation), has a role in the management of contact allergic patients only in the rare instances where allergen avoidance is not possible. Some components of prevention by different actors are outlined in Table 12.2.

Different means, if partly overlapping, are used to achieve above objectives regarding contact allergens in general and fragrance substances in particular. Premarketing screening of newly introduced substances regarding different toxicological endpoints, including contact sensitisation, aims at identifying a hazard at a sufficiently early stage, with the consequence of (1) not marketing the substance, (2) establishing use concentration limits or (3) classifying the substance as 'safe without restrictions'. This process aiming at induction and primary prevention, respectively, has been formalised by industry in terms of a 'quantitative risk assessment (QRA)' [1]; however, several aspects of this process are currently under revision, and it cannot yet be considered as validated. Time and again the premarketing screening fails and substances are introduced into the market, which turns out to be clearly not safe for the consumer in the concentrations and types of products, respectively, they are used in. This is illustrated by clinical data (an infamous example being HICC), which should prompt a reassessment and the redefinition of a safe

Table 12.2 Different measures of prevention concerning an allergen 'X'

Measure	Primary prevention	Secondary prevention
Information (labelling)	Consumer: decision not to buy a product containing X	Dermatologist: enable adequate diagnostics
		Patient: avoidance of all products containing X
Formulation/substitution	Producer: deliberate avoidance to use X in products	…Will increase choice of products for patient with contact allergy to X
Restriction of use concentration	Regulator/producer: reduce substantially the likelihood of new sensitisation to X in consumers	…Will possibly allow the use of X in some product categories for weakly sensitised patients
Prohibition	Regulator/producer: eliminate risk of sensitisation to X in consumers	…X will become irrelevant for patients in those products for which ban is effective

use level, best based on the dose-elicitation relationship in sensitised persons. Thereby, patch test data, beyond the purpose for diagnosing and counselling one given patient, help to improve product safety and thus aid primary prevention, if sufficiently standardised and collected in a surveillance network.

Secondary prevention [the avoidance of relapses of allergic contact dermatitis by avoiding the individual allergen(s)] has an important prerequisite: adequate and comprehensive diagnosis of the individual spectrum of contact sensitisation by patch testing. Patch testing can only be comprehensive if patient and dermatologist know to which potential allergens the patient has been exposed to. Regarding industrial products, this is often virtually impossible to find out, due to a lack of labelling, cooperation and information of producers or distributors. Concerning cosmetics, which are the main source of exposure and sensitisation to fragrances, the situation is more favourable thanks to the introduction of mandatory ingredient labelling in terms of the INCI nomenclature (see CosIng database, see above), at least in the EU. Unfortunately, fragrances were just labelled with 'perfume' until 2003. Only since then the 26 fragrances most important in terms of being contact sensitisers need to be labelled explicitly. A recent reassessment [10] identified more than 100 additional substances which should also be labelled; final legislative decision had not yet been achieved at the time of writing.

Once diagnosed, the patient relies on standardised information on the presence of the substances on product labels, which is achieved to a very large extent by the INCI system. Carefully reading product labels thus enables successful allergen avoidance. As it has been justly criticised that common ingredient labels, especially on small packages, are difficult to read, suggestions to improve readability and compress ability are being developed. Furthermore, intelligent usage of modern IT infrastructure may help allergic patients to even more efficiently scrutinise product ingredients (scanner terminals at points of sale displaying easily legible information, with options to search and order, or smartphone applications also based on the QR code, comparing ingredients with the set of individual allergens entered into the application).

References

1. Api AM, Basketter DA, et al. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. Regul Toxicol Pharmacol. 2008;52(1):3–23.
2. Bonefeld CM, Nielsen MM, et al. Enhanced sensitization and elicitation responses caused by mixtures of common fragrance allergens. Contact Dermatitis. 2011;65(6):336–42.
3. Bruze M, Svedman C, et al. Patch test concentrations (doses in mg/cm^2) for the 12 non-mix fragrance substances regulated by European legislation. Contact Dermatitis. 2012;66(3): 131–6.
4. Buckley DA, Rycroft RJ, et al. The frequency of fragrance allergy in patch-tested patients increases with their age. Br J Dermatol. 2003;149(5):986–9.
5. Frosch PJ, Geier J, et al. Patch testing with the patient's own products. In: Johansen JD, Frosch PJ, Lepoittevin JP, editors. Contact dermatitis. Heidelberg: Springer; 2011. p. 1107–19.
6. Johansen JD, Frosch PJ, et al. Allergic contact dermatitis in humans: experimental and quantitative aspects. In: Johansen JD, Frosch PJ, Lepoittevin JP, editors. Contact dermatitis. Heidelberg: Springer; 2011. p. 241–51.
7. Karlberg A-T, Börje A, et al. Activation of non-sensitizing or low-sensitizing fragrance substances into potent sensitizers - prehaptens and prohaptens. Contact Dermatitis. 2013;69(6):323–34.
8. Pfützner W, Thomas P, et al. Systemic contact dermatitis elicited by oral intake of Balsam of Peru. Acta Derm Venereol. 2003;83(4):294–5.
9. Salam TN, Fowler Jr JF. Balsam-related systemic contact dermatitis. J Am Acad Dermatol. 2001;45(3):377–81.
10. SCCS. SCCS (Scientific Committee on Consumer Safety), opinion on fragrance allergens in cosmetic products. Brussels: European Commission, DG SANCO; 2012.
11. Schnuch A, Oppel E, et al. Experimental inhalation of fragrance allergens in predisposed subjects: effects on skin and airways. Br J Dermatol. 2010;162(3):598–606.
12. Uter W, Geier J, et al. Risk factors associated with sensitization to hydroxyisohexyl 3-cyclohexene carboxaldehyde. Contact Dermatitis. 2013;69(2):72–7.
13. Uter W, Johansen JD, et al. Categorization of fragrance contact allergens for prioritization of preventive measures: clinical and experimental data and consideration of structure-activity relationships. Contact Dermatitis. 2013;69(4):196–230.
14. Uter W, Schnuch A, et al. Association between occupation and contact allergy to the fragrance mix: a multifactorial analysis of national surveillance data. Occup Environ Med. 2001;58(6):392–8.
15. Uter W, Yazar K, et al. Coupled exposure to ingredients of cosmetic products: I. fragrances. Contact Dermatitis. 2013;69:335–41.

Preservatives

13

Klaus Ejner Andersen and Kristian Fredløv Mose

Contents

13.1 Introduction

Preservatives are chemicals added to aqueous and emulsion systems in cosmetics and household products and in industry to prevent microbial growth and spoiling of the products. The use concentrations for preservatives are generally in the range of 1–10,000 ppm (0.0001–1 %). These reactive chemicals can induce allergic contact dermatitis. Their sensitising potential in predictive assays varies considerably from compound to compound. A number of preservatives are included in the European patch test baseline series [1]. The patch test concentration for preservative chemicals is difficult to establish because many of the chemicals are also irritants [2].

A great number of preservative formulations are marketed under various trade names and synonyms, and there is no single source of information about the production, import and use of the different products.

K.E. Andersen, MD, DMSc (✉) • K.F. Mose, MD
Department of Dermatology and Allergy Centre, Odense University Hospital, University of Southern Denmark, Sdr. Boulevard 29, DK-5000 Odense C, Denmark
e-mail: keandersen@health.sdu.dk

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_13

The EU has adopted a directive on the placing of biocidal products on the market in order to harmonise legislation between member states (http://ec.europa.eu/environment/chemicals/biocides/regulation/regulation_en.htm). The use of the different preservatives varies from time to time and probably also from country to country.

The ideal preservative is effective at low concentrations against a wide spectrum of microorganisms; it is soluble in the formulation at the required concentration, non-toxic and non-sensitising at in-use concentration, compatible with other ingredients in the products. Further, it has no physical effect on the product, is stable over a wide range of pH and temperature conditions and biodegradable and does not accumulate in the environment. The challenge is that no single preservative meets all these characteristics. Therefore, preservative mixes are often applied in products. A total of 57 different preservatives are allowed in cosmetics according to the positive list in the EU Biocides Regulation 528/2012. The frequency of contact allergy to a certain preservative among consecutive eczema patients varies from clinic to clinic. This may reflect variations between the patient materials, variations in patch test procedures and readings, choice of patch test concentrations and also the magnitude of exposure.

It may be difficult to determine the clinical importance of a positive patch test to a preservative unless detailed exposure history, product information and the results of use tests are taken into account. The information on the presence of biocides in industrial products is much more limited and depends on registration practises and the quality of product safety data sheets [3].

13.2 When to Suspect Allergic Contact Dermatitis to Preservatives

Any patient with suspected allergic contact dermatitis may have preservative allergy. Therefore, several preservatives are included in the patch test baseline series. The detection of a preservative contact allergy is often a surprise to both the doctor and the patient. The challenge is to determine the clinical relevance and establish the exposure. The EU regulations have improved the situation for dermatologists and consumers in general, because preservatives added to consumer products, as cosmetics, detergents and household products, shall be listed on the product label irrespective of their concentration. Further, the mandatory use of a uniform nomenclature on labels (INCI: International Nomenclature of Cosmetic Ingredients) is a major step forward in determining clinical relevance of the contact allergy and an important help for the patient to avoid further exposure. Contact allergy to preservatives may be severe, and transient and intermittent exposure to products containing the culprit preservative may explain chronic and recurrent dermatitis. Even airborne allergic contact dermatitis from preservatives in consumer products may appear. Methylisothiazolinone (MI) in water-based paint has caused several cases of severe facial allergic contact dermatitis in MI-allergic patients staying in newly painted rooms [4]. The clinical presentation of biocide-related allergic contact dermatitis varies considerably from acute and recurrent dermatitis on the face, trunk and intertriginous skin areas to chronic hand eczema.

13.3 The Most Important Preservative Allergens

The current European baseline series include methylchloro- and methylisothiazolinone (MCI/MI), methylisothiazolinone (MI), methyldibromo glutaronitrile, formaldehyde, quaternium-15 and paraben mixture. The baseline series is under constant development, and additions/removal of allergens and change of test concentration may be introduced based on newly published scientific evidence [5] (Table 13.1).

13.3.1 Methylchloro- and Methylisothiazolinone (MCI/MI) and Methylisothiazolinone (MI)

These isothiazolinones are the active ingredients in Kathon CG (Rohm and Haas, Philadelphia, PA, USA), a cosmetic preservative on the market since the 1980s. They appear in the preservative mixture in the ratio of 3:1. MI alone has been approved as a cosmetic preservative since 2005, as it was considered less sensitising compared to the chlorinated moiety. However, it had to be used in a much higher concentration to be effective and therefore caused the current epidemic of MI allergy [6].

Other isothiazolinones such as benzisothiazolinone (BIT) and octylisothiazolinone (OIT) are used extensively as effective biocides to preserve the water content of industrial products, such as metalworking fluids and water-based paints. Isothiazolinones are marketed under many brand names, which makes it easy to overlook the presence of these chemicals in the formulations. Over the last 15 years, the incidence of MCI/MI contact allergy has remained around 2.0–2.5 % of consecutively tested eczema patients in Europe [7]. However, the introduction of MI alone has caused an epidemic of MCI/MI and MI contact allergy, raising the frequency of contact allergy to these preservatives to 5–7 % among consecutively

Table 13.1 Patch test concentrations for preservatives from different suppliers. The recommendation from the European Society of Contact Dermatitis (ESCD) is presented in the right column

	Suppliers				
			Smart Practice®		
Chemical name	Trolab®	Chemotechnique®	T.R.U.E Test®	allergEAZE®	ESCD
Formaldehyde	1 % aq.	1 % pet., 1 % aq. and 2 % aq.	180 µg/cm^2	1 % aq.	2 % aq.
Paraben mix	16 % pet.	12 % and 16 % pet.	1000 µg/cm^2	16 % pet.	16 % pet.
Quatemium-15	1 % pet.	1 % pet. and 2 % pet.	100 µg/cm^2	1 % pet.	1 % pet.
Cl+Me-isothiazolinone (MCI/MI)	0.01 % aq.	0.01 % pet., 0.01 % aq. and 0.02 % aq.	4 µg/cm^2	0.01 % aq.	0.01 % aq.
Methyldibromo glutaronitrile	–	0.3 % and 0.5 % pet.	5 µg/cm^2	0.5 % pet.	0.5 % pet.
Methylisothiazolinone (MI)	0.05 % aq.	0.02 % and 0.2 % aq.	–	0.2 % aq.	0.2 % aq.

patch-tested dermatitis patients [8]. These allergens are important for hand eczema and facial dermatitis, and it may also cause urticaria and airborne contact dermatitis in the face of sensitised individuals who stay in newly painted rooms, and the diagnosis is easily missed unless specifically considered. In cosmetic products, the permissible level of MCI/MI is 15 ppm, and it appears that this concentration in rinse-off products is rather safe, since most subjects previously sensitised to MCI/MI tolerated the use of a shampoo preserved with MCI/MI for 2 weeks [9]. In leave-on products, a maximum concentration of 7.5 ppm is recommended.

Patch test reactions to MCI/MI may show unusually sharp borders and can still be true allergic reactions. The patch test concentration was 100 ppm in aqueous solution, until recently when it was recommended to raise the test concentration to 200 ppm [6]. Due to the activity of isothiazolinones on the skin, it is imperative that exact dosing be used, when isothiazolinones are used for patch testing. In the T.R.U.E. Test, the concentration is 4 μg/cm^2. There may be cross-sensitisation between MCI/MI and two other isothiazolinones, benzisothiazolinone and octylisothiazolinone [10]. Patients sensitised to MI often also react to MCI while the opposite is not obligatory [11].

13.3.2 Methyldibromo Glutaronitrile

In the mid-1980s, the preservative methyldibromo glutaronitrile (MDBGN) was approved for the use in cosmetic products at a maximum concentration of 1000 ppm in both leave-on and rinse-off cosmetics except for sunscreen products, in which MDBGN was not allowed to exceed a concentration of 250 ppm. MDBGN was effective at low in-use concentrations, and animal tests indicated that the preservative was a weak sensitiser. These attributes were favourable, and MDBGN gradually became more widespread throughout the 1990s in household and industrial products and cosmetics in particular.

The preservative was marketed as Euxyl K400 (Schülke and Mayr, Hamburg, Germany), a combination of MDBGN and phenoxyethanol (1:4), which is a weak sensitiser. Methyldibromo glutaronitrile is the INCI name, and it is synonymous with 1,2-dibromo-dicyanobutane. However, dermatology clinics in Europe found increasing numbers of eczema patients sensitised to the chemical [12]. In 2001, patch test data from 16 European clinics showed an increasing average frequency of sensitivity to MDBGN in eczema patients from 0.7 % in 1991 to 3.5 % in 2000 [13]. This epidemic of MDBGN allergic contact dermatitis from consumer products led the EU authorities to ban the use of MDBGN in cosmetics from 2005. Subsequent epidemiological studies from EU countries showed a decrease in MDBGN contact allergy [14]. The effect of this regulation is a prime example of primary prevention. A repeated short-term exposure, such as frequent hand washing with MDBGN-containing liquid soap, was a significant cause of sensitisation and elicitation of allergic contact dermatitis to this preservative [15]. The current patch test concentration is 5000 ppm in petrolatum. It has been chosen based on consideration of rates of contact allergy, doubtful and irritant reactions, as well as information on

clinical relevance represented by results of a repeated open application test. However, others have recommended 3000 ppm as the optimal patch test concentration due to increased number of false-positive reactions at 5000 ppm. MDBGN is now included in T.R.U.E. Test at a concentration of 5 μg/cm^2.

13.3.3 Formaldehyde and Formaldehyde Releasers

Formaldehyde is a ubiquitous and potent sensitiser, industrially, domestically and medically. Formaldehyde exposure is difficult to estimate because the chemical – besides being manufactured, imported and used as such – is incorporated into a large variety of products and reactants in many chemical processes, including formaldehyde releasers, polymerised plastics, metalworking fluids, medicaments, fabrics, cosmetics and detergents (Table 13.2). Shampoos may contain formaldehyde, but because they are quickly diluted and washed off, only exquisitely formaldehyde-sensitive consumers develop dermatitis on the scalp and face. Nevertheless, hairdressers may get hand dermatitis from similar products due to their more intense exposure, and it is important to note that formaldehyde-releasing preservatives in cosmetics and topical drugs may elicit allergic contact dermatitis in formaldehyde-sensitive consumers [16].

Formaldehyde dermatitis from textiles is rare today because the manufacturers have improved the fabric finish treatment and have reduced the amount of formaldehyde residues in new clothing. Garments made from 100 % acrylic, polyester, linen, silk, nylon and cotton are generally considered to be formaldehyde-free [17].

Table 13.2 Formaldehyde uses and exposure

Clothing, wash and wear, crease-resistant clothing
Medications: wart remedies, anhidrotics
Antiperspirants
Preservative in cosmetics
Photographic paper and solutions
Paper industry
Disinfectants and deodorisers
Cleaning products
Polishes
Paints and coatings
Printing etching materials
Tanning agents
Dry cleaning materials
Chipboard production
Mineral wool production
Glues
Phenolic resins and urea plastics in adhesives and footwear
Fish meal industry
Smoke from wood, coal and tobacco (relevance is controversial)

Formaldehyde sensitivity is not necessarily accompanied by a simultaneous sensitivity to formaldehyde resins and formaldehyde releasers and vice versa [18]. Fifty-three percent of formaldehyde-sensitive patients tested in a UK multicentre study were positive to one or more of the four formaldehyde releasers tested: quaternium-15, imidazolidinyl urea, diazolidinyl urea and 2-bromo-2-nitropropane-1,3-diol [19]. Indeed, some of the formaldehyde releasers might act directly as haptens or be precursors of haptens (the above-mentioned formaldehyde releasers undergo a chemical transformation (hydrolysis)). It depends on the exposure conditions and the actual release of formaldehyde. The frequency of formaldehyde-positive patch tests in consecutive eczema patients is around 2–3 % [3].

Inexplicable positive patch test reactions frequently occur where no clinical relevance is found. A deeper search, however, might often reveal it. Hidden sources of formaldehyde in the home may be a cause of hand eczema in some women with formaldehyde allergy. Occupational formaldehyde allergy is quite common and occurs in metal workers, hairdressers, masseurs and workers using protective creams, detergents and liquid soaps. In certain cases, the positive patch test should be confirmed by a repeated test and by a use test, since false-positive reactions may occur; this may explain why about one-third of allergies reported to formaldehyde, and its releasers can be lost on repeated patch testing, although a lack of reproducibility in patch testing might also account for this phenomenon [20]. In a detailed clinical experiment, the eliciting closed patch test threshold concentration was 10,000 ppm formaldehyde in 10 of 20 formaldehyde-sensitive individuals, 9 reacted to 5000 ppm, 3 reacted to 1000 ppm, 2 reacted to 500 ppm and 1 reacted to 250 ppm. Positive reactions were not observed in non-occluded patch test with a dilution series from 25 to 10,000 ppm or in a repeated open application test (ROAT) with a leave-on cosmetic product containing a formaldehyde releaser (an average of 300 ppm formaldehyde) [21]. Thus, the threshold concentration for occluded patch test to formaldehyde in formaldehyde-sensitive patients seems to be around 250 ppm.

Formaldehyde is widely distributed in the environment and is difficult to avoid because many finished products may contain small amounts of formaldehyde. It may not appear on the label though, as formaldehyde can be present in raw materials that may be released during storage and use. It is a challenge to inform and train formaldehyde-allergic patients how best to avoid exposure to formaldehyde and formaldehyde releasers because there are so many sources in the environment [22].

Immediate reactions from formaldehyde may also occur, both of presumably allergic and nonallergic nature [23].

Formaldehyde releasers used as preservatives in cosmetics and technical products are often concealed by trade names or synonyms (Table 13.3). The epidemiology of formaldehyde sensitisation requires re-evaluation. The patch test concentration has recently been recommended to be increased from 10,000 to 20,000 ppm in aqueous solution, and the T.R.U.E. Test contains 180 μg/cm^2.

The formaldehyde releaser, quaternium-15, is included in the European baseline series, while two other releasers, imidazolidinyl urea and diazolidinyl urea, are included in selected clinics. Chemically, they are linear or cyclic reversible

polymers of formaldehyde, and formaldehyde is released in different amounts, depending mainly on temperature and pH.

Allergic contact dermatitis from a formaldehyde-releasing agent may be due to the entire molecule, to formaldehyde, or to both.

Sensitive patients to formaldehyde should request cosmetics without formaldehyde releasers, even though some alternative formaldehyde releasers might be

Table 13.3 Formaldehyde releasers commercially available for patch testing (in alphabetic order)

	Suppliers			
Chemical name	Trolab®	Chemotechnique®	Brial®	allergEAZE®
Benzylhemiformal	1 % pet.	–	1 % pet.	1 % pet.
Bioban® CS 1135	–	1 % pet.	1 % pet.	1 % pet.
Bioban® CS 1246	–	1 % pet.	1 % pet.	1 % pet.
Bioban® P 1487	–	0.5 % pet.	1 % pet.	1 % pet.
2-Bromo-2-nitropropane-1,3-diol (bronopol)	0.5 % pet.	0.25 % and 0.5 % pet.	0.5 % pet.	0.5 % pet.
Diazolidinyl urea	2 % pet	1 % pet., 2 % pet. and 2 % aq.	2 % pet.	2 % pet.
1,3-Dimethyl-4,5-dihydroxy ethylene urea	–	4.5 % aq.	–	–
Dimethylol dihydroxy ethylene urea	–	4.5 % aq.	4.5 % aq.	4.5 % aq.
DMDM hydantoin	2 % aq.	1 % pet. and 2 % aq.	2 % aq.	1 % pet.
Ethylene urea	–	1 % pet.	2.5 % pet.	2.5 % pet.
Ethylene urea, melamine formaldehyde mix	–	5 % pet.	5 % pet.	5 % pet.
Imidazolidinyl urea	2 % pet.	2 % pet. and 2 % aq.	2 % pet.	2 % pet.
Melamine formaldehyde resin	–	7 % pet.	7 % pet.	7 % pet.
Methenamine (hexamethylenetetramine)	1 % pet.	2 % pet.	1 % pet.	1 % pet.
N,N′-methylenebis (5-methyloxazolidine)	1 % pet.	–	1 % pet.	1 % pet.
N-methylolchloracetamide	–	0.1 % pet.	–	–
Polyoxymethylene urea (urea-formaldehyde resin)	–	10 % pet.	10 % pet.	10 % pet.
Quatemium-15	1 % pet.	1 % and 2 % pet.	1 % pet.	1 % and 2 % pet.
Tris(*N*-hydroxyethyl) hexahydrotriazine	1 % pet.	1 % aq.	1 % pet.	1 % pet.
Tris(hydroxymethyl)nitromethane (Tris Nitro)	–	1 % pet.	–	–

tolerated due to reduced formaldehyde production. Full cosmetic ingredient labelling, as that required today, makes it easy to avoid the use of specific ingredients in sensitised subjects [24]. However, because of the many different formaldehyde-releasing preservatives on the market, it is difficult for many patients to read and comprehend the often extensive list of ingredients on cosmetic products and safety data sheets for industrial products.

13.3.4 Paraben Mix

The most widely used preservatives in foods, drugs and cosmetics are still the parabens (alkyl esters of *p*-hydroxybenzoic acid). Parabens were present in 58 of 67 skin creams (≈87 %) analysed chemically in Denmark [25]. This group of preservatives has been used for more than 60 years and includes methyl-, ethyl-, propyl- and butylparaben (INCI names). The parabens are most often used in combination due to their different solubility and action spectrum. They are less efficient against gram-negative bacteria; therefore, parabens are often used in cosmetic products in combination with other preservatives. Cross-reactions between the four paraben esters methyl-, ethyl-, propyl- and butylparaben are common. The parabens have come into miscredit due to their alleged effect as endocrine disrupters [26]. The EU scientific committee on consumer safety has concluded that parabens as used in cosmetic products are very safe (opinion on parabens, SCCS 1514/13). In diagnostic patch testing, Menné and Hjorth found that approximately 1 % of more than 8000 eczema patients tested were sensitised [27]. Similar frequencies are reported in other large-scale patch test studies [3]. The frequency of positive reactions has been remarkably constant over many years. In spite of the extensive use of parabens, it must be regarded as a very safe preservative in topical products and allergic contact dermatitis, as it is relatively rare. Clinical experience shows that the incidence of paraben sensitisation in healthy individuals is small and in line with the observation that occasional cases of paraben sensitivity occur and are important to the particular patient's welfare. Cosmetics seem to be an uncommon source of paraben sensitisation. Clinical experience shows that patients with chronic dermatitis are at risk, particularly patients with stasis dermatitis and leg ulcers. Alexander A. Fisher coined the term "paraben paradox", denoting the fact that many leg ulcer patients with a paraben allergy tolerate paraben-preserved cosmetics on healthy skin [28]. In spite of the low frequency of paraben contact allergy, it is important to keep the allergen in the baseline series, since it is difficult to verify the suspicion of the existence of paraben allergy. Often, the sufferers are patients with long-lasting dermatitis that do not get better under normal treatment and skin care. If the allergen is not included in the standard series, the diagnosis will be missed.

In the European standard series, the parabens are tested as a mix of 4000 ppm of methyl-, ethyl-, propyl- and butylparaben, a grand total of 16,000 ppm pet. In the T.R.U.E. Test, the concentration is 1000 μg/cm^2 (Table 13.1). Patch testing with products preserved with parabens is often negative in paraben-sensitised patients because the paraben concentration is too low to elicit dermatitis on normal skin, even under occlusive conditions.

The final details of the paraben story remain to be elucidated. Except for high concentration (i.e. >1 %) drug use and application to leg ulcers, the parabens are rare contact sensitisers. Combined with the extensive chronic toxicity data available on their systemic effects, these compounds set the standard for relative safety that new preservatives will have difficulty matching. However, the paraben mix is important in the baseline series because paraben allergy is difficult to detect from the history or clinical appearance of dermatitis.

Key Points for the Clinician

- Collect detailed information on exposure history and product information (contact the manufacturer and ask for the Product Safety Data Sheet (PSDS)). Be sure not to test a single preservative and expect it to be the only cause of the contact allergy – also look for the constituents in preservative mixes since these are often applied in products.
- Intermittent exposure to products containing the culprit preservative may explain chronic and recurrent dermatitis. Be aware that, e.g. isothiazolinones are marketed under many brand names.
- Many finished products may contain small amounts of formaldehyde. Formaldehyde can be present in raw materials that may be released during storage and use.
- Patch testing with products preserved with parabens is often negative in paraben-sensitised patients because the paraben concentration is too low to elicit dermatitis on normal skin, even under occlusive conditions.

Conclusion

Contact allergy to preservatives continues to be a dermatological problem, because preservative effects are needed in the majority of today's consumer products. Alternative preservatives replace the old ones. When advertisements claim that a product is preservative-free, it is a truth with limitations. In order to reduce preservative concentration in the product, manufacturers may include ingredients, which by themselves are not regarded as biocides but have preservative effects, e.g. propylene glycol or some essential oils and ethylhexylglycerin [29].

References

1. Andersen KE, White IR, Goossens A. Allergens from the standard series. In: Johansen JD, Frosch PJ, Lepoittevin JP, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011. p. 545–5902.
2. Andersen KE, Rycroft RJ. Recommended patch test concentrations for preservatives, biocides and antimicrobials. Contact Dermatitis. 1991;25(1):1–18.
3. Flyvholm MA. Preservatives in registered chemical products. Contact Dermatitis. 2005;53(1):27–32.
4. Mose AP, Lundov MD, Zachariae C, Menne T, Veien NK, Laurberg G, et al. Occupational contact dermatitis in painters: an analysis of patch test data from the Danish Contact Dermatitis Group. Contact Dermatitis. 2012;67(5):293–7.

5. Bruze M, Isaksson M, Gruvberger B, Andersen KE, Goncalo M, Goossens A, et al. Patch testing with methylchloroisothiazolinone/methylisothiazolinone 200 ppm aq. detects significantly more contact allergy than 100 ppm. A multicentre study within the European Environmental and Contact Dermatitis Research Group. Contact Dermatitis. 2014;71(1):31–4.
6. Lundov MD, Krongaard T, Menne TL, Johansen JD. Methylisothiazolinone contact allergy: a review. Br J Dermatol. 2011;165(6):1178–82.
7. Schnuch A, Lessmann H, Geier J, Uter W. Contact allergy to preservatives. Analysis of IVDK data 1996–2009. Br J Dermatol. 2011;164(6):1316–25.
8. Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy–growing epidemic. Contact Dermatitis. 2013;69(5):271–5.
9. Frosch PJ, Lahti A, Hannuksela M, Andersen KE, Wilkinson JD, Shaw S, et al. Chloromethylisothiazolone/methylisothiazolone (CMI/MI) use test with a shampoo on patch-test-positive subjects. Results of a multicentre double-blind crossover trial. Contact Dermatitis. 1995;32(4):210–7.
10. Mose AP, Frost S, Ohlund U, Andersen KE. Allergic contact dermatitis from octylisothiazolinone. Contact Dermatitis. 2013;69(1):49–52.
11. Madsen JT, Andersen KE. Further evidence of the methylisothiazolinone epidemic. Contact Dermatitis. 2014;70(4):246–7.
12. McFadden JP, Ross JS, Jones AB, Rycroft RJ, Smith HR, White IR. Increased rate of patch test reactivity to methyldibromo glutaronitrile. Contact Dermatitis. 2000;42(1):54–5.
13. Gruvberger B, Andersen KE, Brandao FM, Bruynzeel DP, Bruze M, Frosch PJ, et al. Patch testing with methyldibromo glutaronitrile, a multicentre study within the EECDRG. Contact Dermatitis. 2005;52(1):14–8.
14. Johansen JD, Veien N, Laurberg G, Avnstorp C, Kaaber K, Andersen KE, et al. Decreasing trends in methyldibromo glutaronitrile contact allergy–following regulatory intervention. Contact Dermatitis. 2008;59(1):48–51.
15. Jensen CD, Johansen JD, Menne T, Andersen KE. Methyldibromoglutaronitrile in rinse-off products causes allergic contact dermatitis: an experimental study. Br J Dermatol. 2004;150(1):90–5.
16. Zachariae C, Hall B, Cupferman S, Andersen KE, Menne T. ROAT: morphology of ROAT on arm, neck and face in formaldehyde and diazolidinyl urea sensitive individuals. Contact Dermatitis. 2006;54(1):21–4.
17. Scheman AJ, Carroll PA, Brown KH, Osburn AH. Formaldehyde-related textile allergy: an update. Contact Dermatitis. 1998;38(6):332–6.
18. de Groot A, White IR, Flyvholm MA, Lensen G, Coenraads PJ. Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. Part 2. Patch test relationship to formaldehyde contact allergy, experimental provocation tests, amount of formaldehyde released, and assessment of risk to consumers allergic to formaldehyde. Contact Dermatitis. 2010;62(1):18–31.
19. Jong CT, Statham BN, Green CM, King CM, Gawkrodger DJ, Sansom JE, et al. Contact sensitivity to preservatives in the UK, 2004–2005: results of multicentre study. Contact Dermatitis. 2007;57(3):165–8.
20. Uter W, Geier J, Land M, Pfahlberg A, Gefeller O, Schnuch A. Another look at seasonal variation in patch test results. A multifactorial analysis of surveillance data of the IVDK. Information Network of Departments of Dermatology. Contact Dermatitis. 2001;44(3):146–52.
21. Flyvholm MA, Hall BM, Agner T, Tiedemann E, Greenhill P, Vanderveken W, et al. Threshold for occluded formaldehyde patch test in formaldehyde-sensitive patients. Relationship to repeated open application test with a product containing formaldehyde releaser. Contact Dermatitis. 1997;36(1):26–33.
22. Noiesen E, Munk MD, Larsen K, Johansen JD, Agner T. Difficulties in avoiding exposure to allergens in cosmetics. Contact Dermatitis. 2007;57(2):105–9.
23. Andersen KE, Maibach HI. Multiple application delayed onset contact urticaria: possible relation to certain unusual formalin and textile reactions? Contact Dermatitis. 1984;10(4): 227–34.

24. de Groot AC, Flyvholm MA, Lensen G, Menne T, Coenraads PJ. Formaldehyde-releasers: relationship to formaldehyde contact allergy. Contact allergy to formaldehyde and inventory of formaldehyde-releasers. Contact Dermatitis. 2009;61(2):63–85.
25. Rastogi SC, Schouten A, De Kruijf N, Weijland JW. Contents of methyl-, ethyl-, propyl-, butyl- and benzylparaben in cosmetic products. Contact Dermatitis. 1995;32(1):28–30.
26. Bledzka D, Gromadzinska J, Wasowicz W. Parabens. From environmental studies to human health. Environ Int. 2014;67:27–42.
27. Menne T, Hjorth N. Routine patch testing with paraben esters. Contact Dermatitis. 1988;19(3):189–91.
28. Fisher AA. The paraben paradoxes. Cutis. 1973;12(6):830–2.
29. Andersen KE. Ethylhexylglycerin-a contact allergen in cosmetic products. Dermatitis. 2012;23(6):291.

Rubber

14

Vera Mahler

Contents

V. Mahler, MD
Department of Dermatology, University Hospital of Erlangen, Friedrich-Alexander-University of Erlangen-Nuremberg, Ulmenweg 18, Erlangen, Bavaria D-91054, Germany
e-mail: vera.mahler@uk-erlangen.de

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_14

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

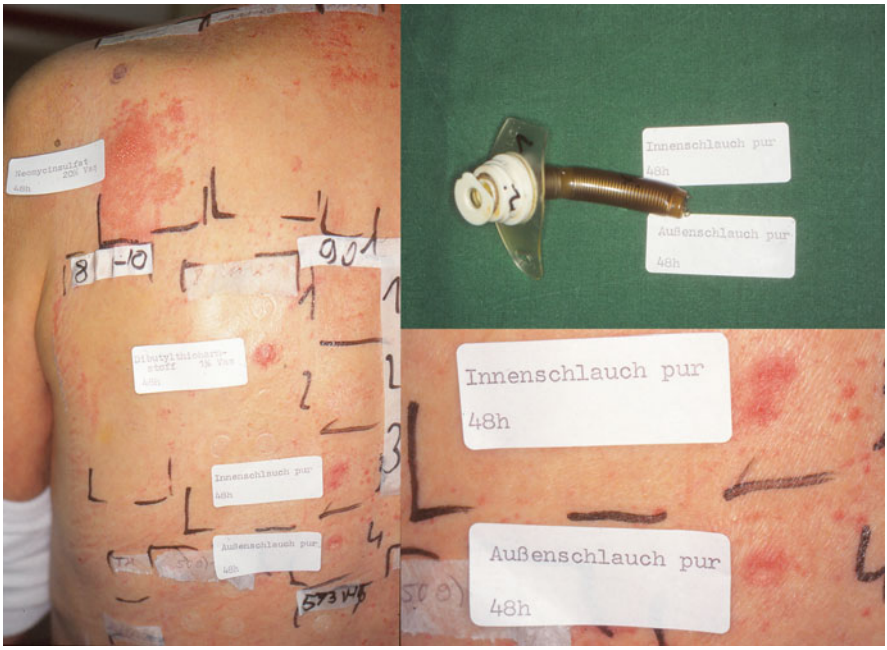


Fig. 14.1 Positive patch test reactions to dibutylthiourea, inner tube (Innenschlauch), and outer tube (Außenschlauch) of the tracheal cannula causing allergic contact dermatitis in a 56-year-old female patient with tracheostoma following surgery for hypopharyngeal carcinoma 6 year earlier. Additionally,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

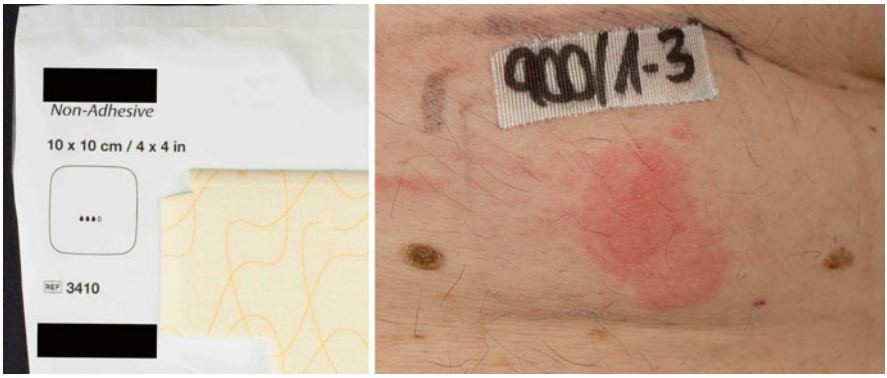


Fig. 14.2 Positive patch test reactions to a polyurethane wound dressing causing acute allergic contact dermatitis in a 70-year-old male patient. According to the manufacturer, no accelerators are used during the production process, and this case was the first case of contact dermatitis to this kind 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).

References

1. Adams AK, Warshaw EM. Allergic contact dermatitis from mercapto compounds. Dermatitis. 2006;17:56–70.
2. Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. J Allergy Clin Immunol. 2004;114:347–51.
3. Andersen BE. Mixed dialkyl thioureas. Dermatitis. 2009;20:3–5.
4. Andersen KE, Burrows D, Cronin E, Dooms-Goossens A, Rycroft RJ, White IR. Recommended changes to standard series. Contact Dermatitis. 1988;19:389–90.
5. Belsito DV. Rubber. In: Rustemeyer T, Elsner P, John SM, Maibach HI, editors. Kanerva's occupational dermatology. Heidelberg: Springer; 2012. p. 727–46.
6. Bergendorff O, Hansson C. Spontaneous formation of thiuram disulfides in solutions of iron (III) dithiocarbamates. J Agric Food Chem. 2002;50:1092–6.
7. Bruze M, Andersen KE, Goossens A. Recommendation to include fragrance mix 2 and hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) in the European baseline patch test series. Contact Dermatitis. 2008;58:129–33.
8. Busch M, Schröder C, Baron JM, Ott H, Bruckner T, Diepgen TL, Mahler V. Glove-derived foreign proteins induce allergen-specific IgE in a mouse model. J Invest Dermatol. 2008;128:890–6.
9. Cao LY, Taylor JS, Sood A, Murray D, Siegel PD. Allergic contact dermatitis to synthetic rubber gloves: changing trends in patch test reactions to accelerators. Arch Dermatol. 2010;146:1001–7.
10. Chipinda I, Hettick JM, Simoyi RH, Siegel PD. Oxidation of 2-mercaptobenzothiazole in latex gloves and its possible haptenation pathway. Chem Res Toxicol. 2007;20:1084–92.
11. Clemmensen KK, Carøe TK, Thomsen SF, Ebbehøj NE, Agner T. Two-year follow-up survey of patients with allergic contact dermatitis from an occupational cohort: is the prognosis dependent on the omnipresence of the allergen? Br J Dermatol. 2014;170:1100–5.
12. Diepgen TL, Dickel H, Becker D, John SM, Geier J, Mahler V, Rogosky E, Schmidt A, Skudlik C, Wagner E, Weisshaar E. Beurteilung der Auswirkung von Allergien bei der Minderung der Erwerbsfähigkeit im Rahmen der BK 5101: Thiurame, Mercaptobenzothiazole, Dithiocarbamate, N-Isopropyl-N-phenyl-p-phenylendiamin. Dermatol Beruf Umwelt. 2008;56:11–24.
13. 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 Dermat. 1995;6:143–9.
14. Geier J, Uter W, Schnuch A, Brasch J, German Contact Dermatitis Research Group (DKG). Diagnostic screening for contact allergy to mercaptobenzothiazole derivatives. Information network of departments of dermatolgy (IVDK). Am J Contact Dermat. 2002;13:66–70.
15. Geier J, Lessmann H, Uter W, Schnuch A, Information Network of Departments of Dermatology. Occupational rubber glove allergy: results of the Information Network of Departments of Dermatology (IVDK). Contact Dermatitis. 2003;48:39–44.
16. Geier J, Uter W, Schnuch A, Brasch J, Gefeller O. Both mercaptobenzothiazole and mercapto mix should be part of the standard series. Contact Dermatitis. 2006;55:314–6.
17. Geier J, Lessmann H, Mahler V, Pohrt U, Uter W, Schnuch A. Occupational contact allergy caused by rubber gloves – nothing has changed. Contact Dermatitis. 2012;67:149–56.
18. Hamilton RG, Adkinson Jr NF, Multicenter Latex Skin Testing Study Task Force. Diagnosis of natural rubber latex allergy: multicenter latex skin testing efficacy study. J Allergy Clin Immunol. 1998;102:482–90.
19. Hamilton RG, Rossi CE, Yeang HY, Bernstein DI, Biagini R. Latex-specific IgE assay sensitivity enhanced using Hev b 5 enriched latex allergosorbent. J Allergy Clin Immunol. 2003;111:S174.

20. Hansson C, Agrup G. Stability of the mercaptobenzothiazole compounds. Contact Dermatitis. 1993;28:29–34.
21. Hansson C, Pontén A, Svedman C, Bergendorff O. Reaction profile in patch testing with allergens formed during vulcanization of rubber. Contact Dermatitis. 2014;70:300–8.
22. IARC (International Agency for Research on Cancer). The rubber industries. IARC Monogr Eval Carcinog Risk Chem Hum. 1982;28:1–486.
23. Liippo J, Ackermann L, Hasan T, Laukkanen A, Rantanen T, Lammintausta K. Sensitization to thiourea derivatives among Finnish patients with suspected contact dermatitis. Contact Dermatitis. 2010;63:37–41.
24. Mahler V. Skin protection in the healthcare setting. Curr Probl Dermatol. 2007;34:120–32.
25. Mahler V, Gutgesell C, Valenta R, Fuchs T. Natural rubber latex and hymenoptera venoms share immunoglobin E-epitopes accounting for cross-reactive carbohydrate determinants. Clin Exp Allergy. 2006;36:1446–56.
26. Merget R, van Kampen V, Sucker K, Heinze E, Taeger D, Goldscheid N, Haufs MG, Raulf-Heimsoth M, Kromark K, Nienhaus A, Bruening T. The German experience 10 years after the latex allergy epidemic: need for further preventive measures in healthcare employees with latex allergy. Int Arch Occup Environ Health. 2010;83:895–903.
27. Pesonen M, Jolanki R, Larese Filon F, Wilkinson M, Krecisz Kiec-Swierczynska, Bauer A, Mahler V, John SM, Schnuch A, Uter W. Patch test results with the European baseline series in patients with occupational dermatitis across Europe – analyses of the ESSCA network, 2002–2010. Contact Dermatitis. 2015;72:154–63.
28. Raulf-Heimsoth M, Rihs HP, Rozynek P, Cremer R, Gaspar A, Pires G, Yeang HY, Arif SA, Hamilton RG, Sander I, Lundberg M, Brüning T. Quantitative analysis of immunoglobulin E reactivity profiles in patients allergic or sensitized to natural rubber latex (Hevea brasiliensis). Clin Exp Allergy. 2007;37:1657–67.
29. Simons FE, Ardusso LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF, Sanchez-Borges M, Senna GE, Sheikh A, Thong BY, Worm M, World Allergy Organization. World allergy organization anaphylaxis guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol. 2013;162:193–204.
30. Sullivan JB, van Ert M, Lewis R. Tire and rubber manufacturing industry. In: Sullivan JB, Krieger GR, editors. Clinical environmental health and toxic exposures. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 475–88.
31. Uter W, Aberer W, Armario-Hita JC, Fernandez-Vozmediano JM, Ayala F, Balato A, Bauer A, Ballmer-Weber B, Beliauskiene A, Fortina AB, Bircher A, Brasch J, Chowdhury MM, Coenraads PJ, Schuttelaar ML, Cooper S, Czarnecka-Operacz M, Zmudzinska M, Elsner P, English JS, Frosch PJ, Fuchs T, García-Gavín J, Fernández-Redondo V, Gawkrodger DJ, Giménez-Arnau A, Green CM, Horne HL, Johansen JD, Jolanki R, Pesonen M, King CM, Krêcisz B, Chomiczewska D, Kiec-Swierczynska M, Larese F, Mahler V, Ormerod AD, Peserico A, Rantanen T, Rustemeyer T, Sánchez-Pérez J, Sansom JE, Silvestre JF, Simon D, Spiewak R, Statham BN, Stone N, Wilkinson M, Schnuch A. 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.
32. Uter W, Hegewald J, Pfahlberg A, Lessmann H, Schnuch A, Gefeller O. Contact allergy to thiurams: multifactorial analysis of clinical surveillance data collected by the IVDK network. Int Arch Occup Environ Health. 2010;83:675–81.
33. van Kampen V, de Blay F, Folletti I, Kobierski P, Moscato G, Olivieri M, Quirce S, Sastre J, Walusiak-Skorupa J, Kotschy-Lang N, Müsken H, Mahler V, Schliemann S, Ochmann U, Sültz J, Worm M, Sander I, Zahradnik E, Brüning T, Merget R, Raulf-Heimsoth M. Evaluation of commercial skin prick test solutions for selected occupational allergens. Allergy. 2013;68:651–8.
34. von Hintzenstern J, Heese A, Koch HU, Peters KP, Hornstein OP. Frequency, spectrum and occupational relevance of type IV allergies to rubber chemicals. Contact Dermatitis. 1991;24:244–52.

35. von Krogh G, Maibach HI. The contact urticaria syndrome- an updated review. J Am Acad Dermatol. 1981;5:328–42.
36. Wagner S, Breiteneder H. Hevea brasiliensis latex allergens: current panel and clinical relevance. Int Arch Allergy Immunol. 2005;136:90–7.
37. Williams PJ, King C, Arslanian V. Allergic contact dermatitis caused by a cell phone cover. Australas J Dermatol. 2012;53:76–7.
38. Ylitalo L, Mäkinen-Kiljunen S, Turjanmaa K, Palosuo T, Reunala T. Cow's milk casein, a hidden allergen in natural rubber latex gloves. J Allergy Clin Immunol. 1999;104:177–80.

Part V

Allergens in Various Products

Textiles

15

Laura Malinauskiene and Kristina Morgardt-Ryberg

Contents

15.1 Introduction

Dyes are any substance, belonging to a class of colored complex compounds, used to color textiles and other materials so that the coloring is not readily altered by washing, light, or other factors to which a material is likely to be exposed. Coloring substances can be classified as dyes and pigments. Dyes differ from pigments,

L. Malinauskiene, MD, PhD
Department of Occupational and Environmental Dermatology, Lund University, Skåne University Hospital, Malmö S-205 02, Sweden

Department of Pulmonology and Allergology, Vilnius University Hospital Santariskiu Clinics, Santariskiu Str. 2, Vilnius LT-0861, Lithuania
e-mail: laura.malinauskiene@med.lu.se

K. Morgardt-Ryberg, MD, PhD (✉)
Department of Occupational and Environmental Dermatology, Lund University, Skåne University Hospital, Malmö S-205 02, Sweden

Department of Dermatology, Uddevalla Hospital, Fjällvägen 1, Uddevalla S-451 80, Sweden
e-mail: kristina.morgardt-ryberg@med.lu.se; kristina.ryberg@vgregion.se

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_15

which are finely ground solids dispersed in a liquid, such as paint or ink, or blended with other materials [1].

Dyes known to the ancients came from the nature, mostly from plants. In 1856 the first synthetic dye, mauve, was discovered by W. H. Perkin. Today most dyes are made from coal tar and petroleum chemicals.

15.2 When to Suspect Textile Dye Allergy: Clinical Signs and Differential Diagnosis?

In order to diagnose allergic contact dermatitis (ACD) from textile dyes, a high index of suspicion is required. Sometimes its appearance is not always confined to sites of direct contact. ACD to textiles most commonly develops on the extremities, followed by the trunk, face, genitalia, buttocks, and in the folds – the neck, armpits, and groin [2]. ACD generally occurs symmetrically on the sites of intimate contact with the garment (especially where friction or perspiration occurs).

Clinical features of ACD related to textile dyes frequently have unusual clinical patterns. It might present as urticarial dermatitis, diffuse itching, erythema multiforme-like eruptions, purpuric or nummular dermatitis, erythroderma, or pseudolymphoma [2, 3]. It could be so monomorphic and infiltrated that at first the diagnosis of ACD is not obvious [4].

15.3 Main Types of Dyes

Textile dyes can be classified by the chemical structure or by the method of application (Table 15.1). Classification according to the color is compiled in the *Colour Index* (C.I.), edited by the Society of Dyers and Colourists and by the American Association of Textile Chemists and Colorists [5, 6]. Each C.I. generic name covers all colorants with the same structure, but these are not necessarily identical products in terms of additive or impurity content.

While there are thousands of C.I. generic names, each manufacturer can invent a trade name for given colorants, and, consequently, there are more than 50,000 names of commercial colorants [1, 5, 6]. All this brings confusion in the identification of the dyes used by the consumer.

15.4 Main Allergens Among Textile Dyes

The main textile dye allergens belong to disperse dyes (DDs) – azo or anthraquinone types. At least 26 DDs are described as contact allergens in the scientific literature [2].

The prevalence of DD contact allergy varies depending on the population and the dyes tested. In those studies in which patients appeared for routine patch testing and DDs were included, prevalence values range from 0.4 to 6.7 %.

Table 15.1 Usage classification of dyes according to Ref. [1] with modifications

Dye class according to application	Main substrates	Dye classes according to chemical structure	Described as allergens
Acid	Nylon, wool, silk (also paper, inks, leather)	Azo, anthraquinone, triphenylmethane, azine, xanthenes, nitro, nitroso	Rare
Azoic	Cotton, rayon, cellulose acetate, PET	Azo	Rare
Basic	Polyacrylonitrile, modified nylon, PET (also paper, inks)	Cyanine, hemicyanine, diazahemicyanine, diphenylmethane, triarylmethane, azo, azine, xanthene, acridine, oxazine, anthraquinone	Rare (Basic Red 46 – important allergen in acrylic socks)
Direct	Cotton, rayon, nylon (also paper, leather)	Azo, phthalocyanine, stilbene, oxazine	Rare (some cases of immediate type allergic reaction)
Disperse	PET, polyamide, acetate, acrylic (also plastics)	Azo, anthraquinone, styryl, nitro, benzodifuranone	Most frequently
Mordant	Wool (also leather)	Azo and anthraquinone	Very rare
Reactive	Cotton, wool, silk, nylon	Azo, anthraquinone, phthalocyanine, formazan, oxazine, basic	Described only as occupational allergens
Solvent	Plastics, fuels, varnishes, lacquers, inks, oils, waxes	Azo, triphenylmethane, anthraquinone, phthalocyanine	Rare
Sulfur	Cotton, rayon	Indeterminate structures	Exceptionally rare/ none
Vat	Cotton, rayon, wool	Anthraquinone, indigoids	Exceptionally rare

Available data indicates that the prevalence of positive test reactions at least to three dyes (D Blue 106, 124, and D Orange 3) is over 1 % when screening dermatitis patients [2].

Some dyes are forbidden by the EU Commission as carcinogens and some are listed as "allergenic," but it is obvious that there are many more allergenic DDs.

15.5 How and What to Test?

1. Patch testing with *commercial textile dye preparations.*

   European baseline series are not suitable for the reliable detection of textile dye allergy. *p*-Phenylenediamine (PPD) once was considered a marker for allergy to disperse azo dyes, but recent studies point out frequent concomitant positive reactions to PPD and disperse azo dyes, which are not always due to cross-reactivity. It is discussed whether a textile dye mix made from several DDs should be included in the European baseline series. Testing with specialized series, created by commercial patch tests suppliers (e.g., Textile Colours &

Finish by Chemotechnique, Sweden), can be very helpful. Of note, patch testing with some dyes can result in *strong or very strong* (++/+++) *reactions*. Some positive reactions may be persistent and itching up to 3 weeks.

2. Testing with *the suspected garment* is very useful, but it is not standardized.
   There are several options how to do this.
   - Patch testing with the *piece of textile*. Pieces are cut from suspected garments according to the pattern of eczema. Textile should be moistened with a drop of water, put onto the back, and secured with an adhesive plaster (e.g., Mepore). It should be removed after 48 h and evaluated as ordinary patch tests.
   - Patch testing with an *extract from clothing* can be more sensitive than the clothing itself. Extract is made by cutting various parts of the garment which come in intimate contact with the lesional skin and put into the jar with a solvent (water, ethanol, or acetone). It could be left either for few days or put into ultrasonic bath to obtain an extract in few minutes. Then patch testing is performed and evaluated as usual.
     Negative patch tests with the suspected garment are frequent. Thus as much of the fabric as possible should be used for testing or making an extract.
   - *A challenge test* (stop and wear again) can also be used.

15.5.1 How to Select Objects to Test?

Identify all textile products that are in contact with the affected skin area. The most frequently "allergenic" textiles are made from synthetic fibers, but it has also been described ACD from white cotton. Long time/frequent use or outwear garments should also be included.

Fiber composition of the "culprit" textile might indirectly point out which dyes can be present in the garment. As DDs are not used to dye all types of synthetic fibers and not used for wool or cotton, a positive patch test reaction to a disperse azo dye and such a type of textile could not be related etiologically.

15.5.2 Is PPD a Good Screening Agent?

Para-amino compounds are known to cross-react with each other and with some azo DDs. Examples of the most common *para*-amino compounds are PPD, *p-aminobenzoic* acid, benzocaine, sulfanilamide, and the black rubber ingredients, e.g., N-isopropyl-N′-phenyl-4-phenylenediamine.

If patient is positive to PPD or other substances mentioned above, the possibility of textile dye allergy should be considered based on clinical data and history findings. If there is a suspicion of textile dye-induced ACD, negative patch test to PPD does not exclude allergy to textile dyes.

15.5.3 Are There Pitfalls in Testing?

Purity of the test preparations is an important issue. Differences also may occur from batch to batch as well as among different manufacturers [7]. It was shown that almost 25 % of patients allergic to commercial D Blue 106 and 124, D Yellow 3, or D Orange 1 did not react to (or not only to) the main dye but to other substances present in the dye preparation [8].

It is also possible that *dermatitis will flare up or even become generalized* even during patch testing with commercial dyes and extracts from the suspected garment [9]. So patch testing should be performed during remission of ACD.

Late readings of the testing (not only on day (D) 2 and D3/D4) should be performed as it is shown that up to 21 % of positive reactions to DDs appear on D7 and majority of them are clinically relevant [9, 10].

When establishing a *clinical relevance* of the positive patch test to the dye, either patch testing with the suspected fabric or with an extract should be done. Furthermore, the relevant dye in the textile should be detected (i.e., exposure to that dye confirmed) in the ideal settings.

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

Reading textile labels may be important as knowing fiber composition and care instructions can help guessing possible allergens. If it is advised to wash garments with the similar colors or in low temperature, it is possible that the dyes did not make strong bonds to the textile fibers; thus, they can migrate onto the skin and possibly sensitize. Besides patients may also look for the OEKO-TEX label which gives some kind of guarantee that the garment does not contain most of the known textile dye allergens.

Wearing white cotton/silk/linen is the best.

Box 15.1. A Checklist of What to Consider: Important Steps

1. Consider possible contact allergy to textile dyes if dermatitis appears on the symmetrical sites of intimate contact with the garment (especially where friction or perspiration occurs) or has unusual clinical patterns.
2. Perform patch testing with European baseline series and additional textile dye series if available.
3. Test with the garment(s).
   - Identify all colored textile products in contact with the affected skin area.
   - Select items for testing using fiber composition.

References

1. Hunger K. Important chemical chromophores of dye classes. In: Hunger K, editor. Industrial dyes: chemistry, properties, applications. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA; 2003. p. 13–4.
2. Malinauskiene L, Bruze M, Ryberg K, Zimerson E, Isaksson M. Contact allergy from disperse dyes in textiles: a review. Contact Dermatitis. 2013;68(2):65–75.
3. Lazarov A. Textile dermatitis in patients with contact sensitization in Israel: a 4-year prospective study. J Eur Acad Dermatol Venereol. 2004;18(5):531–7.
4. Dooms-Goossens A. Textile dye dermatitis. Contact Dermatitis. 1992;27(5):321–3.
5. Society of Dyers and Colourists, American Association of Textile Chemists and Colourists. The colour index international. 4th ed. online. Available from: http://www.colour-index.org.
6. SciFinder Scholar. CAS Registry Database. Available from: www.cas.org/products/scifindr/index.html.
7. Ryberg K, Gruvberger B, Zimerson E, Isaksson M, Persson L, Sorensen O, et al. Chemical investigations of disperse dyes in patch test preparations. Contact Dermatitis. 2008;58(4):199–209.
8. Ryberg K, Goossens A, Isaksson M, Gruvberger B, Zimerson E, Persson L, et al. Patch testing of patients allergic to Disperse Blue 106 and Disperse Blue 124 with thin-layer chromatograms and purified dyes. Contact Dermatitis. 2009;60(5):270–8.
9. Pratt M, Taraska V. Disperse blue dyes 106 and 124 are common causes of textile dermatitis and should serve as screening allergens for this condition. Am J Contact Dermat. 2000;11(1):30–41.
10. Aalto-Korte K, Alanko K, Kuuliala O, Jolanki R. Late reactions in patch tests: a 4-year review from a clinic of occupational dermatology. Contact Dermatitis. 2007;56(2):81–6.

Hair Dyes

16

John McFadden

Contents

16.1 Introduction

Hair dye allergy is one of the commonest forms of allergic contact dermatitis. Most contact dermatitis clinics report a rate of between 3 and 7 % positive to the standard screening agent, p-phenylenediamine (ppd) [1, 2], and although there have been few studies of the prevalence of hair dye contact allergy in the normal population, this figure may approximate in some countries to 1 % or more [3]. Hair dye allergy is commoner in Asia and also in Southern Europe compared to Northern Europe as darker hair dye contains more allergen [2]. In the normal population prevalence of hair dye allergy is commoner in females [3] except in countries where dyeing of male facial hair is common. The incidence of hair dye allergy increases with age, especially over 40 years.

PPD belongs to the family of chemicals known as aromatic amines which are used to dye hair. They have been in use for over 100 years [1]. Hair dye is used by

J. McFadden, BM, DM, FRCP
Department of Cutaneous Allergy, St John's Institute of Dermatology, St Thomas' Hospital, King's College, London SE1 7Eh, UK
e-mail: john.mcfadden@kcl.ac.uk

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_16

a significant number of all populations to both hide grey hair and, in the younger age group, for fashion.

Soon after their commercial introduction over 100 years ago, it was recognised that hair dye chemicals have the potential to cause allergic reactions. Whilst most hair dye preparations have other potential allergens, such as preservatives and fragrances, aromatic amines such as PPD are usually the dominant allergens in such reparations. The actual allergen is PPD or oxidised products of PPD [4]. PPD and other aromatic amines are amongst the most potent haptens in commercial use.

16.2 Clinical Presentation

As with most cosmetic allergens, dermatitis reactions occur through elicitation reactions, i.e. usually within 24–48 h. In subjects who are very sensitive, the reaction can appear within 2 h and be very oedematous and can be mistaken as angioedema. Reactions are commoner on the head and neck off the scalp rather than on the scalp itself (see Chap. 2).

The most commonly affected sites are:

1. Forehead
2. Ears and neck
3. Periorbital area

However, any area of the head and neck can be affected.

The reaction is usually erythematous, but there can be a significant amount of oedema and exudation. Facial oedema can be so severe that it is mistaken for angioedema (pseudoangioedema).

Reactions often occur after a change in the hair dyeing routine, e.g. a darker shade has been used or the dye has stayed on for longer. Predictive 'skin tests' used by hairdresser do not always detect allergy to hair dye and at present are not routinely recommended as the application of hair to the skin gives a risk of sensitisation.

Unusual forms of presentation include:

1. Lichenoid rash
2. Pigmented dermatitis
3. Erythema multiforme (both local and distal sites)
4. Discoid rash
5. Connubial contact dermatitis/contact dermatitis by proxy, there have been case reports of a partner developing unusual forms of allergic contact dermatitis (often on the trunk) to PPD where the source has been the partner's recently dyed hair (see Chap. 2).
6. Facial dermatitis from dyeing beard/moustache. Dyeing of beard/moustache/'sideburns' often leads to allergic contact dermatitis as the facial hair has to be dyed weekly (in comparison to once six monthly for scalp hair). The dermatitis is often of an acute nature.
7. Exacerbation of a pre-existing seborrhoeic or atopic dermatitis.

16.3 Occupational Cases

Allergic contact dermatitis is common amongst hairdressers and usually presents as hand dermatitis [5]. This often occurs early on in a hairdresser's career and can be present in the conjunction with irritant or endogenous dermatitis.

16.4 Temporary 'Henna' Beach Tattoo

These temporary henna tattoos usually contain PPD at very high concentrations (20 % compared to 2 % and less for normal hair dyes) and cause active sensitisation, with the tattoo area becoming severely eczematous and taking several weeks to settle down. Patch testing in this situation with 1 % PPD may induce a marked reaction, so it is advised that testing should be with a reduced concentration (0.01–0.1 %) [6]. These patients are usually exquisitely sensitive to hair dye and may also commonly cross-react with azo/clothing dyes (see Chap. 15).

16.5 Type 1 Hypersensitivity

This is rare, but several cases have been reported. In some cases there has been urticarial reactions and in others angioedema and in some cases constituting a medical emergency. However severe allergic contact dermatitis can mimic angioedema, coming on over a relatively short period of time, with severe facial oedema which can even cause external laryngeal pressure and difficulty in breathing (mimicking angioedema).

16.6 Irritant Reactions

The hair dyeing process is very alkaline and can cause immediate or delayed burning symptoms and/or irritant dermatitis.

16.7 Diagnosis (See Also Sect. 16.4 Above)

The usual screening agent is PPD 1 % in petroleum. This will detect 80–90 % of hair dye allergy cases. The addition of p-toluenediamine will detect a further 5–10 % of cases [2].

Some specialised centres have further chemicals which can be tested. For example, one series of 'extended hair dye chemicals' include m-aminophenol, p-aminophenol, resorcinol, 4-amino-2-hydroxytoluene, 1-hydroxyethyl-4,5-diamino pyrazole, HC blue no2, 2-methyl-5-hydroxyethylaminophenol and 2-methylresorcinol [2].

Although aromatic amines such as p-phenylenediamine and toluenediamine are the usual dominant allergens in hair dye preparations, other agents, such as

sulphites, fragrances, preservatives, persulphates and bleaching agents can also occasionally be the dominant allergen.

A final effort on identifying an allergen is to write to the manufacturer requesting samples for testing.

There is some controversy as to whether 1 % PPD should be included in the baseline series as there is the potential for occasionally inducing active sensitisation. Against this many cases of hair dye allergy would be missed if PPD were not in the baseline series as many patients do not give an obvious history consistent with hair dye allergic reactions but just present with dermatitis on the head and neck.

Further patch test points of note are:

1. If there is a history of either temporary henna tattoo exposure or severe hair dye reaction, patch testing should be performed initially at a lower concentration of PPD (usually between 0.01 and 0.1 %) in order to reduce the risk of a severe patch test reaction.
2. Occasionally a positive reaction may not come up until after 5 days.
3. A significant number of + reactions will not have a history of reacting to hair dye, though it would be expected that they will at some stage go on to develop clinical reactions, if they continue to dye their hair.
4. There is a small risk of active sensitisation with PPD 1 % (1 in 600 patch tests).
5. Self-reading of patch tests by patients (not recommended!) will often give a false-positive result, with the patient mistaking the black discolouration of the skin as a positive result.
6. Do not include the hair dye product in the patch test as this could increase chances of active sensitisation.

16.7.1 Cross-Reactions

p-Phenylenediamine and other aromatic amines can immunologically cross-react with other contact allergens:

1. Benzocaine, an ester caine used as a local anaesthetic topical agent especially for haemorrhoids.
2. Black rubber chemicals present in tyres, squash balls and handles.
3. The sunscreen agent para-aminobenzoic acid (which is not commonly used anymore).
4. Azo/clothing dyes. This is the commonest cross-reaction noticed, and, as with other cross-reactions, the frequency increases with increased PPD patch test reaction (+ or +++). Azo orange is the commonest cross-reactor. Patients with clothing dye sensitivity usually give a history of dermatitis in the groin, axillae or neck or with dye exposure from socks a rash on the feet (Chap. 15).

16.8 Management

Acute allergic contact dermatitis to PPD may necessitate the short-term use of oral steroids if there is a significant amount of oedema or exudation. Lesser cases can be treated with topical steroids.

There is a high degree of cross-reactivity between the different hair dye aromatic amines, and there is no obvious alternative than to advice discontinuation of dyeing.

Some hair dye allergic patients continue dyeing their hair, even when advised to give up; these can usually be found amongst patients with patch test + reactions [7]. From a medical point of view, this is not advisable as their sensitivity may increase and then result in severe reactions.

In one study all patch test +++ patients had to give up hair dyeing [7]. Some try to use lighter shades and avoid getting the dye onto non-hair-bearing skin.

There are active attempts by the industry to invent new, less allergenic hair dye systems.

References

1. McFadden JP, Yeo L, White J. Clinical and experimental aspects of allergic contact dermatitis to para-phenylenediamine. Clin Dermatol. 2011;29(3):316–24.
2. Søsted H, Rustemeyer T, Gonçalo M, Bruze M, Goossens A, Giménez-Arnau AM, Le Coz CJ, White IR, Diepgen TL, Andersen KE, Agner T, Maibach H, Menné T, Johansen JD. Contact allergy to common ingredients in hair dyes. Contact Dermatitis. 2013;69(1):32–9.
3. Søsted H, Hesse U, Menné T, Andersen KE, Johansen JD. Contact dermatitis to hair dyes in a Danish adult population: an interview-based study. Br J Dermatol. 2005;153(1):132–5.
4. White JM, Kullavanijaya P, Duangdeeden I, Zazzeroni R, Gilmour NJ, Basketter DA, McFadden JP. p-Phenylenediamine allergy: the role of Bandrowski's base. Clin Exp Allergy. 2006;36(10):1289–93.
5. Lyons G, Roberts H, Palmer A, Matheson M, Nixon R. Hairdressers presenting to an occupational dermatology clinic in Melbourne, Australia. Contact Dermatitis. 2013;68(5):300–6.
6. Ho SG, White IR, Rycroft RJ, McFadden JP. A new approach to patch testing patients with para-phenylenediamine allergy secondary to temporary black henna tattoos. Contact Dermatitis. 2004;51(4):213–4.
7. Ho SG, Basketter DA, Jefferies D, Rycroft RJ, White IR, McFadden JP. Analysis of para-phenylenediamine allergic patients in relation to strength of patch test reaction. Br J Dermatol. 2005;153(2):364–7.

Dental Materials

17

Marléne Isaksson

Contents

17.1 When to Suspect Dental Allergy in the Dental Professionals and the Dental Patients

Dental personnel are exposed to a variety of contact allergens, the most important being acrylates and methacrylates (here called acrylics), rubber additives, fragrances, formaldehyde, and metals. Dental professionals with occupational contact dermatitis present with foremost hand eczema even if facial eczema has been described and even respiratory symptoms [1]. The clinical picture of acrylic allergic contact dermatitis is predominantly eczema on the fingertips [2], usually affecting the first three fingers, but the lateral and dorsal aspects of the fingers and back of the hands may be affected [2] (Fig. 17.1). Signs and symptoms range from very dry skin

M. Isaksson, MD, PhD
Department of Occupational and Environmental Dermatology, Skåne University Hospital, Jan Waldenströms gata 16, level 5, Malmö, Skåne SE 205 02, Sweden
e-mail: Marlene.isaksson@med.lu.se

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_17

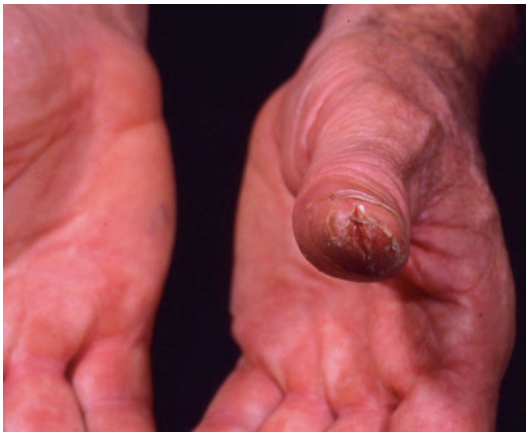


Fig. 17.1 A dentist with allergic contact dermatitis on his fingertips from 2-hydroxyethyl methacrylate (2-HEMA) in a bonding product. The dentist never wore gloves

with scaling, erythema, fissures, rhagades, vesicles, and bullae to pruritus, pain, stinging, burning, tingling, slight numbness of the fingertips, and reduced sensitivity. Mild paresthesia, which may persist for weeks or months after the dermatitis has subsided, may also develop without contact allergy. This is caused by a local effect of acrylics on the peripheral nerves without systemic neural effects [3]. Ectopic allergic dermatitis may present in the face and on the eyelids from contaminated hands or via airborne exposure [4].

In dental patients it is the mouth that is mostly affected if a contact allergy to a dental material is prevailing. The clinical picture is allergic contact stomatitis/gingivitis or cheilitis. In patients with clinical symptoms, the contact allergy frequency to denture base materials was 28 % [5, 6]. Contact allergy to acrylics is however uncommonly reported. It is delayed hypersensitivity to metals, cosmetics, food additives, flavors, and acrylates that dominates [1]. Clinical manifestations of gingivostomatitis are variable and include painful burning sensations in the mouth, local irritation, erythema, erosions, ulcerations, white plaques, mucosal swelling, sore mouth, and tingling. Clinical signs are often less pronounced than subjective symptoms. Allergic stomatitis is also rare [7]. Acrylics and metals such as mercury, gold, palladium, and manganese have caused stomatitis. Facial eruptions and systemic reactions can be seen. Diffuse erythema-like prosthesis stomatitis with stinging is seldom due to contact allergy but most often caused by *Candida albicans* in combination with an ill-fitting denture.

17.2 What Chemicals Should Be Tested When Suspecting Dental Materials?

17.2.1 Methacrylates and Acrylates

In particular methacrylates have been identified as major occupational contact sensitizers, both in dentists, dental nurses, and dental technicians. Three groups of acrylics are important in dentistry: (a) *monofunctional methacrylates* such as

methylmethacrylate (MMA) and 2-hydroxyethylmethacrylate (2-HEMA), the latter common in bonding products, both MMA and 2-HEMA are semi-volatile; (b) *multifunctional methacrylates* such as ethyleneglycol dimethacrylate (EGDMA), triethyleneglycol dimethacrylate (TREGDMA), and triethyleneglycol diacrylate (TREGDA); and (c) *acrylated and methacrylated prepolymers* such as 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]-propane (bis-GMA) and urethane dimethacrylate (UEDMA), the former in dentin bonding products and both present in dental filling materials [8].

Dental composite resins (DCRs) are the filling material in white plastic fillings, and the most commonly used dental composite resin (DCR) is bis-GMA. This substance can be manufactured by an addition-reaction between diglycidyl ether of bisphenol A (DGEBA) resin and methacrylic acid. Hence, bis-GMA can be classified as a dimethacrylated epoxy, even if it lacks a reactive epoxy group [8]. DCRs may as a result contain DGEBA resin as an impurity. Therefore, a person sensitized to DGEBA resin may react to bis-GMA or vice versa, especially if that individual has a very strong hypersensitivity to DGEBA resin and/or bis-GMA. This can be elucidated if the patient is patch tested to these two preparations in serial dilutions and reacts to very dilute concentrations [4].

Dentin bonding agents are plastics without fillers, called resins. They are used as an adhesive to make the white plastic filling stick to the cavity of the tooth. After etching the surface to be treated with 37 % phosphoric acid, the dentin is covered with the bonding agent, which is pressed out into the cavity with pressurized air. Polymerization is then accomplished by blue visible light, and subsequently the DCR is applied to the cavity of the tooth in layers and cured. Curing is performed either with chemicals or with the same light as above. 2-HEMA is most often present in bonding systems as it is water soluble and hence does not damage the pulp, but bis-GMA, TREGDMA, and UEDMA can also be present. Because bis-GMA may be used in dentin bonding agents, DGEBA resin may also be present as an impurity.

17.2.2 Metals

There are few metals that seem to be important in relation to dental patients and their signs and symptoms from the oral mucosa and lips. These metals are mercury, gold, nickel, palladium, and titanium. For the dental profession these metals do not pose a risk in the occupational setting.

17.2.2.1 Mercury

In many countries mercury in amalgams has been replaced by acrylics due to environmental risks and the public's opinion on worry of toxic effects. In Sweden it is prohibited to be used in dental practice since 2009. However, many people still have amalgams intraorally, and why this substance must be patch tested in dental patients. A Swedish study reported 9.3 % contact allergy to mercury in 1364 dental patients during a period of 11 years. The most common reasons for referral from the dentists were oral lichenoid lesions (39 %) and inflammation in the oral mucosa

(16 %), whereas the most common subjective symptoms were burning sensation in the oral mucosa (13 %) [9]. Over 30 % of the mercury contact allergies would have been missed had not a day 7 reading been performed. In a recent study of 134 patch-tested dental patients, mercury allergy was noted in 9.9 %. Amalgam fillings may cause lichenoid lesions in the mouth as a contact reaction with or without contact allergy.

17.2.2.2 Gold

Contact allergy to gold is very common in dental patients, even in the oral absence of signs of contact allergy. A frequency around 25 % has been reported [10]. Studies have shown that there is a statistically significant correlation between dental gold and gold allergy. There is also a quantitative relationship between contact allergy to gold and the amount of gold areas in the oral cavity. A patient allergic to gold should not have new gold restorations fitted in their mouth, but removal of gold restorations in an allergic patient without apparent signs of contact allergy should not be done automatically. Metallic gold in crowns and other restorations has caused allergic contact stomatitis and gingivitis [11] (Fig. 17.2).

17.2.2.3 Nickel

Even if nickel allergy is common in the general population, it does not give any major problems when it comes to dental materials, as nickel is not used in permanent dental materials such as casting alloys in Sweden. However, in other countries, nickel has been used in such alloys without any major problems even in nickel-allergic individuals. As nickel and cobalt often are present in the same alloy, it is difficult to separate the two. Therefore nickel alloys often contain small amounts of cobalt (less than 1 %) and vice versa. If more than 0.1 % nickel is present in an alloy, it must be declared, but alloys containing less than 0.1 % nickel are considered nickel-free. In orthodontic alloys that are meant to be used only temporary, such as used in wires and brackets, stainless steel containing 18 % chromium and 8 % nickel is mostly used, but one may also use nickel-titanium thread, containing 54 % nickel and 46 % titanium. Orthodontic treatment with nickel-containing material in the mouth prior to ear piercing (nickel sensitization) does not seem to sensitize but

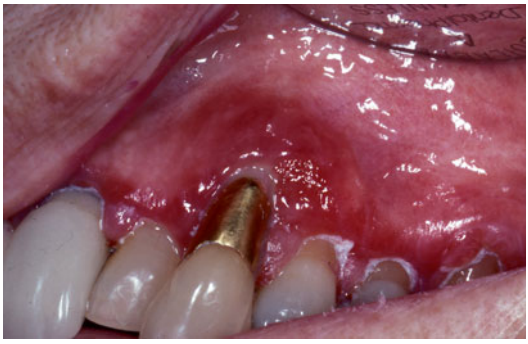


Fig. 17.2 A patient with gingivitis due to gold allergy. The patient has a metal ceramic crown containing gold

rather give tolerance, and adverse reactions in nickel-allergic patients with orthodontic appliances containing nickel are uncommon [12].

17.2.2.4 Palladium

Palladium is one of the platinum group metals in the periodic table of elements. It is also resistant to corrosion. Palladium is a very common component of dental casting alloys of all types, e.g., together with dental gold, silver, zinc, and copper [1], in dental plates and as a catalyst in white gold. However, the risk of using palladium in dental casting alloys appears to be extremely low due to the low dissolution rate of the palladium ions from these alloys [13]. This can be interpreted such that even allergic patients tolerate these alloys. Thirty percent of those allergic to nickel react to palladium when patch tested, especially those with a strong contact allergy to nickel. Cross-reactivity between the two metals has been proposed and also shown in a scientific study when nickel was administered systemically [14]. The clinical significance of allergic reactions caused by palladium remains unclear, and only a few cases on contact allergy and allergic symptoms from palladium have been published.

17.2.2.5 Titanium

Dental implants based on titanium have been used since decades. Titanium allergy among dental patients is considered more or less nonexisting, even if some reports indicate that titanium may act as an allergen [15]. A retrospective study on dental patients tested to three titanium preparations (calcium titanate 10.0 % pet, elemental titanium as powder 50 % pet, titanium nitride 5.0 % pet) during 11 years and titanium oxalate 5.0 % pet for 1 year revealed 1 patient out of 1373 to react to calcium titanate on day 7 and not on day 3. There were 31 doubtful reactions in total. The authors concluded that titanium does not seem to sensitize dental patients and that it can be recommended for dental implants and frameworks for removable partial dentures [16].

17.3 Indications for Patch Testing: Who Should Be Patch Tested and When?

In dental professionals those with evident or suspected occupational contact dermatitis or worsening of an endogenous dermatitis in dental work should at least be patch tested with the baseline series and a dental series to find contact allergies or to out-rule them.

For dental patients, there are three major indications for patch testing:

1. When a patient has objective signs in the oral mucosa localized next to a dental restorative material and when the clinical picture is a lichenoid reaction or when there is a strong suspicion of contact allergy to a dental restorative material.
2. When a patient has a history of dermatitis in the face or elsewhere on the body and when there is a temporal relation to some dental treatment.

3. When a patient is going to have a major dental restorative treatment and there is a history of intolerance to dental materials that will be used to out-rule contact allergy.
4. A relative indication is the burning mouth syndrome.

In the burning mouth syndrome, physical signs of mucosal disease are missing, and patch testing is usually negative [17, 18], even though one study showed that 6 of 22 to have contact allergy to acrylics [19]. Most patients are denture wearers and some have infection with *Candida albicans*. Some consider "psychological factors" to be the most important [1]. In denture wearers with previous allergic diseases and the burning mouth syndrome, a high incidence of allergic skin reactions to denture allergens, especially methacrylates and formaldehyde, has been reported [20].

17.4 Which Dental Materials Should Be Tested and How Should the Test Procedure Be Carried Out?

A dental patient should be patch tested to a commercial dental patch test series. To date only few companies supply such a series. Two examples are Chemotechnique Diagnostics, Vellinge, Sweden, and Trolab Hermal, Hamburg, Germany.

The Swedish Contact Dermatitis Research Group has suggested two different dental series, based on previous patch test data from 15 Swedish clinics, one for the investigation of dental patients and one for the dental personnel (Tables 17.1 and 17.2). Dental personnel with suspected contact dermatitis from dental materials should be patch tested with a dental series plus a baseline series, whereas in dental patients a dental series is sufficient. Sometimes it may be difficult to judge the clinical relevance between a positive test and the dental patient's signs and symptoms. The connection is best judged by the patient's dentist in cooperation with the dermatologist.

In Malmö we have seen that 2-HEMA would have picked up all our dental personnel looking at figures 10 years back and that 2-HEMA in addition to bis-GMA would have picked up all of our dental patients [21]. Over time the frequencies for

Table 17.1 The dental screening series for dental personnel as recommended by the Swedish Contact Dermatitis Research Group

Number	Test substance	Concentration % w/w
1.	Methyl methacrylate	2.0
2.	Triethyleneglycol dimethacrylate	2.0
3.	Ethyleneglycol dimethacrylate	2.0
4.	bis-GMA	2.0
5.	2-Hydroxyethyl methacrylate	2.0
6.	Tetrahydrofurfuryl methacrylate	2.0
7.	1,4-Butanediol methacrylate	2.0
8.	Mercury	0.5
9.	Eugenol	2.0
10.	Glutaraldehyde	0.2

Vehicle is petrolatum

Table 17.2 The dental screening series for dental patients as recommended by the Swedish Contact Dermatitis Research Group

Number	Test substance	Concentration % w/w
1.	Methyl methacrylate	2.0
2.	Triethyleneglycol dimethacrylate	2.0
3.	Ethyleneglycol dimethacrylate	2.0
4.	bis-GMA	2.0
5.	bis-EMA	2.0
6.	2-Hydroxyethyl methacrylate	2.0
7.	N,N-Dimethylaminoethyl methacrylate	0.2
8.	Tetrahydrofurfuryl methacrylate	2.0
9.	1,4-Butanediol methacrylate	2.0
10.	1,6-Hexanediol diacrylate	0.1
11.	Potassium dichromate	0.5
12.	Mercury	0.5
13.	Cobalt chloride	0.5
14.	Gold sodium thiosulfate	2.0
15.	Nickel sulfate	5.0
16.	Eugenol	2.0
17.	Colophony	20.0
18.	N-Ethyl-4-toluenesulfonamide	0.1
19.	Palladium chloride	2.0
20.	R-carvone	5.0
21.	2-(2′-Hydroxy-5′-methylphenyl)-benzotriazole	1.0
22.	*Myroxylon pereirae*	25.0
23.	Epoxy resin of bisphenol A	1.0

Vehicle is petrolatum
Reprinted with kind permission of Springer Science+Business Media

the various allergens change [22]. Hence, no single abbreviated series could be recommended for different centers.

Acrylic products often contain undeclared acrylates/methacrylates, and the material safety data sheets are often inadequate. This means that if a clinic tests with acrylic products, they must be very careful when choosing the test concentration. To be on the safe side, the product may be diluted to 0.1 % if the declaration says it contains acrylates and to 2.0 % if it says methacrylates.

When it comes to the test chamber material, it is important that the chamber is made of plastic, as, e.g., the aluminum in a Finn Chamber may act as a catalyst facilitating polymerization if the acrylic monomers are close enough together [23]. This could happen if the acrylic material is diluted in a liquid such as acetone or some other solvents and not in a more solid material such as petrolatum.

Acrylates and methacrylates are volatile substances and therefore may evaporate from the patch test preparation [24–26]. This means that preloading of test chambers may lead to false-negative reactions in an allergic patient. The evaporation is higher in those acrylates/methacrylates that have a high vapor pressure. Therefore,

preloading of test chambers should never be carried out. Also, acrylic test preparations should be kept in the refrigerator or better in the freezer, when not used for patch testing. This will diminish the evaporation substantially.

Patch test readings should be carried out on day 3 or 4 and also on day 7 (late reading), as allergic reactions to acrylics [27], gold [28], and mercury [1, 9] have a tendency to appear after day 4, i.e., late. Concerning mercury, 30 % of the contact allergy would have been missed if no day 7 reading would have taken place [9]. For 2-HEMA our figures would have been 25 % missed reactions if no day 7 reading had taken place [21].

17.5 Patch Test Sensitization

Acrylics are strong allergens and should never be applied undiluted to the skin. A single exposure can induce sensitization [29]. Acrylate products can usually be tested in 0.1 % and methacrylate products in 2.0 %. A dental patient was actively sensitized to acrylics by her dentist who performed a "use test" on intact skin with undiluted glass ionomer containing 2-HEMA [29].

17.6 Key Message

Acrylics are strong allergens and should never be tested undiluted. Acrylate products can usually be tested in 0.1 % and methacrylate products in 2.0 %. Use a plastic test chamber, and never preload the patch test chambers with (meth) acrylates, but apply the test preparations to the chambers right before the application to the patient's back, and perform the patch test readings both day 3 or 4 and day 7. No single abbreviated acrylate test series can be recommended for different centers because over time the frequencies for the various allergens change.

17.7 Checklists

1. Use a commercial dental series for patch testing the dental patients – both the professionals and the dental patients with oral symptoms.
2. Never patch test with commercial (meth)acrylate products undiluted. If testing acrylates, the total acrylate test concentration should not exceed 0.1 %, and if testing methacrylates, the total methacrylate test concentration should not exceed 2.0 %.
3. Never preload the patch test chambers with (meth)acrylates.
4. Patch test with plastic chambers when patch testing to (meth)acrylates.
5. Always read patch tests on day 3 or 4 and also on day 7.

References

1. Gawkrodger DJ. Investigation of reactions to dental materials. Br J Dermatol. 2005; 153:479–85.
2. Rustemeyer T, Frosch PJ. Occupational skin diseases in dental laboratory technicians. (I). Clinical picture and causative factors. Contact Dermatitis. 1996;34:125–33.
3. Kanerva L, Mikola H, Henriks-Eckerman ML, Jolanki R, Estlander T. Fingertip paresthesia and occupational allergic contact dermatitis caused by acrylics in a dental nurse. Contact Dermatitis. 1998;38:114–6.
4. Isaksson M, Zimerson E, Svedman C. Occupational airborne allergic contact dermatitis from methacrylates in a dental nurse. Contact Dermatitis. 2007;57:371–5.
5. Kaaber S, Thulin H, Nielsen E. Skin sensitivity to denture base materials in the burning mouth syndrome. Contact Dermatitis. 1979;5:90–6.
6. Wakkers-Garritsen BG, Timmer LH, Nater JP. Etiological factors in the denture sore mouth syndrome: an investigation of 24 patients. Contact Dermatitis. 1975;1:337–43.
7. Tosti A, Piraccini BM, Peluso AM. Contact and irritant stomatitis. Semin Cutan Med Surg. 1997;16:314–9.
8. Kanerva L, Estlander T, Jolanki R. Occupational skin allergy in the dental profession. Dermatol Clin. 1994;12:517–32.
9. Jalili S, Bruze M, Isaksson M. Contact allergy to mercury in dental amalgam. Elective study, Faculty of Medicine, Lund University, Malmö; 2008.
10. Isaksson M. Dental materials. In: Duus Johansen J, Frosch PJ, Lepoittevin J-P, editors. Contact dermatitis. 5th ed. Heidelberg: Springer; 2011. p. 763–91.
11. Laeijendecker R, van Joost T. Oral manifestations of gold allergy. J Am Acad Dermatol. 1994;30:205–9.
12. Kerosuo H, Kullaa A, Kerosuo E, Kanerva L, Hensten-Pettersen A. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. Am J Orthod Dentofacial Orthop. 1996;109:148–54.
13. Wataha JC, Hanks CT. Biological effects of palladium and risk of using palladium in dental casting alloys. J Oral Rehabil. 1996;23:309–20.
14. Hindsén M, Spirén A, Bruze M. Cross-reactivity between nickel and palladium demonstrated by systemic administration of nickel. Contact Dermatitis. 2005;53:2–8.
15. Schweitzer A. Erstfeststellung einer Titan-Allergie. Dermatosen. 1997;45:190.
16. Jalili S, Bruze M, Isaksson M. 11 years of patch testing with titanium in the dental series. Abstract European Society of Contact Dermatitis meeting, Estoril; 2008.
17. Helton J, Storrs F. The burning mouth syndrome: lack of a role for contact urticaria and contact dermatitis. J Am Acad Dermatol. 1994;31:201–5.
18. Virgili A, Corazza M, Trombelli L, Arcidiacono A. Burning mouth syndrome: the role of contact hypersensitivity. Acta Derm Venereol. 1996;76:488–90.
19. Dutree Meulenberg RO, Kozel MM, van Joost T. Burning mouth syndrome: a possible etiological role for local contact hypersensitivity. J Am Acad Dermatol. 1992;26:935–40.
20. Kaaber S. Allergy to dental materials with special reference to the use of amalgam and polymethylmethacrylate. Int Dent J. 1990;40:359–65.
21. Goon AT, Isaksson M, Zimerson E, Goh CL, Bruze M. Contact allergy to (meth)acrylates in the dental series in southern Sweden: simultaneous positive patch test reaction patterns and possible screening allergens. Contact Dermatitis. 2006;55:219–26.
22. Goon ATJ, Bruze M, Zimerson E, Goh CL, Isaksson M. Contact allergy to acrylates/methacrylates in the acrylate and nail acrylics series in southern Sweden: simultaneous positive patch test reaction patterns and possible screening allergens. Contact Dermatitis. 2007;57:21–7.
23. Bruze M, Björkner B, Lepoittevin JP. Occupational allergic contact dermatitis from ethyl cyanoacrylate. Contact Dermatitis. 1995;32:156–9.

24. Goon AT, Bruze M, Zimerson E, Sörensen O, Goh CL, Koh DS, et al. Correlation between stated and measured concentrations of acrylate and methacrylate allergens in patch-test preparations. Dermatitis. 2011;22:27–32.
25. Goon AT, Bruze M, Zimerson E, Sörensen Ö, Goh CL, Koh DS, et al. Variation in allergen content over time of acrylates/methacrylates in patch test preparations. Br J Dermatol. 2011;164:116–24.
26. Goon AT, Bruze M, Zimerson E, Sörensen O, Isaksson M. Effect of air transport on acrylate/methacrylate allergens in syringes and IQ chambers. Contact Dermatitis. 2010;63:297–8.
27. Isaksson M, Lindberg M, Sundberg K, Hallander A, Bruze M. The development and course of patch-test reactions to 2-hydroxyethyl methacrylate and ethyleneglycol dimethacrylate. Contact Dermatitis. 2005;53:292–7.
28. Bruze M, Hedman H, Björkner B, Möller H. The development and course of test reactions to gold sodium thiosulfate. Contact Dermatitis. 1995;33:386–91.
29. Kanerva L, Lauerma AI. Iatrogenic acrylate allergy complicating amalgam allergy. Contact Dermatitis. 1988;38:58–9.

Shoes

18

Sherry H. Yu, Apra Sood, and James S. Taylor

Contents

18.1 Epidemiology

Allergic contact dermatitis (ACD) of the feet is fairly common, and data on its prevalence range from 1.5 to 12 % in the general population [1, 2, 4, 6]. Approximately 10 % of the patients presenting for patch testing have foot dermatitis [3], and the feet are one of the most common sites for contact dermatitis in children [2]. Shoe allergy is more common in warm, humid climates [3] and is the most common source of ACD in India [1, 5].

S.H. Yu, BS, BA
Department of Dermatology, Case Western Reserve University School of Medicine,
Room T408, 10900 Euclid Avenue, Cleveland, OH 44106, USA
e-mail: sherry.yu@case.edu

A. Sood, MD • J.S. Taylor, MD (✉)
Dermatology-Plastic Surgery Institute, Cleveland Clinic,
9500 Euclid Ave, Cleveland, OH 44120, USA
e-mail: sooda1@ccf.org; taylorj@ccf.org

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_18

18.2 Risk Factors

Major risk factors for shoe dermatitis include heat, friction, occlusion, sweating, and atopy [4, 7]. Our feet have the highest concentration of eccrine glands on the plantar surface, which increases maceration of the skin and absorption of chemicals [8]. Allergens leach from shoes in the setting of heavy sweating and traverse clothing to contact skin [1]. Thus, military personnel, sportsmen, and others who wear heavy, non-breathable footwear are at especially high risk of developing ACD to shoe allergens [1].

18.3 Clinical Presentation and Clues

Patients with intermittent or chronic isolated foot dermatitis should be considered as having ACD to shoe allergens until proven otherwise [1].

Shoe dermatitis often has sudden onset with a history of reaction to a new pair of shoes [1]. Clinical manifestations include erythema, papules, vesicles and/or blisters, with oozing, scaling, and crusting at the sites of contact [1]. Lichenification and hyperpigmentation may occur in chronic cases [1].

Any part of the foot may be affected by ACD to shoes; it is frequently localized to the dorsa of the feet and toes, sparing the interdigital spaces [1, 4, 6, 7, 9]. The dorsal foot has a large surface area and thin stratum corneum, as well as prolonged exposure to the shoe. The lesions are often accentuated around the metatarsophalangeal joints, over the central dorsal aspect of the foot, or over the plantar aspect of the foot [1]. The calves and shins may be affected in patients wearing boots. Bilateral, symmetrical dermatitis is often found with sparing of the thicker-skinned heel area, side of the foot, instep, and flexural creases of the toes [1, 4].

It is often difficult to determine causative allergens, but initial presentation may provide clues for patch testing to a specific group of chemicals [1]. Dorsal foot dermatitis should lead a clinician to suspect allergy to the shoe upper or tongue. Plantar dermatitis suggests allergy to the insole, shoe lining, or adhesive. Instep involvement may suggest athletic shoe dermatitis or eczema. Interdigital dermatitis is most likely a microbial infection [1].

18.4 Differential Diagnosis

Shoe allergy can mimic or be superimposed on other foot dermatoses often leading to diagnostic delay [7, 8]. ACD to 2-mercaptobenzothiazole (MBT) may simulate palmoplantar psoriasis or pustular psoriasis [1]. Leukoderma can also be associated with shoe dermatitis and is most commonly seen in developing countries where monobenzyl ether of hydroquinone in rain shoes has been found to cause dorsal foot depigmentation [1].

Allergy to textile dyes has been reported to comprise up to 10 % of foot dermatitis and is related to the ease with which dyes leach from shoes [1]. Shoe dermatitis

may also be mistaken for sock or stocking allergy caused by disperse and non-disperse azo dyes.

ACD of the feet may also be iatrogenic, resulting from topical medications used to treat other foot dermatoses. Topical antibiotics, including neomycin and bacitracin, corticosteroids, NSAIDs, antimycotics, or any other topical cosmetic or pharmaceutical component can all lead to ACD of the feet [1, 4, 8].

Foot dermatitis that presents with hand dermatitis may have a systemic, endogenous cause, such as dietary metal sensitivity [9]. This presentation may also be due to exposure to personal care products, occupational exposure, or hobby exposure. When the hands and feet are the only affected areas, clinicians should also suspect psoriasis, hyperkeratotic eczema, and chronic vesicular dermatitis, in addition to allergic contact dermatitis [9].

In young children, usually aged 3–14, juvenile plantar dermatosis (JPD) should be considered. JPD characteristically presents with symmetrical glazed skin with significant cracking in weight-bearing areas, sparing the interdigital spaces. It is associated with pain and erythema, usually with pruritus, and is thought to be the result of excessive sweating and overdrying of the feet in children with a history of atopy [1]. JPD is made worse by modern occlusive footwear. Patch tests and fungal scrapings are consistently negative in these patients. Atopic eczema, JPD, and ACD represent the majority of pediatric cases of dermatoses affecting the soles [3]. As with adults, ACD of the feet may be superimposed on other foot dermatoses. One study found that 29 % of children with JPD and 76 % of children with a family history of atopy had at least one relevant positive patch test reaction [3].

Other diagnoses to consider include irritant contact dermatitis, atopic eczema, tinea pedis, lichen planus, and dyshidrotic eczema, each of which may be superimposed on ACD to shoe components [1, 3–5].

18.5 Common Shoe Allergens

Table 18.1 shows common shoe allergens and the sites that are commonly affected [1, 4, 9].

It is nearly impossible to identify all constituents of a shoe [1], as components may gradually change as shoe manufacturing, fashion, and technology evolve [5, 9]. Leather and shoe dyes were the most common shoe allergens in the early twentieth century [1]; however, chromium compounds, used for leather and non-leather synthetic uppers are still the most important shoe allergens throughout Europe and India [1, 4, 5, 10]. In the USA, Canada, Brazil, and Asia, rubber allergens have predominated shoe allergy since the 1950s [1]. Overall, the most common allergens to consider in patients with allergic contact dermatitis of the feet include constituents of rubber, leather adhesives, and less commonly, shoe linings and dyes .

The most important allergens include para-tertiary-butylphenol formaldehyde resin (PTBPF-R), mercaptobenzothiazoles (MBT), thiurams, potassium dichromate, colophony, and PPDA derivatives [1, 5, 7, 8]. Components containing rubber resins, including heel and toe counters and leather finish coats, may include MBT or

Table 18.1 Comparison of top shoe-derived allergens, with distribution, shoe component, and possible sources

Allergen	Location	Shoe component	Avoid
Mercaptobenzothiazole and thiurams	Dorsum of foot sparing webspace	Rubber Neoprene adhesives Leather finish coats	Rubber foam uppers + insoles
Dibenzothiazyl disulfide (MBT mix)	Sole of foot	Solid or adhesive neoprene Rubber	Sock lining adhesive Rubber soles and heels Rubber insole
Thioureas	Sole of foot	Solid or foam neoprene	Insoles
Chromium	Whole foot	Leather tanning	Leather, athletic shoe uppers
Formaldehyde	Whole foot	Leather tanning Biocides	Lutidine-positive leather (spot test for formaldehyde) and soft perspiration-proof leather
Cobalt and nickel	Dorsum of foot	Metal trim	Decorative items and trim on shoes
Para-tertiary-butylphenol formaldehyde resin	Sole of foot	Tackifying resin	Neoprene adhesives Heel and toe counters
Colophony	Sole of foot	Tackifying resin	Neoprene adhesives Heel and toe counters

thiurams [1]. One retrospective study found that positive patch test reactions to potassium dichromate, PTBPF-R, mercapto mix, and MBT were significantly associated with foot dermatitis, as opposed to dermatitis of other body areas [8]. Similarly, in another retrospective study PTBPF-R, potassium dichromate, and carba and thiuram mixes were identified as the most common positive patch test allergens identified in patients with primary foot dermatitis [2].

PTBPF-R has been used as an adhesive in rubber glues since the 1950s and was found to be the most common individual shoe allergen in a recent USA study [1, 2] Currently, it is found as a component of neoprene adhesives used for shoe linings. Glues containing this allergen are also found in other leather products including watch straps, handbags, building materials, and electrical products. PTBPF-R is commonly found in shoe lining and insole glues and, along with chromate, is an important allergen to consider in persons wearing orthopedic shoes and using prostheses [1].

Colophonium and modified colophonium are also found in heel and toe stiffeners; rubber latex and neoprene adhesives are used to glue insoles and linings in place [1, 6, 11]. Colophonium is a mixture of over 100 compounds derived from pine trees, and the resin acids contained are easily oxidized, becoming allergenic. Allergic patients should be counseled to wear unlined shoes or shoes with stitched linings; it is very difficult to find any lined shoe free from these tackifiers [11].

Leather is often tanned with trivalent chromium (Cr(III)) to maintain suppleness and durability. Hexavalent chromium (Cr(VI)) can occur as an impurity, is a potent sensitizer, and is the chromate used in patch testing [2, 10]. Contact allergy to chromium often results in particularly severe foot dermatitis. The incidence of chromium allergy was found to have significantly increased between 1995 and 2007 in Europe,

most likely due to increasing leather shoe exposure, especially in women [4, 10]. In fact, in July 2007 the German Risk Assessment Institute (Bundesinstitut für Risikobewertung) recommended reducing the use of chromium salts in leather production as much as possible [10]. Beginning in 2015 the European Union will no longer allow leather shoes to be sold which contain more than 3 mg/kg chromium VI.

Other common shoe allergens include formaldehyde (used in leather tanning) and nickel, which is found in decoration and trim or buckles [1]. Metal salts like nickel and cobalt may be found in plastic footwear worn by medical personnel [1, 4, 12]. A recent report [12] suggested that cobalt may even be found in leather footwear and cause sensitization, and another study [4] reported that cobalt sensitization may often occur with chromium allergy. Allergies to dyes are much less common, with the exception of re-dyed leather or fabric shoes [1]. The most commonly used dyes are related to para-phenylenediamine and para-aminoazobenzene [1, 5].

Cases of occupational dermatitis from work in shoe production or shoe repair are uncommon; the major allergens were PTBPF-R and MBT [1].

In Europe several cases of severe ACD have been reportedly caused by dimethylfumarate present in antifungal packets in footwear or retail shoeboxes [1, 13]. Additionally, dimethylfumarate was responsible for a widespread epidemic of contact dermatitis caused by Chinese-imported furniture in Europe [13, 14]. Following this dimethylfumarate was banned in the European Union. Vesicular dermatitis of the soles bilaterally due to cinnamon powder used in odor-neutralizing agents has also occurred [15].

In patients with unremitting shoe dermatitis, consider lesser-known allergens. Warshaw et al. found that in 12.7 % of foot dermatitis cases, the specific shoe allergen could not be identified with patch testing to the North American Contact Dermatitis Group (NACDG) standard series alone [2]. Lanolin is present in shoe polish and may cause ACD [1]. Other allergens are dyes, including 4-aminoazobenzene, disperse orange 3, disperse yellow 3, and disperse red 1. Styrenated phenol is an allergen in athletic shoes, and diaminodiphenylmethane is a polyurethane precursor that can be an allergen in urethane-containing rubber foams. In addition to PTBPF-R itself, PTBPF may be an allergen and cause of leukoderma in some cases of foot dermatitis [1]. Biocides and fungicides, such as 2-*n*-octyl-4-isothiazolin-3-one and 2-(thiocyanomethylthio)-benzothiazole used in leather finishing and tanning, should also be considered [8].

18.6 Patch Testing for Shoe Allergy/Pitfalls

The diagnosis of shoe allergy is difficult to make without patch testing [7]. In addition to the standard series, an expanded shoe series [10, 16] and physical pieces of shoes worn by the patient should be tested [1, 15]. Several reports suggest specific chemicals to include in an expanded shoe series: *N, N*-dibutyl thiourea, disperse yellow 3, 1,3-diphenyl guanidine, dioctyl gallate, and disperse orange 3 [17]. It is very important to remember that patients with ACD to shoes may be patch test

negative to everything except for the shoe pieces [1]. Thus, testing to physical pieces of the shoe material is an important step in diagnosis.

Shoe pieces used for patch testing should be made as thin as possible and at least 1 cm^2 in size to avoid irritant pressure reactions [1, 2]. Figure 18.1 shows a positive patch test reaction to physical shoe pieces. It may be helpful to leave these pieces on for at least 4–5 days; soaking the pieces in water prior to testing replicates sweaty conditions.

It is important to consider any topical medications that may have been absorbed by the shoes; in which case shoe pieces may cause false-positive patch test reactions from the medication, rather than the shoe itself. Finally, consider any chemicals contacted at work that may have fallen on footwear and caused sensitization [1].

18.7 Prognosis and Outcome/What to Tell Patients

The only effective treatment of shoe ACD is avoidance of shoes, which likely contain the identified allergens. Patch testing can also identify shoes to which the patient is not allergic and can continue wearing. Patients are often advised to wear

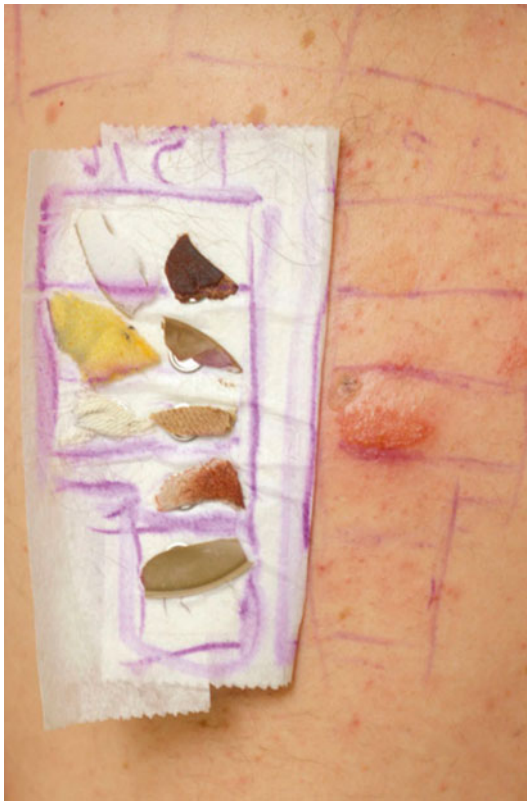


Fig. 18.1 Positive patch test reaction to physical shoe pieces

hypoallergenic shoes because it is especially difficult to identify all components used in shoe manufacturing [1, 9]. In the USA, information on footwear alternatives and custom shoemakers is commonly available. A recent review lists several companies, as well as type of hypoallergenic shoe available, that patients should be directed to [16]. There are shoes available which lack metal tanning agents, biocides, formaldehyde and epoxy resins, carbamates, as well as shoes made with glue-free linings [16]. Lanolin-free socks and barrier socks are also becoming increasingly available. Additionally, some patients improve with adequate control of pedal hyperhidrosis, which decreases allergen leaching [9].

Dermatitis involving only the soles may be treated with insole replacement with cork or felt, glued in place with nonrubber cement. Whole shoe replacement options include moccasins with no insole and no outer sole, injection-molded plastic shoes, and wooden shoes for rubber allergy [1, 4]. Vinyl shoes are an acceptable alternative as well. Purchase of new socks is also recommended because allergens from previous shoes or topical medications may remain on sock material even after washing and boiling [9].

In patients with chromium allergy, discarding leather shoes after a few months of wear may be sufficient because of incomplete allergen leaching [7]. Patients can also wear thick cotton socks to avoid shoe allergen contact [16]. Hypoallergenic leather shoes may be an option, although, these should also be patch tested prior to use since extracts may also cause ACD [1]. Thyssen et al. [13] reported a case of a chromium-allergic patient with chronic foot dermatitis despite using chromium-free shoes, highlighting the need to patch test patients to hypoallergenic shoes prior to use. Further alternatives include all fabric or all plastic shoes or wooden clogs with vegetable-tanned leather.

Chronic, recalcitrant foot dermatitis can be disabling, resulting in painful fissuring and secondary infections including cellulitis and lymphangitis [1, 7]. Despite this, outcome and prognosis is generally good. Studies have shown that up to 87.5 % of patients with shoe dermatitis improve or have complete resolution after a mean of 2.0 years from patch testing [1, 7].

References

1. Goossens A, Taylor JS. Shoes. In: Johansen JD, Frosch PJ, Lepoittevin JP, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011.
2. Warshaw EM, Schram SE, Belsito DV, DeLeo VA, Fowler Jr JF, Maibach HI, Marks Jr JG, Mathias CG, Pratt MD, Rietschel RL, Sassevile D, Storrs FJ, Taylor JS, Zug KA. Shoe allergens: retrospective analysis of cross-sectional data from the North American Contact Dermatitis Group, 2001–2004. Dermatitis. 2007;18(4):191–202.
3. Darling MI, Horn HM, McCormack SKA, Schofield OMV. Sole dermatitis in children, patch testing revisited. Pediatr Dermatol. 2012;29(3):254–7.
4. Nardella A, Taveirne M, Drieghe J, Degreef H, Goossens A. The relation between the localization of foot dermatitis and causative allergens in shoes: a 13-year retrospective study. Contact Dermatitis. 2005;53(4):201–6.
5. Chowdhuri S, Ghosh S. Epidemio-allergological study in 155 cases of footwear dermatitis. Indian J Dermatol Venereol Leprol. 2007;73(5):319–22.

6. Strauss RM, Wilkinson SM. Shoe dermatitis due to colophonium used as leather tanning or finishing agent in Portuguese shoes. Contact Dermatitis. 2002;47(1):59.
7. Freeman S. Shoe dermatitis. Contact Dermatitis. 1997;36:247–51.
8. Landeck L, Uter W, John SM. Patch test characteristics of patients referred for suspected contact allergy of the feet- retrospective 10-year cross-sectional study of the IVDK data. Contact Dermatitis. 2012;66(5):271–8.
9. Nedorost S. Clinical patterns of hand and foot dermatitis: emphasis on rubber and chromate allergens. Dermatol Clin. 2009;27(3):281–7.
10. Thyssen JP, Strandesen M, Poulsen PB, Menné T, Johansen JD. Chromium in leather footwear-risk assessment of chromium allergy and dermatitis. Contact Dermatitis. 2012;66(5):279–85.
11. Lyon CC, Tucker SC, Gäfvert E, Karlberg AT, Beck MH. Contact dermatitis from modified rosin footwear. Contact Dermatitis. 1999;41:102–3.
12. Thyssen JP, Johansen JD, Jellesen MS, Møller P, Sloth JJ, Zachariae C, Menné T. Consumer leather exposure: an unrecognized cause of cobalt sensitization. Contact Dermatitis. 2013;69(5):276–9.
13. Thyssen JP, Jellesen MS, Møller P, Menné T, Johansen JD. Allergic chromium dermatitis from wearing 'chromium-free' footwear. Contact Dermatitis. 2014;70(3):185–7.
14. Lefranc A, Flesch F, Cochet A, Daoudi J, Crinier R, French Dimethylfumarate Working Group. Epidemiological description of an outbreak of dermatitis related to dimethylfumarate, France 2008. Arch Environ Occup Health. 2008;66(4):217–22.
15. Hartmann K, Hunzelmann N. Allergic contact dermatitis from cinnamon as an odour-neutralizing agent in shoe insoles. Contact Dermatitis. 2004;50(4):253–4.
16. Matthys E, Zahir A, Ehrlich A. Shoe allergic contact dermatitis. Dermatitis. 2014;25(4): 163–71.
17. Holden CR, Gawkrodger DJ. 10 years' experience of patch testing with a shoe series in 230 patients: which allergens are important. Contact Dermatitis. 2005;53(1):37–9.

Gloves

19

Kristiina Aalto-Korte

Contents

19.1 Introduction

The role of protective gloves is of great importance in the prevention of hand dermatitis when skin contact with hazardous substances cannot otherwise be prevented. However, gloves often also cause contact dermatitis: they may irritate the skin (irritant contact dermatitis) and cause either immediate or delayed contact allergy (contact urticaria/protein contact dermatitis and allergic contact dermatitis). Contact allergy to gloves is a significant problem in occupational dermatology.

K. Aalto-Korte, MD, PhD
Health and Work Ability, Finnish Institute of Occupational Health,
Topeliuksenkatu 41 aA, Helsinki 00250, Finland
e-mail: kristiina.aalto-korte@ttl.fi

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_19

19.2 Correct Use of Protective Gloves

Gloves must be chosen according to work tasks and the materials that are handled. They must protect the skin from hazardous chemicals, but on the other hand, impermeable gloves should not be used needlessly, for example, in dry cleaning work. Disposable gloves should not be reused. Reusable gloves must be clean and the use of cotton inner gloves is recommended. Gloves must be pulled off with caution so that the soiled outer surface does not touch the skin.

19.3 When to Suspect Glove Allergy/Clinical Signs

Glove allergy must be considered an option in every case in which the patient has skin symptoms on their hands, especially if they are aggravated by glove use or are persistent despite the correct use of gloves. It is important to ascertain the type (material) of gloves the patient has used and the timing of the symptoms in relation to glove use. Gloves usually cause symptoms in the dorsal aspects of the hands, wrists and lower forearms corresponding to glove contours [1, 2]. In contact urticaria, wheals appear quickly, usually within 5–30 min of wearing the gloves, but they also disappear soon, often within 2 h. The eczematous lesions of allergic and irritant contact dermatitis have different timings: they appear only after several hours or even days, and they last longer, usually several days or even weeks. Respiratory and systemic symptoms are possible in patients with immediate natural rubber latex (NRL) allergy, but in delayed contact allergy, the symptoms are limited to the skin.

19.4 Glove Materials and Allergens

Nowadays, leather is the major cause of *chromium* allergy in many countries [3] (Table 19.1). In addition to leather shoes, leather gloves are significant sources of chromium contact allergy. Leather gloves typically exacerbate hand dermatitis when they are wet.

Rubber gloves have long been the main cause of delayed rubber chemical allergy, and the main sensitizers include *thiurams*, *dithiocarbamates* and *benzothiazoles* (Table 19.2). Both natural and synthetic rubbers contain these additives. Table 19.3 contains other sensitizing chemicals in rubber gloves.

Table 19.1 Main glove materials that cause contact allergy

Material	Subtypes	Main allergens
Leather		Chromium
Rubber	Natural rubber latex (NRL)	NRL, rubber additives
	Nitrile	Rubber additives
	Other synthetic rubber	Rubber additives
Plastic	Polyvinyl chloride (PVC)	Large number of rare allergens

Table 19.2 Allergens in the rubber additive series with possible relevance to glove allergy

Rubber additive series	
Main allergens	**Comments**
Thiuram mix components: *Tetraethylthiuram disulfide (TETD)* *Tetramethylthiuram monosulfide (TMTM)* *Tetramethylthiuram disulfide (TMTD)* *Dipentamethylenethiuram disulfide (PTD)*	Patients should avoid both thiurams and dithiocarbamates
Mercapto mix components (benzothiazoles): *N-Cyclohexyl-2-benzothiazylsulfenamide (CBS)* *Morpholinylmercaptobenzothiazole (MOR)* *Dibenzothiazyl disulfide (MBTS)* *2-Mercaptobenzothiazole (MBT)*	Quite commonly used in rubber gloves Patients should avoid all benzothiazoles
Dithiocarbamates: *Zinc diethyldithiocarbamate (ZDC)* *Zinc dibutyldithiocarbamate (DBC)* *Zinc dimethyldithiocarbamate*	Used in the production of most rubber gloves Patients should avoid both thiurams and dithiocarbamates
Rare allergens	
1,3-Diphenylguanidine (DPG)	Used in some rubber gloves, usually together with benzothiazoles Irritant patch test reactions very common
Alkylthioureas: *N,N'-Diethylthiourea* *N,N'-Dibutylthiourea* *N,N'-Diphenylthiourea*	Mainly in neoprene gloves Also used in the production of other types of rubber
N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD) N-cyclohexyl-N-phenyl-4-phenylenediamine (CPPD)	Possibly in some black/dark coloured gloves for industrial use
Cyclohexylthiophthalimide	Possibly in some gloves Irritant patch test reactions common

Table 19.3 Rare commercial glove allergens in plastic and rubber gloves

Allergen	Source of sensitization	Reference
Cetylpyridinium chloride	NRL Synthetic polyisoprene	[8]
Bisphenol A	PVC gloves	[11]
Benzisothiazolinone	In some powder-free PVC gloves	[12]
Tricresyl phosphate	PVC gloves	[13]
Formaldehyde	May occur in reusable PVC and rubber gloves with flocked lining	[14]

Immediate allergy to the proteins of *natural rubber latex* is mostly caused by natural rubber gloves. Healthcare workers are a major risk group for occupational sensitization. This allergy has, however, become quite rare in several European countries, for example, in Germany [4].

Plastic gloves may also cause delayed contact allergy. Most reported cases have been due to polyvinyl chloride (PVC) gloves. The reported allergens have been

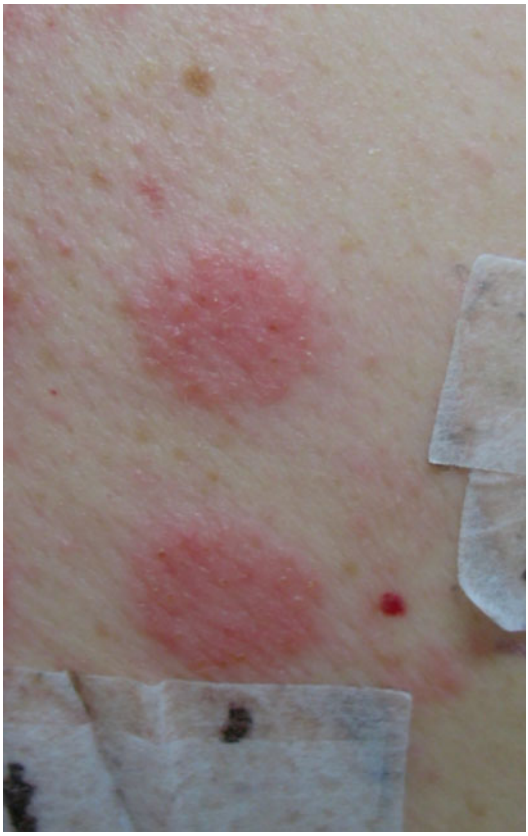


Fig. 19.1 Allergic patch test reactions to a polyvinyl chloride (PVC) glove in a patient with benzisothiazolinone (BIT) allergy and skin symptoms related to the use of these gloves. BIT was detected in the chemical analysis of the gloves

additives such as plasticizers, antioxidants, antimicrobials or colouring agents [5]. None of the allergens in PVC gloves have had worldwide importance, probably because they vary greatly and can be easily replaced by other compounds. Table 19.3 contains some of the rare allergens that are available as commercial allergens. The actual sensitizer in plastic gloves often remains undetermined [2] (Fig. 19.1).

Colouring agents are also rare causes of delayed contact allergy in textile and leather gloves.

19.5 Diagnosis

Most patients with suspected glove allergy need patch testing (Table 19.4). If they have used NRL gloves, a prick test or determination of specific IgE in the sera must be performed, especially when contact urticaria is suspected.

Table 19.4 Basic screening of glove allergy

Test method	What to test
Patch tests	European baseline series
	Pieces of suspected glove material
	Rubber additive series
Prick test/specific IgE	Natural rubber latex

19.5.1 Diagnosis of Immediate NRL Allergy

Immediate allergy to NRL is diagnosed with a prick test or determination of NRL-specific IgE in the serum. Commercial prick test substances are easy to use, and their quality is usually good [6]. An alternative is an in-house test solution prepared from the patient's gloves or from some NRL glove brand with a high allergen content. *Glove provocation* confirms the diagnosis of NRL contact urticaria. It is first performed on one finger for 20 min, with a control test on the corresponding finger of the PVC glove on the other hand. If no wheals are provoked, a whole glove is used with a PVC control glove on the other hand for 20 min. Anaphylactic symptoms are possible.

Immediate NRL allergy may also cause eczematous symptoms, i.e. protein contact dermatitis. The mechanism is largely unknown, and there are no diagnostic methods that reliably differentiate between protein contact dermatitis and, for example, irritant contact dermatitis. The diagnosis is based on the incidence of immediate allergy to NRL and eczematous symptoms provoked by NRL gloves that heal after changing the glove material.

19.5.2 Patch Tests in the Diagnosis of Delayed Contact Allergy to Gloves

The European baseline series covers the main allergens in gloves, namely, potassium dichromate, thiuram mix, mercapto mix and 2-mercaptobenzothiazole (MBT; also a component of mercapto mix).

It is useful to test a specific rubber additive series when the patient has used rubber gloves or when rubber chemical allergy is suspected. This series usually contains the components of the rubber mixes of the baseline series at higher concentrations and other potential allergens, such as dithiocarbamates, diphenylguanidine (DPG) and alkylthioureas (Table 19.2).

Most rubber gloves are currently manufactured using dithiocarbamates as accelerators. Contact allergy to thiurams and dithiocarbamates is closely related. Their chemical structure is quite similar. Corresponding thiuram disulphides and dithiocarbamates constitute a redox pair: during the oxidation of a dithiocarbamate, the corresponding thiuram disulphide is formed, and the reduction of the thiuram disulphide restores the dithiocarbamate [7]. These changes may occur during vulcanization, i.e. the manufacture of rubber gloves, and the additives in the gloves are not

necessarily the same as those that were added during vulcanization. Concomitant reactions to several thiurams are common due to cross allergy or concomitant sensitization. Allergic reactions to dithiocarbamates usually occur in patients with strong allergic reactions to corresponding thiurams. Thiurams are better markers of sensitization to a dithiocarbamate/thiuram redox pair [7].

Diphenylguanidine (DPG) has been a rare sensitizer in rubber gloves, but recently, a relatively large number of cases due to sterile synthetic polyisoprene gloves have been reported in Sweden [8] and Belgium [9]. Another sensitizer in these gloves has been cetylpyridinium chloride [8]. The latter is not included in the rubber additive series.

19.5.3 Plastic Gloves

Contact allergy to plastic gloves is not extremely rare, but the diagnosis can only occasionally be made using commercial patch test substances. Some of these commercial allergens are presented in Table 19.3. However, the relevance of the allergic reactions can only be confirmed if their presence in the glove material can be demonstrated by chemical analyses or inquiries to the manufacturer or sales representative. The diagnosis usually requires testing with the gloves themselves and the individual chemicals that have been used in their production.

19.5.4 Testing Patients' Own Gloves

Gloves can usually be tested as they are. Small cut pieces can be tested in chambers (first moistened with water, ethanol or acetone). Larger pieces can be tested semi-open, covered with surgical test tape without a chamber. Sometimes it is worth testing both sides of the gloves as their composition may vary. Tests can be falsely negative if not enough allergen is released onto the skin. Pressure effects and mechanical traumas due to sharp particles must be differentiated from allergic reactions.

The use of ultrasonic bath extracts is an alternative to testing gloves as such. Small pieces of the material are placed in water or organic solvent (ethanol, acetone, ether), then extracted in an ultrasonic cleaner device and finally filtered [10].

19.6 Pitfalls in Testing

Various rubber chemical mixes can cause false-positive reactions. In occupational settings, it is especially important to test the components of the positive mix separately before the final diagnosis. Carba mix, which contains dithiocarbamates and diphenylguanidine, is used in some centres. It causes nonspecific irritant reactions quite often, and for accurate diagnosis, it is especially important to test its components separately in the rubber additive series.

Patients' own glove materials can also induce irritant reactions. When the ingredients of the gloves are tested, it is recommendable to use several concentrations in a dilution series to determine the threshold concentration and to perform adequate control tests on other patients. If the actual allergen cannot be found, the diagnosis of glove allergy remains uncertain.

19.7 Differential Diagnosis

The skin symptoms in connection with glove use can represent irritant contact dermatitis due to glove material or other factors. Endogenous eczemas of the hands are often aggravated by the use of occlusive gloves.

Dermographismus and cholinergic urticaria can provoke symptoms similar to those of NRL allergy.

19.8 What to Tell to a Patient with a Positive Skin Test

Patients may be exposed to glove allergens in other products. Patients allergic to rubber additives should avoid skin contact with all rubber items that may contain the same chemicals. Thiurams, dithiocarbamates and benzothiazoles occur in most rubber types, and patients allergic to these must avoid skin contact with all kinds of rubber.

19.8.1 Alternatives

Patients are advised to use gloves that do not contain the chemicals/proteins to which they are allergic (Table 19.5). The new gloves should protect the skin from the hazards of the task.

Synthetic rubber gloves are safe in NRL allergy because they do not contain the sensitizing proteins of the rubber tree. The use of powder-free gloves is recommended to prevent NRL allergy, because NRL proteins adhere to glove powder and powdered gloves usually contain more NRL allergens [2].

Patients with allergic reactions to thiurams and dithiocarbamates are instructed in a similar way: they should avoid all thiurams and dithiocarbamates, which in practice means avoiding skin contact with all rubber gloves. 'Accelerator-free nitrile gloves' are currently marketed by many companies. Some thiuram/dithiocarbamate-allergic patients have been able to use these without any skin symptoms for at least some time (personal experience).

Additives are usually not declared on the packaging of gloves. Some information on the chemicals that have been used in the production of protective gloves can be obtained from websites such as http://www.bgbau.de/gisbau/service/allergene, but detailed information must usually be sought from the manufacturers or sales representatives. Moreover, additives undergo chemical changes during the manufacturing

Table 19.5 Alternative materials for sensitized patients

Allergen(s)	Source of sensitization	Alternative glove
Natural rubber latex (NRL)	NRL gloves	Any synthetic rubber, e.g. nitrile, polyisoprene Plastic (e.g. PVC)
Thiurams, dithiocarbamates	Rubber gloves, both synthetic and NRL	Plastic gloves (e.g. PVC) (Accelerator-free nitrile gloves?)
Benzothiazoles incl. mercaptobenzothiazole	Rubber gloves	Plastic gloves (e.g. PVC) (Accelerator-free nitrile gloves?)
Chromium	Leather gloves	Textile, plastic and rubber
Diphenylguanidine (DPG)	Rubber gloves, especially synthetic polyisoprene	Plastic Rubber gloves not manufactured with DPG
Cetylpyridinium chloride (CPC)	NRL, synthetic polyisoprene	Rubber gloves not manufactured with CPC Plastic
Alkyl thioureas	Mainly neoprene gloves Also used in the production of other types of rubber	Rubber other than neoprene can be tried (?) Plastic

process, and chemicals added during the manufacture are not necessarily present in the final product, i.e. the glove. Chemical analyses of gloves are often quite difficult, especially analyses of rubber additives.

19.9 Key Messages

- Contact allergy to protective gloves is common in occupational settings.
- The possibility of glove allergy should be considered in all cases of hand dermatitis.
- Proteins in natural rubber latex (NRL) induce immediate-type allergy. These are only present in NRL gloves.
- Gloves made of synthetic rubber (e.g. nitrile) are safe as regards NRL allergy.
- Thiurams, dithiocarbamates and benzothiazoles are the most significant rubber additives in rubber gloves that cause delayed allergic contact dermatitis.
- The European baseline patch test series contains the most significant sensitizers in gloves made of either rubber or leather.
- Additional tests include testing with pieces of the glove material and rubber additive series.
- Contact allergy to plastic gloves is not extremely rare. Most reported cases have been due to polyvinyl chloride (PVC) gloves.
- The diagnosis of plastic glove allergy often requires testing with the individual components of the suspected gloves.

References

1. Estlander T, Jolanki R. Allergic contact dermatitis from rubber and plastic gloves. In: Boman A, Estlander T, Wahlberg JE, Maibach HI, editors. Protective gloves for occupational use. 2nd ed. Boca Raton: CRC Press; 2005. p. 127–44.
2. Flores SK, Estlander T, Jolanki R, Maibach HI. Disadvantages of gloves. In: Rustemayer T, Elsner P, John SM, Maibach HI, editors. Kanerva's occupational dermatology. Berlin: Springer; 2012. p. 1923–33.
3. Caroe C, Andersen KE, Thyssen JP, Mortz CG. Fluctuations in the prevalence of chromate allergy in Denmark and exposure to chrome-tanned leather. Contact Dermatitis. 2010;63: 340–6.
4. Allmers H, Schmengler J, John SM. Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. J Allergy Clin Immunol. 2004;114:347–51.
5. Rose RF, Lyons P, Horne H, Mark WS. A review of the materials and allergens in protective gloves. Contact Dermatitis. 2009;61:129–37.
6. Van Kampen V, De Blay F, Folletti I, Kobierski P, Moscato G, Olivieri M, Quirce S, Sastre J, Walusiak-Skorupa J, Kotschy-Lang N, Musken H, Mahler V, Schliemann S, Ochmann U, Sultz J, Worm M, Sander I, Zahradnik E, Bruning T, Merget R, Raulf-Heimsoth M. Evaluation of commercial skin prick test solutions for selected occupational allergens. Allergy. 2013;68:651–8.
7. Hansson C, Ponten A, Svedman C, Bergendorff O. Reaction profile in patch testing with allergens formed during vulcanization of rubber. Contact Dermatitis. 2014;70:300–8.
8. Ponten A, Hamnerius N, Bruze M, Hansson C, Persson C, Svedman C, Thorneby Andersson K, Bergendorff O. Occupational allergic contact dermatitis caused by sterile non-latex protective gloves: clinical investigation and chemical analyses. Contact Dermatitis. 2013;68: 103–10.
9. Baeck M, Cawet B, Tennstedt D, Goossens A. Allergic contact dermatitis caused by latex (natural rubber)-free gloves in healthcare workers. Contact Dermatitis. 2013;68:54–5.
10. Bruze M, Trulsson L, Bendsöe N. Patch testing with ultra-sonic bath extracts. Am J Contact Dermatitis. 1992;3:133–7.
11. Aalto-Korte K, Alanko K, Henriks-Eckerman ML, Estlander T, Jolanki R. Allergic contact dermatitis from bisphenol A in PVC gloves. Contact Dermatitis. 2003;49:202–5.
12. Aalto-Korte K, Alanko K, Henriks-Eckerman ML, Jolanki R. Antimicrobial allergy from polyvinyl chloride gloves. Arch Dermatol. 2006;142:1326–30.
13. Crepy MN, Langlois E, Melin S, Descatha A, Bensefa-Colas L, Jonathan AM, Ameille J. Tricresyl phosphate in polyvinylchloride gloves: a new allergen. Contact Dermatitis. 2014;70:325–8.
14. Ponten A. Formaldehyde in reusable protective gloves. Contact Dermatitis. 2006;54:268–71.

Glues

20

Suchismita Paul and Peter C. Schalock

Contents

20.1 Introduction

Cutaneous exposure to glues and adhesives is common in occupations such as construction, manufacturing and packaging, medicine/dentistry, and beauty salon industries as well as in many household activities, hobbies, cosmetic products, shoes, and medical/dental materials. Glue-induced contact dermatitis may be caused by exposure to a wide variety of glues such as acrylates, epoxy resins, formaldehyde resins, colophony, and others. Skin reactions occur due to irritant contact dermatitis

S. Paul, BA
Harvard Medical School, Boston, MA USA
e-mail: Suchismita_paul@hms.harvard.edu

P.C. Schalock, MD (✉)
Department of Dermatology, Massachusetts General Hospital, Harvard Medical School,
BAR 622, 55 Fruit St., Boston, MA 02114, USA
e-mail: schalock.prof@gmail.com

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_20

(direct chemical cytotoxic effect) as well as allergic contact dermatitis (ACD) (T-cell-mediated, delayed-type hypersensitivity immune reaction). Some adhesives such as epoxy resins are formed by the polymerization of monomer components. During this process, additives are introduced which include curing agents, stabilizers, accelerators, antioxidants, plasticizers, and catalysts. When fully polymerized (cured), the final product rarely causes dermatitis; however, any remaining monomer can cause contact dermatitis especially by boosting a preexisting sensitization. The additives used in production also may be skin irritants and sensitizers.

20.2 Clinical Presentation

The clinical presentation of glue-induced dermatitis is similar to that of contact dermatitis induced by most other irritants and allergens. Lesions are usually confined to the site of contact; however, occasionally passive transfer of allergen may cause eruptions in distant sites from the initial site of exposure. Acute lesions consist of erythematous plaques with vesiculation and bullae, whereas chronic disease consists of lichenification, fissuring, scale, and hyperpigmentation. The severity of the clinical presentation increases with repeat exposures.

20.3 Diagnosis

The diagnosis of glue-induced dermatitis is based on a thorough history of possible exposure to irritants and allergens at work, hobbies, household activities, or through products such as cosmetics (artificial nails), medical/dental materials, or shoes. The clinical appearance of the lesions is important in terms of the anatomic distribution of the dermatitis with respect to the site of exposure [22]. The temporal relationship between the exposure and appearance of lesions is also crucial. Patch testing can be performed to determine causes of allergic contact dermatitis due to glue.

The chemical composition of the glue or adhesive should be determined by asking the manufacturer or through material data safety sheets, because patch testing should be performed with individual allergenic glue ingredients. It is important to note that safety data sheets are often incomplete and manufacturers should be asked for the full recipe.

Products which are normally in contact with the skin such as tapes and medical self-adhesive dressings should be included in the patch test. While products containing strong allergens such as acrylic or epoxy resins should only be tested after careful consideration of ingredients, concentrations, and appropriate dilution, as patch testing of the product as is may lead to active sensitization or strong irritant reactions. Furthermore, unknown ingredients of the epoxy resin- or acrylic-based glues may lead to possible active sensitization during the patch testing process [19, 31]. See Chap. 17 for more information concerning patch testing acrylates and Chap. 5 concerning patch testing of own products. Common categories of glues and adhesives will be discussed in this chapter. A summary of the most common relevant allergen groups is found in Table 20.1.

Table 20.1 Common allergens found in adhesives

Concentration and vehicle	
Epoxy resin	
Bisphenol A	1.0 % pet
Bisphenol F	0.25 % pet
Epichlorohydrin	Epoxy resin mixes
Diglycidyl ether of bisphenol A	No standard allergen
Diethylenetetramine	1 % pet
Triethylenetetramine	0.5 % pet
Acrylic resins	
Acrylic acid	
Tripropyleneglycol diacrylate (TPGDA)	0.1 % pet
Dipropylene glycol diacrylate (DPGDA)	0.1 % pet
Methacrylic acid	
2-Hydroxyethyl methacrylate (2-HEMA)	2.0 % pet
Ethylene glycol dimethacrylate (EGDMA)	2.0 % pet
Hydroxypropyl methacrylate (2-HPMA)	2.0 % pet
Methyl methacrylate (MMA)	2.0 % pet
Triethylene glycol dimethacrylate (TREGDMA)	2.0 % pet
Tetrahydrofurfuryl methacrylate (THFMA)	2.0 % pet
Ethyl cyanoacrylate	10 % pet
Epoxy acrylates	
2,2-bis[4-(2-Hydroxy-3-acryloxypropoxy)phenyl]-propane (bis-GA)	No standard allergen
2,2-bis[4-(2-Hydroxy-3-methacryloxypropoxy) phenyl]propane (bis-GMA)	2.0 % pet
2,2-bis[4-(Methacryl-oxyethoxy)phenyl] propane (bis-EMA)	2.0 % pet
2,2-bis[4-(Methacryloxy)phenyl]-propane (bis-MA)	2.0 % pet
Glycidyl methacrylate (GMA)	
Colophony derivatives	
Colophonium (rosin)	20 % pet
Abietic acid	10 % pet
Formaldehyde resins	
Phenol-formaldehyde resin	1.0 % pet
Para-tertiary butylphenol formaldehyde resin	1.0 % pet
Para-tertiary butylphenol	1.0 % pet
Urea-formaldehyde resins	10 % pet
Melamine-formaldehyde resins	7.0 % pet
Toluene-sulfonamide formaldehyde resins	10 % pet

pet petrolatum

20.4 Management

The management of glue-induced dermatitis involves the identification of the irritants and allergens through detailed history and patch testing, avoidance of exposure and use of alternative allergen-free products, and finally treatment of skin inflammation using topical corticosteroids or other medications depending on the severity of the symptoms. For irritant contact dermatitis, restoration of the epidermal barrier is important.

20.5 Different Categories of Glue

20.5.1 Epoxy Resin Systems

Epoxy resin systems are composed of monomers such as bisphenol A and epichlorohydrin, curing agents or hardeners, reactive diluents, and several other additives such as fillers, pigments, plasticizers, and solvents. Most uncured epoxy resins are formed by the condensation of bisphenol A and epichlorohydrin. Hardeners, comprising of amines, amides, anhydrides, or inorganic compounds, are cross-linking agents for the resin that then lead to cured, hard, and insoluble products. Reactive diluents, mainly glycidyl ethers and sometimes glycidyl esters, are added to reduce viscosity and improve polymerization. About 75 % of epoxy resins used worldwide are based on diglycidyl ether of bisphenol A (DGEBA).

20.5.1.1 Use

Epoxy resins are used in the production of electrical and electronic devices; sport equipment manufacturing; construction industry; production of cars, ships, and airplanes; and glass fiber industry as well as the paint and glue industry. At home, epoxy adhesives are also used in a variety of manners for household projects. They are also used as high-performance adhesives in the construction industry.

20.5.1.2 Clinical Presentation

The clinical presentation of epoxy-induced dermatitis mainly involves the fingers, interdigital spaces, forearms, wrists, and to a lesser extent the face and the neck [16]. Facial dermatitis is more likely to occur due to epoxy resin hardeners which are more volatile than the resin.

20.5.1.3 Occupational Aspects and Use of Gloves

Epoxy resins are one of the main causes of occupational contact dermatitis [18]. Several reports describe epoxy sensitization to glues and bonding agents [17]. When fully cured, they do not cause contact allergy; however, any remaining monomers may induce sensitization or elicit allergic contact dermatitis.

Epoxy resins rapidly penetrate regular gloves, within minutes. Nitrile gloves are much less permeable to epoxies and should be used for personal protection when working with epoxy resins [27]. Standard industrial protective equipment such as thin body suits provides only short-term protection to epoxy penetration.

20.5.1.4 Main Sensitizers

The main sensitizer in the epoxy resin system is diglycidyl ether of bisphenol A (DGEBA) [31]. This epoxy resin is therefore included in the baselines series worldwide.

However, allergic contact dermatitis could also be due to hardeners, reactive diluents, or other epoxy resins (e.g., diglycidyl ether of bisphenol F) [18]. Patch testing with only DGEBA will miss other potential allergens. Therefore, it is

important to obtain information about the individual ingredients of the specific epoxy resin system the patient has been exposed to.

Sensitization occurs mainly due to glycidyl ethers among several other reactive diluents. Among a large variety of epoxy hardeners, amines are the most potent sensitizers. On the other hand, contact dermatitis caused by bisphenol A and epichlorohydrin is rare. Irritant contact dermatitis may result from epoxy compounds, often from amine and anhydride hardeners, glycidyl ethers, benzol, toluol, and epichlorohydrin.

For patch testing of epoxy resin system, the components of the patient's adhesive exposure should be taken into consideration, and several chemicals including hardeners, diluents, and non-DGEBA epoxy resins should be tested in addition to DGEBA. Bisphenol A and epichlorohydrin should also be included. Active sensitization has been reported during patch testing of epoxy chemicals [18, 19]. Epoxy allergens to consider for testing are summarized in Table 20.1.

20.5.2 Acrylic Resin

Acrylic resins are synthetic polymers derived from monomers such as acrylic acid, methacrylic acid, cyanoacrylic acid, and their esters (acrylates, methacrylates, and cyanoacrylates), acrylamides, and acrylonitrile. These polymers are used in a wide variety of products such as plastics, paint, artificial nails, and dental and orthopedic materials as well as in glues, adhesives, and sealants. Adhesives based on acrylates, methacrylates, and epoxy diacrylates include anaerobic sealants, ultraviolet-cured sealants, cyanoacrylates, methyl methacrylate, metal and glass glues, epoxy diacrylates (vinyl resins), and acrylic dental bonding material. Allergic and irritant contact dermatitis has been reported to many acrylic resins [6]. Gloves are not protective against acrylates since they rapidly penetrate through latex gloves [27].

20.5.2.1 Anaerobic Sealants

Anaerobic sealants are adhesives based on esters of acrylates and methacrylates that polymerize rapidly in the absence of air [23]. They also contain initiators, accelerators, and other additives. Anaerobic adhesives are mainly used in the manufacturing of machines, mechanical devices, and automotives. Contact allergy to anaerobic sealants has been reported [28]. The clinical presentation usually involves allergic contact dermatitis in the distal fingers. Anaerobic sealants mainly induce sensitization to aliphatic methacrylates; however, they may also induce sensitization to epoxy methacrylates (see "epoxy acrylates") [3].

20.5.3 Cyanoacrylate-Based Glues

Cyanoacrylate-based glues (Krazy Glue, Super Glue) are used for binding biological materials such as human tissues and to seal wounds in surgery as well as adhesives for metal, rubber, glass, plastics, and textiles. Cyanoacrylates are rare

sensitizers, although some cases have been reported [4]. Skin irritation is more common with cyanoacrylate-based glues compared to allergic reactions.

20.5.4 Acrylate-Based Adhesives

Acrylate-based adhesives are used extensively in tapes and stickers. Pressure-sensitive adhesives adhere by application of light pressure, and they are used mostly in the tape and label industries. Irritant and allergic reactions both can be caused by acrylates [6]. Medical adhesive tapes or bandages consist of a pressure-sensitive adhesive and a backing. Reported acrylic allergens include ethylhexyl acrylate and dodecyl maleamic acid [13]. Adhesive bandages (Band-Aid) contain multiple allergenic components (Table 20.2), though the actual incidence of dermatitis compared to perceived reactions is very low. In the study by Widman and Storrs examining patients with self-reported adhesive bandage reactions, none had positives to the actual adhesive components other than Mastisol liquid adhesive [32]. Contact dermatitis to medical adhesive bandages is most often due to irritant contact dermatitis or trauma, rather than ACD [32].

Glue-induced contact dermatitis has been reported from several other acrylic resin-based adhesives. Ultraviolet-cured acrylic glues, which mainly contain acrylates, may also cause contact allergy. Bone cement used in orthopedic devices contains methyl methacrylate monomers, which rapidly penetrate through the latex gloves of orthopedic surgeons and cause allergic contact dermatitis [9]. Methyl methacrylate allergy in the patient is a rare cause of prosthesis failure [26].

Allergic dermatitis due to acrylic resins in glue is mainly due to uncured monomers. Glue-induced contact allergy to methacrylates is more common than acrylates. The most common methacrylate allergens include 2-hydroxyethyl methacrylate (2-HEMA), ethylene glycol dimethacrylate (EGDMA) and 2-hydroxypropyl methacrylate (2-HPMA), ethyl methacrylate (EMA), methyl methacrylate (MMA), triethylene glycol dimethacrylate (TREGDMA), and tetrahydrofurfuryl methacrylate (THFMA) [1]. The main acrylate allergens include tripropyleneglycol diacrylate (TPGDA) and dipropylene glycol diacrylate (DPGDA). Exposure to methacrylates

Table 20.2 Allergens causing allergic contact dermatitis found in adhesive bandages [32]

2,5-di(Tertiary-amyl)hydroquinone (antioxidant)
Benzoyl peroxide (increase stretch potential)
Diethyldithiocarbamate (preservative)
Dodecyl maleamic acid/octadecyl maleamic acid (adhesive)
Epoxy resin (adhesive)
Glycerol ester of hydrogenated abietic acid (adhesive)
Hydroabietic acid (adhesive)
p-Tert-butylphenol formaldehyde resin (adhesive)
Tetrahydrofurfuryl acrylate (adhesive)
Tricresyl phosphate(plasticizer)

may lead to cross-reaction with acrylates but not vice versa. Cyanoacrylates are patch tested separately because they do not cross-react with other methacrylates.

Many standard acrylate patch test trays are available; mainly commercially available allergens are given in Table 20.1.

20.5.5 Epoxy Acrylate

Epoxy resins react with acrylic resin monomers to form epoxy acrylates, which are used in glues and dentistry. DGEBA epoxy resin and its raw materials, bisphenol A and epichlorohydrin, react with acrylates and methacrylates to form epoxy (meth)acrylates. Five such compounds which are common allergens are 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]-propane (bis-GA), 2,2-bis [4-(2-hydroxy-3-methacryloxypropoxy) phenyl]propane (bis-GMA), 2,2-bis[4-(methacryl-oxyethoxy)phenyl] propane (bis-EMA), 2,2-bis[4-(methacryloxy) phenyl]-propane (bis-MA), and glycidyl methacrylate (GMA) (Aalto-Korte et al. 2009). Some glues contain bis-GMA, bis-GA, bis-EMA, and GMA. Allergic reactions to epoxy acrylates are usually seen in patients with ACD to DGEBA epoxy resin due to probable cross-allergy [2]. In a study by Lee et al., 20 % of patients with allergic reactions to DGEBA epoxy resin also reacted to some epoxy acrylates, usually bis-GMA [21]. However, some patients have specific allergy to epoxy acrylates, such as bis-GA from anaerobic glue. Hence, epoxy acrylates should be patch tested separately as patients might not have allergy to epoxy resins or acrylates.

20.5.6 Colophony/Rosin

Colophony, a term widely used in Europe, whereas rosin, the preferable term in North America, is a naturally occurring mixture of >100 compounds primarily derived from pine trees. Colophony and modified colophony is found universally at home and at work, and allergic reactions have been reported in the paper manufacturing industry, electronics industry, furniture-making industry, printing ink, fabrics, and cosmetics [7]. Unmodified and modified colophony (through glycerol esterification, pentaerythritol esterification, polymerization, and disproportionation) is also commonly used in glues and adhesives [7]. Colophony-induced allergic reactions have been reported to adhesive in adhesive tapes [15], sealant in dental prostheses and impression pastes [10], pulp capping preparations, surgical packs, and varnish for pulp protection as well as hydrocolloid dressings [12]. Allergic contact dermatitis due to colophony in the adhesive of hydrocolloid dressing may occur (DuoDerm or DuoDerm E, Bristol-Myers Squibb Co., Princeton NJ) [25, 29] (Fig. 20.1). Colophony in adhesives for shoe linings is also an important cause of contact dermatitis.

Colophony is a component of many commercially available baseline series. The major chemical constituent of colophony is abietic acid, which is available as a patch

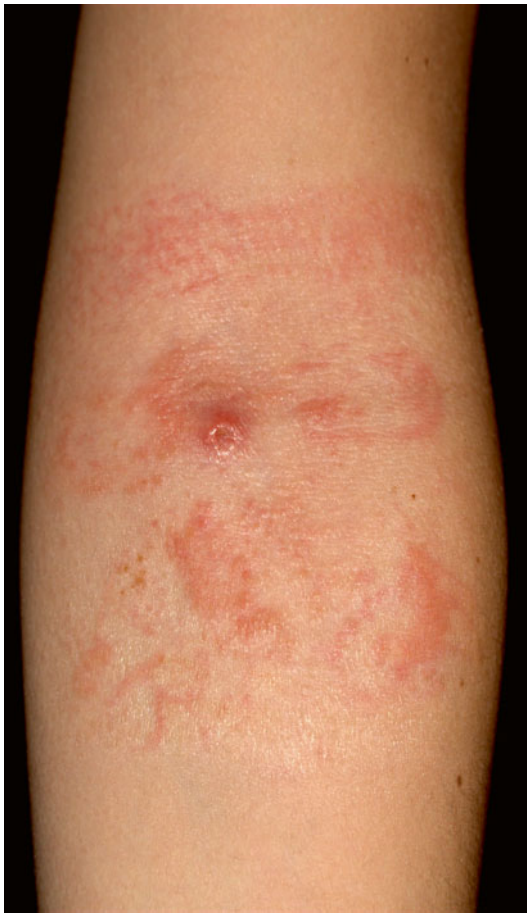


Fig. 20.1 Discrete pruritic dermatitis, recurrent with each use of DuoDerm dressing at PICC line site. Separate reaction occurred centrally from a Band-Aid adhesive dressing

test allergen. Abietic acid is easily oxidized by air, and one of its major oxidation product, 15-hydroperoxyabietic acid, is a strong allergen [20]. Several other oxidation products of abietic acids and other resin acids are thought to be allergenic [11].

Comparatively, pure resin acids are less allergenic. A comprehensive list of allergens can be found in a review on colophony allergy by Downs and Sansom [7]. Unmodified colophony is known to cause contact allergy; however, new allergens are also created during the modification processes. Cross-reactions occur with balsam of Peru, wood tars, oil of turpentine, pine resin, spruce resin, tea-tree oil, and fragrances [14].

20.5.7 Formaldehyde Resins

Formaldehyde can be combined with several chemicals such as phenols (including para-tertiary butylphenol), urea, melamine, cashew nutshell oil, and resorcin to form different resins. Phenol-formaldehyde resins, particularly para-tertiary butylphenol

formaldehyde resin (PTBFR), are mainly used as glues and adhesives. PTBFR and formaldehyde are components of many commercially available baseline series. In a study by Tarvainen, among 839 Finnish patients patch tested with a series of 31 plastics and glue allergens, PTBFR was reported to be the most common allergen [30].

20.5.7.1 Use

PTBFR is a well-known allergen in neoprene-based leather glues used in shoemaking [8]. Additionally, it causes contact dermatitis when used as a glue in watch straps, automobile upholstery, belts, purses, artificial nails, athletic tapes, adhesive labels, hearing aids, orthopedic prostheses, and other leather and vinyl goods [24].

Urea-formaldehyde resins and melamine formaldehyde resins are used as glues in the wood industry. Toluene-sulfonamide formaldehyde resins in nail lacquer and hardeners cause contact dermatitis often involving the eyelids after being transferred there.

20.5.7.2 Clinical Presentations

In addition to allergic contact dermatitis, phenol-formaldehyde resins cause irritant contact dermatitis as well as depigmentation, chemical burns, and contact urticaria. The formaldehyde or phenols itself are not important allergens; however, monomers and dimers with hydroxymethyl phenols are strong allergens.

20.5.7.3 Main Allergens

Patch testing with formaldehyde resins should include phenol-formaldehyde resin, PTBFR, para-tertiary butylphenol, formaldehyde, hexamethylenetetramine, urea-formaldehyde resin, and melamine formaldehyde (Rietschel and Fowler 2001). Additionally, to detect allergy to phenol-formaldehyde resins based on phenols other than para-tertiary butylphenol, patch testing should be performed with the specific phenol-formaldehyde resin that the patient is exposed to [5]. Cross-reactions may occur between phenol-formaldehyde resins and formaldehyde, resin monomer, and other formaldehyde-based resins.

References

1. Aalto-Korte K, Alanko K, Kuuliala O, Jolanki R. Occupational methacrylate and acrylate allergy from glues. Contact Dermatitis. 2008;58(6):340–6.
2. Aalto-Korte K, Jungewelter S, Henriks-Eckerman ML, Kuuliala O, Jolanki R. Contact allergy to epoxy (meth)acrylates. Contact Dermatitis. 2009;61(1):9–21.
3. Aalto-Korte K, Pesonen M, Henriks-Eckerman M. Occupational contact allergy to the epoxy methacrylate 2,2-bis[4-(2-methacryloxyethoxy)phenyl] propane in an anaerobic glue. Contact Dermatitis. 2013;68(5):314–5.
4. Bruze M, Bjorkner B, Lepoittevin J. Occupational allergic contact dermatitis from ethyl cyanoacrylate. Contact Dermatitis. 1995;32(3):156–9.
5. Bruze M, Fregert S, Zimerson E. Contact allergy to phenol-formaldehyde resins. Contact Dermatitis. 1985;12(2):81–6.
6. Cavelier C, Jelen G, Herve-Bazin B, Foussereau J. Irritation and allergy to acrylates and methacrylates. – part I: common monoacrylates and monomethacrylates. Ann Dermatol Venereol. 1981;108(6-7):559–66.

7. Downs A, Sansom J. Colophony allergy: a review. Contact Dermatitis. 1999;41(6):305–10.
8. Freeman S. Shoe dermatitis. Contact Dermatitis. 1997;36(5):247–51.
9. Fries I, Fisher A, Salvati E. Contact dermatitis in surgeons from methylmethacrylate bone cement. J Bone Joint Surg Am. 1975;57(4):547–9.
10. Garcia-Bravo B, Pons A, Rodreguez-Pichardo A. Oral lichen planus from colophony. Contact Dermatitis. 1992;26(4):279.
11. Hausen B, Krohn K, Budianto E. Contact allergy due to colophony (VII), Sensitizing studies with oxidation products of abietic and related acids. Contact Dermatitis. 1990;23(5):352–8.
12. Hausen B, Kulenkamp D. Allergische kontaktdermatitis auf einem hydrokolloidverband bei kolophoniumallergikern. Aktuelle Dermatol. 1998;24:174–7.
13. Heskel N, Sarnour C, Storrs F. Allergic contact dermatitis from dodecyl maleamic acid in Curad adhesive plastic bandages. J Am Acad Dermatol. 1982;7(6):747–51.
14. Hjorth N. Eczematous allergy to balsams, perfumes and flavouring agents. Dan Med Bull. 1961;8:143–4.
15. James W. Allergic contact dermatitis to a colophony derivative. Contact Dermatitis. 1984;10(1): 6–10.
16. Jolanki R, Kanerva L, Estlander T, Tarvainen K, Keskinen H, Henriks-Eckrmaan M. Occupational dermatoses from epoxy resin compounds. Contact Dermatitis. 1990;23(3):172–83.
17. Jolanki R, Kanerva L, Estlander T, Tarvainen K. Epoxy dermatitis. Occup Med. 1994;9(1):97–112.
18. Jolanki R. Occupational skin diseases from epoxy compounds. Epoxy resin compounds, epoxy acrylates and 2,3-epoxypropyl trimethyl ammonium chloride. Acta Derm Venereol Suppl. 1991;159:1–80.
19. Kanerva L, Estlander T, Jolanki R. Active sensitization caused by 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, ethyleneglycol dimethacrylate and N, N-dimethylaminoethyl methacrylate. J Eur Acad Dermatol Venereol. 1992;1(3):165–9.
20. Karlberg A, Bohlinder K, Boman A, Hacksell U, Hermansson J, Jacobsson S, et al. Identification of 15-hydroperoxyabietic acid as a contact allergen in Portuguese colophony. J Pharm Pharmacol. 1988;40(1):42–7.
21. Lee H, Pokorny C, Law S, Pratt M, Sasseville D, Storrs F. Cross-reactivity among epoxy acrylates and bisphenol F epoxy resins in patients with bisphenol a epoxy resin sensitivity. Dermatitis. 2002;13(3):108–15.
22. Lushniak B. Occupational contact dermatitis. Dermatol Ther. 2004;17:272–7.
23. Malten K. Dermatological problems with synthetic resins and plastics in glues. Part I. Derm Beruf Umwelt. 1984;32(3):81–6.
24. Matrolonardo M, Loconsole F, Conte A, Rantuccio F. Allergic contact dermatitis due to para-tertiary-butylphenol-formaldehyde resin in a hearing aid. Contact Dermatitis. 1993;28(3):197.
25. Sasseville D, Tennstedt D, Lachapelle JM. Allergic contact dermatitis from hydrocolloid dressings. Am J Contact Dermat. 1997;8(4):236–8.
26. Schalock P, Menne T, Johansen J, Taylor J, Maibach H, Liden C, et al. Hypersensitivity reactions to metallic implants – diagnostic algorithm and suggested patch test series for clinical use. Contact Dermatitis. 2012;66(1):4–19.
27. Schalock P, Zug K. Protection from occupational allergens. Curr Probl Dermatol. 2007;34:58–75.
28. Sood A, Taylor J. Acrylic reactions: a review of 56 cases. Contact Dermatitis. 2003;48(6):346–7.
29. Suhng E, Byun J, Choi Y, Myung K, Choi H. A case of allergic contact dermatitis due to DuoDERM ExtrathinÂ®. Ann Dermatol. 2011;23 Suppl 3:S387.
30. Tarvainen K. Analysis of patients with allergic patch test reactions to a plastics and glues series. Contact Dermatitis. 1995;32(6):346–51.
31. Thorgeirsson A, Fregert S. Allergenicity of epoxy resins in the guinea pig. Acta Derm Venereol. 1977;57(3):253–6.
32. Widman T, Oostman H, Storrs F. Allergic contact dermatitis to medical adhesive bandages in patients who report having a reaction to medical bandages. Dermatitis. 2007;18(2):103.

Metalworking Fluids

21

Johannes Geier

Contents

21.1 Introduction

Metalworking fluids (MWFs) are indispensable for lubricating and cooling workpieces and tools and for flushing away metal chips in lathing, turning, drilling, etc. Basically, there are two types of MWF.

- Water-based MWF (wb MWF) are aqueous dilutions of MWF concentrates.
- Neat oils are non-water-miscible oily preparations used undiluted.

According to the respective needs, emulsifiers, buffers, stabilisers, anti-fog additives, foam inhibitors, corrosion inhibitors, biocides, and other components are added to the MWF base material. Being used for weeks or months, wb MWF has to be effectively protected from degradation by microorganisms. Therefore, additional

J. Geier, MD
IVDK, University of Göttingen, Von-Bar-Str. 2-4, Göttingen 37075, Germany
e-mail: jgeier@gwdg.de

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_21

biocides are added during the working process, and these may differ from the biocides contained in the original product. MWF may be contaminated by slideway oils or hydraulic oils leaking from the processing machines [3, 7, 15].

Chronic or repetitive exposure to MWF can lead to occupational contact dermatitis (OCD). Bacterial superinfections do occur. Long-term prognosis of MWF dermatitis may be unsatisfactory because acceptance of barrier creams is rather low among metalworkers and wearing protective gloves is prohibited at many MWF workplaces because of the risk of injury from rotating tools [3, 4, 13].

21.2 Irritant Contact Dermatitis Caused by Metalworking Fluids

Skin contact with wb MWF means wet work, and their alkaline pH (usually 8.5–9.6) as well as the contents of emulsifiers and biocides increases their irritant properties. Most metalworkers have no continuous but repetitive exposure to wb MWF (e.g. when changing the workpiece). Splashes of wb MWF on the skin dry up within minutes, resulting in an increased concentration and enhanced irritancy. In addition, mechanical factors, such as pressure and friction, and exposure to metal chips and dust contribute to the epidermal barrier damage in metalworkers [3, 4, 12].

In most studies on OCD in metalworkers, irritant contact dermatitis (ICD) is more frequently reported than allergic contact dermatitis (ACD). However, like in other professional settings, ICD often precedes and promotes sensitization.

21.3 Contact Allergens in Metalworking Fluids

The most frequently reported allergens in MWF are monoethanolamine (MEA), colophonium/abietic acid, formaldehyde, and formaldehyde releasers [5, 6, 8]. Many other MWF components have been reported as relevant allergens in single cases, such as diglycolamine; ethylenediamine; alkanolamine borates, a condensate of boric acid, MEA, and fatty acids; fatty acid polydiethanolamide; oleyl alcohol; tertiary-butylhydroquinone; imazalil; iodopropynyl butylcarbamate; sodium pyrithione; ethylhexylzinc dithiophosphate; oak moss resin; glyoxal; 2,5-dimercapto-1, 3,4-thiadiazole; and phenyl-alpha-naphthylamine [4]. Patch testing with the MWF allergens listed in Table 21.1 is recommended. Some baseline series allergens are also relevant in MWF dermatitis; see Table 21.2. The most important and most discussed allergens are described in detail in the following sections.

21.3.1 Monoethanolamine, Diethanolamine, and Triethanolamine

MEA, diethanolamine (DEA), and triethanolamine (TEA) serve as rust preventive agents with emulsifying properties in wb MWF. In several recent studies, MEA

Table 21.1 MWF allergens recommended for patch testing in patients with suspected MWF dermatitis

No.	Substance	Patch test concentration
Biocides		
1	7-Ethylbicyclooxazolidine (Bioban CS 1246)	1 % pet
2	Benzylhemiformal	1 % pet
3	4,4-Dimethyl-1,3-oxazolidine/3,4,4-trimethyl-1,3-oxazolidine (Bioban CS 1135)	1 % pet
4	N,N′-Methylene-bis-5-methyl-oxazolidine	1 % pet
5	1,3,5-Tris(2-hydroxyethyl)-hexahydrotriazine (Grotan BK)	1 % pet
6	4-(2-Nitrobutyl) morpholine/4,4′-(2-ethyl-2-nitro-trimethylene) dimorpholine (Bioban P 1487)[a]	1 % pet
7	1,2-Benzisothiazolin-3-one, sodium salt	0.1 % pet
8	Octylisothiazolinone	0.025 % pet
9	Methylisothiazolinone	0.05 % aq[a]
10	Iodopropynyl butylcarbamate (IPBC)	0.2 % pet
11	Sodium-2-pyridinethiol-1-oxide (Sodium Omadine)	0.1 % aq
12	2-Phenoxyethanol	1 % pet
Other components		
13	Morpholinyl mercaptobenzothiazole (MOR)[b]	0.5 % pet
14	Monoethanolamine (MEA)	2 % pet
15	Diethanolamine (DEA)[b]	2 % pet
16	Triethanolamine (TEA)	2.5 % pet
17	Diglycolamine (2-(2-aminoethoxy)ethanol)	1 % pet
18	Abietic acid	10 % pet
19	p-tert-Butylphenol	1 % pet
20	Benzotriazole	1 % pet

Modified from Refs. 5, 7, 8
Allergen nos. 1–18 are used in wb MWF, no. 19 in neat oils, and no. 20 in both
Allergen nos. 1–6 are formaldehyde releasers
[a]Higher patch test concentrations are also recommended by some authors
[b]Used until about 1995. No current usage in MWF

Table 21.2 Allergens of the baseline series which may be present in wb MWF (except no. 7, see below)

No.	Substance	Patch test concentration
1	Formaldehyde	1 % aq[a]
2	(Chloro-)methylisothiazolinone (MCI/MI)	0.01 % aq[a]
3	Lanolin alcohol	30 % pet
4	Cetearyl alcohol	20 % pet
5	Colophonium	20 % pet
6	Mercaptobenzothiazole	2 % pet
7	Zinc diethyldithiocarbamate (ZDEC)[b]	1 % pet

[a]Higher patch test concentrations are also recommended by some authors
[b]Tested as a marker for sodium diethyldithiocarbamate, used as anti-wear additive in neat oils

ranked first among the MWF allergens. The use of DEA in wb MWF has declined since the mid-1990s, due to a potential formation of carcinogenic N-nitrosamines. This led to a far lower frequency of sensitization to DEA compared to MEA. TEA is a rare MWF allergen. It is not only used in MWF, but also a frequent component of creams and cosmetics [5, 6, 8, 14].

21.3.2 Colophonium/Abietic Acid

The main sensitizers in colophonium are oxidation products of abietic acid and other resin acids. The same allergens are found in distilled tall oil (DTO), which is a base material of wb MWF. About 30 % of the DTO are resin acids, and of these, about one-third is abietic acid. Resin acids oxidise rather quickly on exposure to air, which occurs on a large scale during normal use of wb MWF [7, 11]. In this way, the used wb MWF at the workplace contains the same allergens as the colophony or abietic acid patch test preparations. A relevant exposure to these allergens is given, even though their concentration in the MWF may be rather low, because the MWF dries up on the contaminated, mostly pre-damaged skin [12]. Epidemiological data confirmed the high risk of sensitization to colophonium in metalworkers with OCD and exposure to wb MWF [4].

21.3.3 Formaldehyde and Formaldehyde Releasers

Decades ago, formaldehyde solution was a common additional preservative for wb MWF during usage. Nowadays, primarily formaldehyde releasers are used. Several studies showed an increased frequency of sensitization to formaldehyde among metalworkers with OCD exposed to wb MWF. Allergic reactions to formaldehyde releasers may be directed towards the whole molecule or to the formaldehyde released. Patch test reactions to formaldehyde releasers are often weak and poorly reproducible which makes assessing the relevance of positive test reactions difficult [2, 6]. The first six allergens in Table 21.1 are formaldehyde releasers.

21.3.4 Isothiazolinones

The biocide combination methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) is not used as a preservative in MWF concentrate production, but it may be added to the wb MWF at the workplace during usage [7]. Concentrated MCI/MI solution must be handled with care: a single skin contact may cause sensitization. In recent years, MI without MCI, but in combination with other preservatives, has been increasingly used, particularly in cosmetic and body care products. This caused an epidemic of sensitization to MI since 2009 all over Europe [10]. Many patients primarily sensitised to MI also cross-react to MCI. Both, MCI/MI and MI, are also used in other areas of application, such as water-based paints, household

products, cleansers, etc. Therefore, the allergen source has to be established carefully in every individual case. Benzisothiazolinone (BIT) and octylisothiazolinone (OIT) are also used for preservation of wb MWF and may cause sensitization in this context [8].

21.3.5 Cobalt, Nickel, and Chromium

Cobalt, nickel, and chromium are not present in fresh, unused MWF. In used MWF, concentrations usually are below 3 ppm. However, if hard metals containing cobalt are processed, cobalt concentrations up to 300 ppm were found [3, 4]. If this amount of cobalt is present in MWF as dissolved ions, it can be sufficient to elicit and possibly even to induce allergic reactions [1]. In a large epidemiological data analysis, metalworkers had no increased risk of sensitization to cobalt, nickel, or dichromate, indicating that occupational relevance of contact allergy to these metals is rare [4]. Therefore, the source of exposure and clinical relevance of positive test reactions has to be assessed thoroughly in every individual case. Other occupational exposures (e.g. metal workpieces, tools, handles) or private exposures (e.g. jeans button, costume jewellery, piercing) have to be considered.

21.3.6 Fragrances

Fragrances were mentioned as common components of wb MWF until about 1990 [4]. According to information from the lubricant producing industry, no fragrances are added to the MWF concentrates nowadays. However, it cannot be excluded that so-called odour masks are added by the metalworking companies during the usage of the wb MWF. In a German study on occupational contact sensitization performed in 1999–2001, metalworkers exposed to wb MWF with OCD had an increased risk of sensitization to fragrance mix and *Myroxylon pereirae* (balsam of Peru), when compared to metalworkers with OCD who were *not* exposed to wb MWF [6]. However, more recent data (2002–2003 and 2005–2009) showed that the proportions of allergic reactions to fragrance mix and *Myroxylon pereirae* (balsam of Peru) among metalworkers with OCD presumably caused by MWF were not significantly increased [5, 8]. Like with other allergens, a complete history has to be taken in every individual case, particularly with respect to other allergen sources (e.g. aftershave, deodorant, etc.).

21.4 Patch Testing with MWF from the Patient's Workplace

Patch testing with commercially available MWF patch test series does not cover all potentially allergenic MWF components. Therefore, MWF from the patient's workplace and their components should be tested in compliance with the following recommendations [3, 9, 15].

Checklist for Patch Testing with MWF from the Patient's Workplace [15]

1. Test both fresh and used MWFs.
2. Take the sample of used MWF from the inflow of the machine (and not from the so-called sump) to avoid contamination with metal chips, which may cause irritant patch test reactions.
3. Store samples of used wb MWF in a refrigerator and test within 4 days or less, because of microbial contamination.
4. Check pH before patch testing. Usually, wb MWF is alkaline (pH 8.6–9.5), but experience shows that this is tolerated.
5. Get information:
   About used wb MWF: concentration and pH at the time of sampling, date of the last change of the MWF, system cleaner used, date of last additional preservation, name of bactericide and fungicide used, name of other additives and date of addition, material processed in the machine, possible influx of hydraulic oils, slideway oils, or other oils by leakage.
   About used neat oils: date of the last change of the MWF, additives, material processed in the machine, or possible influx of other oils.
6. Recommended patch test concentrations:
   Fresh and used neat oil: 50 % in olive oil
   Fresh wb MWF: MWF concentrate 5 % in water
   Used wb MWF: pure or diluted in water, until the concentration of the MWF concentrate is 4–8 %

Dilution of the used wb MWF for patch testing depends on the workplace concentration of the MWF concentrate. If it is above 8 %, dilution with water to an end concentration of 4–8 % is recommended. False-negative test reactions to MWF may occur because single allergen concentration may be too low. Therefore, single components of the MWF should not only be patch tested in case of a positive test reaction to the MWF from the workplace, but also in clinically suspected cases, in which no test reaction to the individual MWF is seen [15].

References

1. Allenby CF, Basketter DA. Minimum eliciting patch test concentrations of cobalt. Contact Dermatitis. 1989;20:185–90.
2. de Groot AC, Flyvholm M-A. Formaldehyde and formaldehyde-releasers. In: Rustemeyer T, Elsner P, John SM, Maibach HI, editors. Kanerva's occupational dermatology. 2nd ed. Berlin: Springer; 2012. p. 397–413.
3. Foulds IS. Cutting fluids. In: Rustemeyer T, Elsner P, John SM, Maibach HI, editors. Kanerva's occupational dermatology. 2nd ed. Berlin: Springer; 2012. p. 715–25.
4. Geier J, Lessmann H. Metalworking fluids. In: Johansen JD, Frosch PJ, Lepoittevin JP, editors. Contact dermatitis. 5th ed. Berlin: Springer; 2011. p. 681–94.

5. Geier J, Lessmann H, Dickel H, Frosch PJ, Koch P, Becker D, et al. Patch test results with the metalworking fluid series of the German contact dermatitis research group (DKG). Contact Dermatitis. 2004;51:118–30.
6. Geier J, Lessmann H, Schnuch A, Uter W. Contact sensitizations in metalworkers with occupational dermatitis exposed to water-based metalworking fluids. Results of the research project "FaSt". Int Arch Occup Environ Health. 2004;77:543–51.
7. Geier J, Lessmann H, Schumacher T, Eckert C, Becker D, Boveleth W, et al. Vorschlag für die Epikutantestung bei Verdacht auf Kontaktallergie durch Kühlschmierstoffe. 1. Kommerziell erhältliche Testsubstanzen. Dermatol Beruf Umwelt. 2000;48:232–6.
8. Geier J, Lessmann H, Skudlik C, Weisshaar E, Schnuch A. Kontaktallergie gegen Bestandteile von Kühlschmierstoffen. IVDK-Daten der Jahre 2005–2009. Dermatol Beruf Umwelt. 2013;61:137–49.
9. Geier J, Uter W, Lessmann H, Frosch PJ. Patch testing with metalworking fluids from the patient's workplace. Contact Dermatitis. 2004;51:172–9.
10. Goncalo M, Goossens A, on behalf of the ESCD. Whilst Rome burns: the epidemic of contact allergy to methylisothiazolinone. Contact Dermatitis. 2013;68:257–8.
11. Karlberg A-T. Air oxidation increases the allergenic potential of tall-oil rosin. Colophonium contact allergens also identified in tall-oil rosin. Am J Contact Dermatol. 1991;2:43–9.
12. Krbek F, Schäfer T. Untersuchungen an Tropfen und Rückständen von wassermischbaren Kühlschmierstoffen. Arbeitsmed Sozialmed Präventivmed. 1991;26:411–6.
13. Kütting B, Weistenhöfer W, Baumeister T, Uter W, Drexler H. Current acceptance and implementation of preventive strategies for occupational hand eczema in 1355 metalworkers in Germany. Br J Dermatol. 2009;161:390–6.
14. Lessmann H, Uter W, Schnuch A, Geier J. Skin sensitizing properties of the ethanolamines mono-, di-, and triethanolamine. Data analysis of a multicentre surveillance network (IVDK) and review of the literature. Contact Dermatitis. 2009;60:243–55.
15. Tiedemann K-H, Zoellner G, Adam M, Becker D, Boveleth W, Eck E, et al. Empfehlungen für die Epikutantestung bei Verdacht auf Kontaktallergie durch Kühlschmierstoffe. 2. Hinweise zur Arbeitsstofftestung. Dermatol Beruf Umwelt. 2002;50:180–9.

Plants

22

Christopher Lovell

Contents

22.1 Introduction

In order to manage a patient with suspected plant dermatitis, it is important to take a careful history, including the patient's occupation and leisure activities, including gardening and use of cosmetics, toiletries or household products. Which parts of the body are affected? Is the rash recurrent? Is there seasonal variation (e.g. compositae dermatitis is worse during the growing season – summer months in northern Europe)?

Precise identification of the suspected plants is important; patients are often well informed, but beware common names, which often apply to several different

C. Lovell, MB, ChB, MD, FRCP
Department of Dermatology, Royal United Hospital, Bath NHS Trust – RD1, Combe Park, Bath BA13NG, UK
e-mail: Christopher.lovell@nhs.net

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_22

unrelated species. Illustrated books on wild flowers and common garden plants (e.g. the RHS Encyclopedia of Plants and Flowers [1]) are valuable in the patch testing clinic. It may be necessary to send photographs or plant material to a botanical expert; representative specimens of plant material (including leaf, stem and flower if possible) can be pressed between paper towels before sending; never send plant material in a sealed polythene bag, which will result in a rotting squashed pulp! Ideally the botanical name should include an attribution to the botanist who described it (e.g. L for Linnaeus).

Several books (mostly out of print) have been written on plant dermatitis, both in English and German [2–7]. The pioneering text by Mitchell and Rook [2] has been made available electronically and updated by RJ Schmidt (www.botanical-dermatology-database.info).

22.2 Skin Reactions to Plants

Many plants are *irritant*. In common with other mechanical irritants, hairs and spines on the surface of the plant can induce pruritus (e.g. the hairlike material in rose hips has been used to make itching powder) and even inflammatory skin lesions. Chronic exposure to mechanical irritants may induce a lichenified contact dermatitis. Several plants contain chemical irritants, such as calcium oxalate crystals in *Narcissus* and phorbol esters in the milky sap (latex) of *Euphorbia* species. Others, such as the stinging nettle (*Urtica* spp.), employ irritants and pharmacologically active chemicals, such as histamine, as chemical warfare to deter predators. Occlusion in a patch test chamber or under a dressing will enhance irritancy, and it is inadvisable to patch test with an unidentified, and potentially irritant, plant; a painful chemical burn and even keloid scarring may result.

Some plant families contain linear furocoumarins (psoralens) as part of their immune defence against fungi. These substances are *phototoxic* to man, inducing painful bullous lesions, often in streaks, in areas exposed to the plant sap and long wave ultraviolet light (UVA) (Fig. 22.1).

Children playing outdoors and scantily clad gardeners operating string trimming tools are especially at risk. Careful history and examination can usually distinguish phototoxic from allergic reactions to plants (Table 22.1). Members of the Apiaceae (Umbelliferae) family, including food plants such as parsnip, celery and parsley, as well as common wildflowers such as *Heracleum* spp. (Fig. 22.2) are common culprits.

Other plant families containing phototoxic species are Moraceae (fruiting figs) and Rutaceae, including *Ruta* (rue) (Fig. 22.3), *Dictamnus* (burning bush) and citrus fruit, notably limes. Phototoxicity can occur in any individual; it does not represent an idiosyncratic response to the plant, and patch testing is not helpful. Prevention includes identification of potentially phototoxic plants and adequate photoprotection against UVA when coming into contact with them. For example, rue should not be planted near a swimming pool or on a sun terrace.

Immediate hypersensitivity may present as urticarial lesions, conjunctivitis, rhinitis, bronchospasm or even anaphylaxis. Grass and tree pollens are often

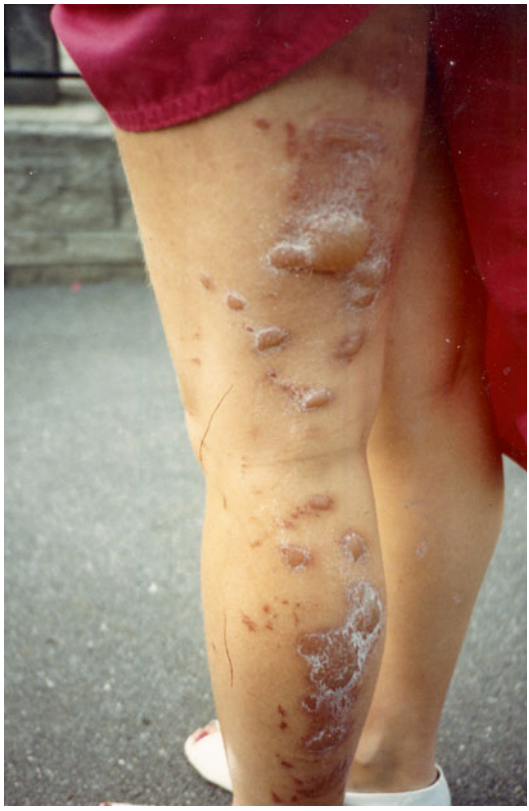


Fig. 22.1 Phototoxic reaction after harvesting parsnips on a sunny day

Table 22.1 Distinction between phototoxic and allergic reactions to plants

Phototoxic	Allergic
All lesions present simultaneously	Lesions may gradually evolve over hours/days
Sharply demarcated	Often less clearly demarcated
Restricted to areas of sun exposure	Not restricted to areas of sun exposure
Typically streaky, vesicular or bullous	Often streaky, erythematous, may be vesicular or bullous
Often painful	Pruritic
Followed by hyperpigmentation, which may persist for several months	Minimal, if any, hyperpigmentation
No scaling	Scaling during resolution
Commoner in children at play	Commoner in adults
Often a single episode	May be a history of recurrent episodes, sometimes worsening with each episode

implicated in asthma and hay fever. Vegetables are an important cause of contact urticaria and protein contact dermatitis in food handlers [8]. Skin prick testing with fresh produce is preferable to reliance on commercial extracts as antigens can be destroyed or modified by processing [8].

Fig. 22.2 *Heracleum sphondylium*, a phototoxic member of the Apiaceae

Fig. 22.3 *Ruta graveolens* (rue)

This chapter concentrates on *delayed hypersensitivity* (allergic contact dermatitis), caused by plants or plant products. Although nearly 19,000 plant species may be implicated in allergic contact dermatitis [5], most commonly encountered culprits belong to a small number of plant families (listed in bold type in Table 22.2). The major chemical groups of allergens implicated in plant dermatitis are listed in Table 22.3 [9]. Many allergenic plants are also irritant. As with other allergens, extensive exposure, e.g. pruning or removing dead leaves, increases the risk of becoming sensitised. Thus, a greenhouse worker handling large numbers of specimens may become sensitised to a plant which is generally a low risk to the casual grower.

Table 22.2 Allergenic plant families

Anacardiaceae (poison ivy/oak, etc.)
Asteraceae (Compositae) daisy family
Primulaceae (*Primula obconica*)
Araliaceae (ivy)
Lamiaceae (lavender, rosemary, thyme, mint)
Alstroemeriaceae (*Alstroemeria*)
Alliaceae (garlic, onion, shallot)
Jubulaceae (liverworts, e.g. *Frullania*)
Apiaceae (carrots, celery)
Myrtaceae (tea tree, eucalyptus)
Ginkgoaceae (*Ginkgo*)
Hydrophyllaceae (*Phacelia*, *Eriodictyon*)
Orchidaceae (*Vanilla*, *Paphiopedilum*)
Simaroubaceae (tree of heaven (*Ailanthus*))
Tropical hardwood families, including Leguminosae, Ebenaceae, Sapotaceae
Cupressaceae and Pinaceae (conifers)
Graminae (grasses, cereals)
Lichens

Table 22.3 Important allergens in the plant kingdom

α-Methylene γ-butyrolactones
Sesquiterpene lactones in Asteraceae (Compositae), Liverworts, e.g. *Frullania* (Jubulaceae), *Magnolia* (Magnoliaceae)
Tuliposide A (hydrolysed to α-methylene γ-butyrolactone plus glucose) in *Alstroemeria*, *Tulipa*
Quinones
In *Primula*, *Phacelia*, *Eriodictyon*, tropical hardwoods
Phenol derivatives
In *Rhus* (*Toxicodendron*)
Terpenoids
In *Lavandula* (lavender, Lamiaceae), *Citrus* (Rutaceae), tea tree (*Melaleuca*, Myrtaceae)
Miscellaneous
Disulphides, in garlic, onion (*Allium spp.*)
Isothiocyanates, in mustard oil (*Brassica nigra*, Brassicaceae)
Polyacetylene derivatives, e.g. falcarinol in ivy (*Hedera helix*)

22.3 Major Plant Families Which Cause Allergic Contact Dermatitis (Table 22.2) [2–5]

22.3.1 Anacardiaceae (Figs. 22.4 and 22.5)

Poison ivy and poison oak (*Rhus* spp.) are major causes of allergic dermatitis in the USA, but rare in western Europe, although occasional outbreaks are attributed to the Japanese lacquer tree (*Rhus verniciflua*), planted as an ornamental. This family is an important cause of dermatitis worldwide, including mango (*Mangifera indica*) in the tropics, cashew nut tree (*Anacardium occidentale*) and marking nut tree (*Semecarpus anacardium*) in India and *Smodingium argutum* in Southern Africa. Allergic reactions present typically as a florid vesiculobullous dermatitis, often in streaks, affecting the face, limbs and sometimes genitalia. Black specks of oxidised urushiol may be found on skin or clothes. Patch testing with these plants or their allergens (pentadecylcatechols) carries a high risk of active sensitisation and should be avoided.

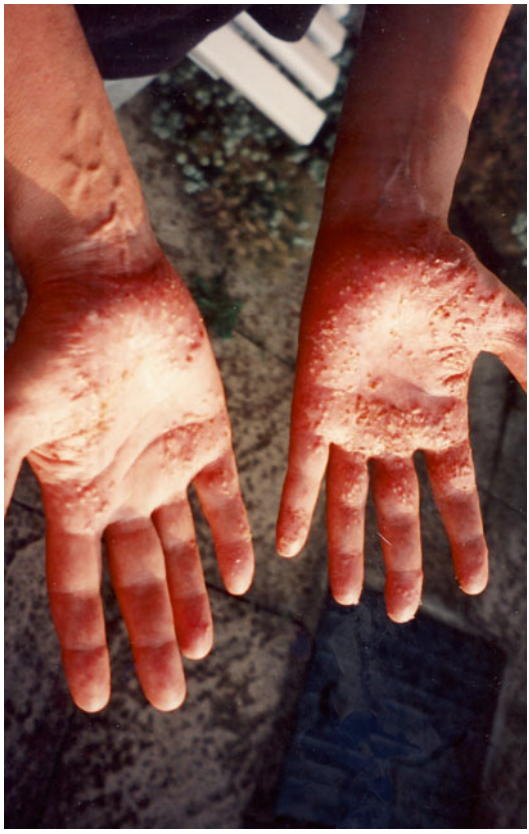


Fig. 22.4 Vesicular allergic contact dermatitis after handling poison ivy

Fig. 22.5 *Rhus* (*Toxicodendron*) *succedaneum*, an allergenic member of the Anacardiaceae

22.3.2 Asteraceae (Compositae)

Members of this huge family (over 20,000 species) are the commonest causes of plant dermatitis reports worldwide. It includes ornamental plants such as the florist's chrysanthemum (*Dendranthema* cvs.), vegetables and herbs and native and introduced weeds, such as *Parthenium hysterophorus* in India and Africa. Dermatitis may initially affect the hands, but an airborne pattern is characteristic, mimicking photosensitivity but affecting skin folds and areas shielded from sunlight (Fig. 22.6). Photoallergy to Asteraceae rarely, if ever, occurs; however, secondary photosensitivity (chronic actinic dermatitis) may follow repeated episodes of airborne antigenic challenge from material shed from the surface of the plants.

Together with Anacardiaceae, Asteraceae may cause systemic contact dermatitis after ingestion of material to which the individual has been previously sensitised by contact. Feverfew, taken orally for migraine, is an example. This resembles the "baboon syndrome" or *S*ystemic *D*rug-*R*elated *I*ntertriginous and *F*lexural *E*xanthema (SDRIFE) caused by drugs [10].

There are over 5,000 sesquiterpene lactones, the terpenoids responsible for Asteraceae contact dermatitis. The "sesquiterpene lactone mix", comprising three pure chemicals, costunolide, dehydrocostus lactone and alantolactone, has traditionally been used as a screen for Asteraceae allergy [11]. Active sensitisation is rare with this mix, but it only detects around 30–35 % of allergic patients [12]. Additional patch testing with parthenolide, with careful addition of extracts of locally important Asteraceae, increases the sensitivity [13]. The compositae mix [14] is comprised of ether extracts of five wild plants (Table 22.4); it detects more patients but carries a higher risk of active sensitisation and can give false-positive irritant

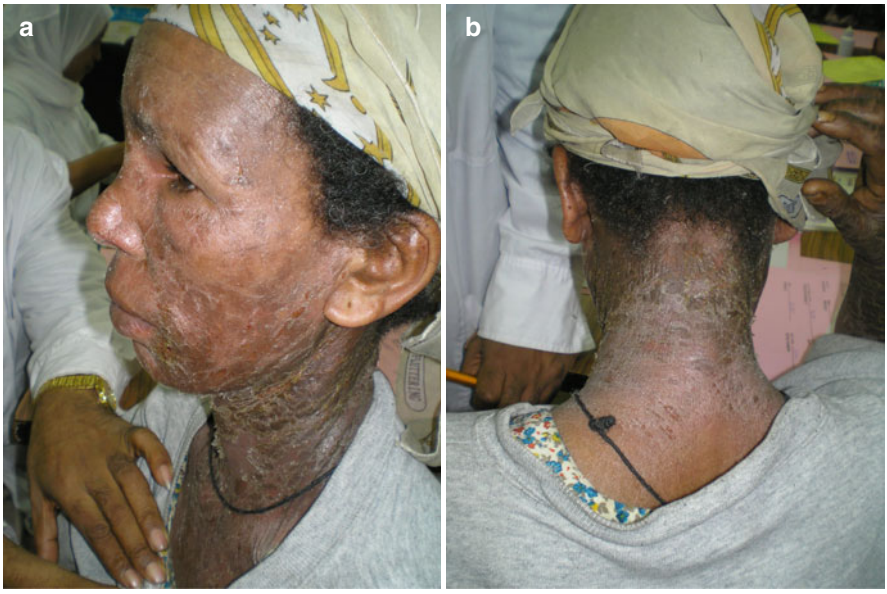


Fig. 22.6 (**a**, **b**) Allergic contact dermatitis to Asteraceae (Compositae) in an Ethiopian farmer

Table 22.4 Constituents of two commercial compositae mixes [13]

6 % pet
Tanacetum parthenium (feverfew) extract 1 %
Tanacetum vulgare (tansy) extract 1 %
Chamomilla recutita (German chamomile) extract 2.5 %
Achillea millefolium (yarrow) extract 1 %
Arnica montana (arnica) extract 0.5 %
5 % pet
Parthenolide 0.1 %
Tanacetum vulgare extract 1 %
Chamaemelum nobile (Roman chamomile) extract 2.4 %
Achillea millefolium extract 1 %
Arnica montana extract 0.5 %

reactions in higher concentrations. Furthermore, the potential variability of chemical constituents in wild populations of these plants can affect the reproducibility of such a mix. The 6 % mix devised by Hausen elicits more positive reactions than the 5 % mix currently available commercially [13]. Recently a modified sesquiterpene lactone mix has been proposed, which better reflects the structural range of different sesquiterpene lactones and may prove to be a more sensitive testing material [15].

22.3.3 Primulaceae

The classical streaky eruption on the forearms from handling *Primula obconica* is now rare, since the development of "hypoallergenic" cultivars which contain less primin [16]. Primin, a quinone, is the principal allergen, although miconidin can also sensitise [17]. In common with dermatitis induced by other quinones, primin may induce an erythema multiforme – like eruption. Primin appears not to be responsible for the dermatitis induced by hardy *Primula* species in alpine gardeners [18].

22.3.4 Araliaceae

So-called English ivy, *Hedera helix* and its varieties (Fig. 22.7) are unrelated to poison ivy. It is an underreported cause of contact dermatitis [19] which is typically florid and oedematous; dermatitis often affects gardeners hacking back ivy in the spring when it is in full growth. Children playing in undergrowth are also at risk. The major allergen is falcarinol, also found in carrots. Unfortunately purified falcarinol is expensive to produce and unstable; it is not currently commercially available. At present it is best to patch test with dried ivy leaf, if dermatitis is suspected, but there is a slight risk of active sensitisation.

22.3.5 Alstroemeriaceae

Alstroemeria cultivars are widely used in floristry; the attractive flowers (Fig. 22.8) last well when cut. Unfortunately the stems are leafy, and florists are often sensitised by stripping off the stem leaves or picking individual flowers for wreaths. The plants contain tuliposide A, which is rapidly hydrolysed to the more allergenic α-methylene γ-butyrolactone, which is available commercially. This is also found in tulip bulbs, which can cause fingertip dermatitis in bulb handlers. Patch testing with *Alstroemeria* plant material may sensitise a previously unaffected florist. Newer cultivars of *Alstroemeria* appear to be less allergenic.

Fig. 22.7 *Hedera helix* (English ivy) leaves

Fig. 22.8 *Alstroemeria ligtu* hybrid

22.3.6 Other Families

Some other plant causes of allergic dermatitis are listed in Table 22.2.

Garlic (*Allium sativum*) and onion (*Allium cepa*) are members of the *Alliaceae*. Typically, garlic dermatitis affects the tips of the thumb, index and middle fingers of the nondominant hand, which holds the clove during food preparation. The major allergen is diallyl disulphide, which is present to a lesser amount in onions and is commercially available. There are several reports of garlic inducing severe chemical burns when occluded on the skin (e.g. [20]), and garlic should not be used "as is" in patch testing.

Colophony and turpentine are derived from conifers. Sawing or burning the fast-growing hybrid conifer *Cupressocyparis leylandii* (*Cupressaceae*) or other conifers can elicit a florid dermatitis, often in an airborne distribution, in colophony-sensitive individuals.

Melaleuca leucadendron (*Myrtaceae*) is the source of tea tree oil, popularly used in toiletries and over-the-counter medications for its antiseptic properties. Although dermatitis from tea tree oil is often irritant, the constituent terpenoids are also allergenic [21] and may cross-react with other terpenoids widely used in cosmetics and household products, such as limonene, derived from lemons and other citrus fruit (*Rutaceae*), and linalool, derived from lavender oil (*Lavandula spp*., *Lamiaceae*). Oxidation of these and related terpenoids to hydroperoxides greatly increases their allergenic potential. Sources of sensitisation include partly used bottles of perfume and lavender bags [22].

Lichens comprise a symbiotic relationship between fungi and *algae*. Foresters, agriculturalists and timber workers may be occupationally sensitised, but most allergic dermatitis results from the use of lichen extracts, such as oak moss, in perfumery. This may explain a high incidence of perfume dermatitis in foresters and agricultural workers [23].

Allergenic quinones, e.g. dalbergiones, are found in several species of tropical hardwoods, many of which are threatened by habitat destruction. Because of the

rarity and expense of these timbers, allergic reactions are encountered chiefly in specialist antique restorers (Fig. 22.9) or musicians such as recorder players. Wood dust induces an airborne pattern of dermatitis. Irritant reactions are common on patch testing with wood dust and shavings, and control subjects should be tested if a positive result is obtained. Active sensitisation is a significant risk, particularly with strong sensitisers such as pau ferro ("Santos rosewood", *Machaerium scleroxylon*) and teak (*Tectona grandis*). A technique for making ethanol extracts from tropical woods is recommended by Hausen [24]. Quinones, such as geranylhydroquinone, also occur in the family *Hydrophyllaceae*, which includes ornamental plants such as *Phacelia* (often grown as a bee plant); this genus, and the related *Eriodictyon* (*Turricula parryi*), is native to California and induces contact dermatitis in walkers and ramblers [25].

Ferns, such as *Arachniodes adiantiformis* (*Dryopteridaceae*), cause occasional occupational dermatitis in florists, who use the fronds in arrangements as a substitute for *Asparagus plumosus*. Fruit of the Asian genus *Ginkgo* (*Ginkgoaceae*) is malodorous, but surrounds a sweet-tasting nut (Fig. 22.10). They are rarely produced in colder climates. Dermatitis affects chefs handling the fruit as well as children playing marbles with the nuts. The allergens, ginkgolic acids, are structurally related to poison ivy urushiol and may cross-react.

Fig. 22.9 *Ginkgo biloba* leaves and fruit

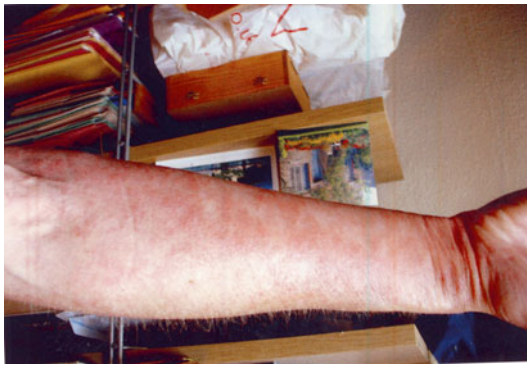


Fig. 22.10 Allergic contact dermatitis from tropical woods in an antique restorer

"Botanicals" (plant extracts) are increasingly used in cosmetics and toiletries, as well as household products, partly because of the popular misconception that they are harmless (although some of the most potent poisons, such as ricin, are entirely natural products). Some products labelled as "fragrance-free" may contain plant extracts which are fragranced, such as *Pelargonium graveolens*, a source of geranium oil. Plant extracts such as tea tree oil and lavender oil, as well as lichen acids, are a significant cause of cosmetic dermatitis [26, 27], and many fragrance components, such as Balsam of Peru, are plant derived. Propolis (bee glue) is derived from poplar trees (*Populus spp*.); it is extensively used in cosmetics and is an important allergen [28].

22.4 Individuals at Risk

Gardening is one of the most popular leisure activities, and outdoor sports such as golf bring the participant into contact with plants. In the home, handling fruit and vegetables or houseplants may elicit allergic dermatitis, and increasing numbers of plant extracts are used in cosmetics and toiletries. Several occupations involve exposure to plant products, and some are listed in Table 22.5.

22.5 Investigating Suspected Plant Dermatitis

Before patch testing, it is essential to take detailed history, including occupation, leisure activities and use of toiletries and cosmetics. If one has the opportunity to examine the patient with an active eruption, it should be possible to distinguish an

Table 22.5 Some occupations exposed to allergenic plants and plant products

Gardeners, horticulturalists, nursery workers, fruit pickers
Farmers, agricultural workers (e.g. Asteraceae (compositae), notably *Parthenium hysterophorus* in India/Africa)
Florists, flower arrangers, flower pickers and packers
Carpenters, joiners, antique restorers (tropical woods)
Botanists, naturalists, laboratory workers
Herbalists, aromatherapists, masseurs, homoeopaths
Pharmacists, pharmacologists, organic chemists, plant biochemists
Dentists (e.g. oil of cloves), veterinary surgeons (plant contaminants in animal fur)
Perfumiers (e.g. essential oils, lichen acids), beauticians, cosmetologists
Food handlers, chefs, sandwich makers, salad makers, food/grain processing workers
Bar tenders (e.g. mint in cocktails)
Sports (e.g. golf, fishing, climbing)
Military (plant exposure on exercise, dhobi marking in India)
Delivery drivers, packers
Tobacco workers
Musicians (e.g. cane reeds used for saxophones/clarinets, tropical hardwood recorders)
Office workers (e.g. foliage plants such as *Philodendron*, *Schefflera*)
Textile/flax workers
Beekeepers (propolis)

allergic from a phototoxic eruption (see Table 22.1). Following exposure to Anacardiaceae (e.g. poison ivy), the characteristic "black spots" of oxidised urushiol may persist on the skin. On dermoscopy, these exhibit a characteristic jagged appearance, with a dark brown centre and red rim [29].

Patch testing should include a standard series and an appropriate plant series. Unfortunately, only a few plant-derived haptens are available commercially, although these will detect allergy to the majority of plants or provide clues by cross-reaction. Sometimes it is necessary to test with plant material itself. Always try to identify the plant before testing, and check that it is not a potent irritant or sensitiser before occluding it on the patient's back. Maceration of the plant material will break down hairs on the plant surface and reduce mechanical irritancy. Where possible, it is better to test with an extract made from air-dried plant material using an organic solvent and dispersing the dried extract in petrolatum. A 60-s wash with diethyl ether is often enough to extract allergens such as many sesquiterpene lactones, which occur in glandular structures on the plant surface [30]. However, diethyl ether is potentially explosive and overnight extraction with 3:1 chloroform: methanol may be preferable [5]. Some sesquiterpene lactones, such as parthenolides, are water soluble [31]. Before reporting a new plant allergen, it is essential to test control subjects to exclude irritancy.

22.5.1 Clues from Standard Series

Many standard haptens are derived from the plant kingdom, including colophonium resin and M*yroxylon pereirae* (Balsam of Peru), several perfume ingredients and propolis. Most standard series will include the sesquiterpene lactone mix and one or both perfume mixes, together with terpenoids such as oxidised tea tree oil.

22.5.2 Plant Series

A suggested plant series is listed in Table 22.6. This will need to be adapted to local needs, depending on the native flora or plants grown in local nurseries.

22.6 Information, Prevention and Treatment

Always give the patient precise information about positive reactions to plants and their relevance. Reference to illustrated floras or gardening books is helpful.

Glove use may help to reduce exposure when handling plants, although some gloves are permeable to allergens and many are easily punctured. Nitrile gloves resist tuliposide A, present in *Alstroemeria* and tulips [32]. "Barrier creams" in general are of limited value, although an organoclay preparation, 5 % quaternium-18 bentonite (trade name Ivy Block), can limit or prevent reactions to poison ivy urushiol [33]. A topical skin protectant (TSP) devised to resist lipophilic toxins used in

Table 22.6 Suggested plant series

(Commercially available extracts in petrolatum)
Sesquiterpene lactone mix 0.1 % (if not in standard series)
Compositae mix 5 %
Extracts of individual Asteraceae (Compositae) – may need modification to reflect local exposure
Anthemis nobilis 1 %
Arnica montana 0.5 %
Achillea millefolium 1 %
Chrysanthemum cinerariaefolium 1 %
Tanacetum vulgare 1 %
Chamomilla recutita 1 %
Parthenolide 0.1 %
Propolis 10 % (if not in standard series)
Diallyl disulphide 1 %
α-Methylene- γ-butyrolactone 0.01 %
Lichen acid mix 0.3 % (atranorin 0.1 %, evernic acid 0.1 %, (+) usnic acid 0.1 %)
Primin 0.01 %
Consider adding dried ivy leaf if history suggests ivy dermatitis

chemical warfare also protects against urushiol [34]. Urushiol persists on the skin after contact, and techniques to inactivate it or remove it, using surfactant detergents or oil solvents, reduce the severity of the dermatitis reaction [35]. Attempts at hyposensitisation have so far proved ineffective.

Treatment of acute contact dermatitis involves the use of potent topical corticosteroids and tacrolimus; pimecrolimus appears ineffective [36]. Systemic corticosteroids are often justified in severe reactions; thus, a 5-day course of prednisolone 40 mg followed by tailing off the drug over a further 10-day period is recommended for poison ivy dermatitis [37]. Chronic actinic dermatitis due to airborne allergens and persistent *Parthenium* dermatitis may require a steroid-sparing agent such as azathioprine, cyclosporine or mycophenolate mofetil [38, 39]. Resolution occurs in around 50 % of cases of chronic actinic dermatitis over a 15-year period if the causative allergens can be avoided [39].

References

1. Brickell C, editor. RHS encyclopedia of plants and flowers. 5th ed. London: Dorling Kindersley; 2010.
2. Mitchell J, Rook A. Botanical dermatology. Plants and plant products injurious to the skin. Vancouver: Greengrass; 1979.
3. Benezra C, Ducombs G, Sell Y, Foussereau J. Plant contact dermatitis. Toronto: BC Decker; 1985.
4. Ott A. Haut und Pflanzen. Stuttgart: Gustav Fischer Verlag; 1991.
5. Lovell CR. Plants and the skin. Oxford: Blackwell Scientific; 1993.
6. Hausen BM, Vieluf IK. Allergiepflanzen Handbuch u. Atlas. 2nd ed. Hamburg: Nikol-Verlag; 1997.
7. Avalos J, Maibach HI. Dermatologic botany. Boca Raton: CRC Press; 2000.

8. Vester L, Thyssen JP, Menné T, Johansen JD. Occupational food-related hand dermatitis seen over a 10-year period. Contact Dermatitis. 2012;66:264–70.
9. Rozas-Muñoz E, Lepoittevin JP, Pujol RM, et al. Allergic contact dermatitis to plants: understanding the chemistry will help our diagnostic approach. Actas Dermosifilogr. 2012;103:456–77.
10. Kulberg A, Schliemann S, Elsner P. Contact dermatitis as a systemic disease. Clin Dermatol. 2014;32:414–9.
11. Ducombs G, Benezra C, Talaga P, et al. Patch testing with the sesquiterpene lactone mix: a marker for contact allergy to Compositae and other sesquiterpene-lactone-containing plants. Contact Dermatitis. 1990;22:249–52.
12. Green C, Ferguson J. Sesquiterpene lactone mix is not an adequate screen for Compositae allergy. Contact Dermatitis. 1994;31:151–3.
13. Paulsen E, Andersen K. Patch testing with constituents of Compositae mixes. Contact Dermatitis. 2012;66:241–6.
14. Hausen BM. A six-year experience with Compositae mix. Am J Contact Dermat. 1996;7:94–9.
15. Jacob M, Brinkmann J, Schmidt T. Sesquiterpene lactone mix as a diagnostic tool for Asteraceae allergic contact dermatitis: chemical explanation for its poor performance and Sesquiterpene lactone mix II as a proposed improvement. Contact Dermatitis. 2012;66:233–40.
16. Zachariae C, Engkilde K, Johansen JD, et al. Primin in the European standard patch test series for 20 years. Contact Dermatitis. 2007;56:344–6.
17. Paulsen E, Christensen LP, Andersen KE. Miconidin and miconidin methyl ether from Primula obconica Hance: new allergens in an old sensitizer. Contact Dermatitis. 2006;55:203–9.
18. Aplin CG, Lovell CR. Contact dermatitis due to hardy Primula spp and their cultivars. Contact Dermatitis. 2001;44:23–9.
19. Paulsen E, Christensen LP, Andersen KE. Dermatitis from common ivy (Hedera helix L subsp helix) in Europe: past present and future. Contact Dermatitis. 2010;62:201–9.
20. Xu S, Heller M, Wu PA, et al. Chemical burn caused by topical application of garlic under occlusion. Dermatol Online J. 2014;20(1):21261.
21. Larson D, Jacob SE. Tea tree oil. Dermatitis. 2012;23:48–9.
22. Audrain HA, Kenward C, Lovell CR, et al. Allergy to oxidized limonene and linalool is frequent in the UK. Br J Dermatol. 2014;171:292–7.
23. Bilcha KD, Ayele A, Shibeshi D, et al. Patch testing and contact allergens in Ethiopia – results of 514 contact dermatitis patients using the European baseline series. Contact Dermatitis. 2010;63:140–5.
24. Hausen BM. Contact allergy to woods. Clin Dermatol. 1986;4:65–76.
25. Czaplicki CD. Contact dermatitis from Eriodictyon parryi: a novel cause of contact dermatitis in Claifornia. Wilderness Environ Med. 2013;24:253–6.
26. Jack AR, Norris PL, Storrs FJ. Allergic contact dermatitis to plant extracts in cosmetics. Semin Cutan Med Surg. 2013;32:140–6.
27. Corazza M, Borghi A, Gallo R, et al. Topical botanically derived products; use, skin reactions and usefulness of patch tests. A multicentre Italian study. Contact Dermatitis. 2014;70:90–7.
28. de Groot AC. Propolis: a review of properties, applications, chemical composition, contact allergy and other adverse effects. Dermatitis. 2013;24:263–82.
29. Rader RK, Mu R, Shi H, et al. Dermoscopy of black-spot poison ivy. Dermatol Online J. 2012;18:8.
30. Hausen BM. A simple method of extracting crude sesquiterpene lactones from Compositae plants for skin tests, chemical investigations and sensitising experiments in guinea pigs. Contact Dermatitis. 1977;3:58–60.
31. Hausen BM. A simple method of isolating parthenolides from *Tanacetum* and other sensitizing plants. Contact Dermatitis. 1991;24:153–5.
32. Marks JG. Allergic contact dermatitis to *Alstroemeria*. Arch Dermatol. 1988;124:914–6.
33. Lee NP, Arriola ER. Poison ivy, oak and sumac dermatitis. West J Med. 1999;171:354–5.

34. Vidmar DA, Iwane MK. Assessment of the ability of the topical skin protectant (TSP) to protect against contact dermatitis to urushiol (Rhus) antigen. Am J Contact Dermat. 1999;10:190–7.
35. Stibich AS, Yagan M, Sharma V, et al. Cost-effective post-exposure prevention of poison ivy dermatitis. Int J Dermatol. 2000;39:515–8.
36. Amrol D, Keitel D, Hagaman D, et al. Topical pimecrolimus in the treatment of human allergic contact dermatitis. Ann Allergy Asthma Immunol. 2003;91:563–6.
37. Curtis G, Lewis AC. Treatment of severe poison ivy: a randomized, controlled trial of long versus short course oral prednisolone. J Clin Med Res. 2014;6:429–34.
38. Sharma VK, Varma P. Parthenium dermatitis in India: past, present and future. Indian J Dermatol Venereol Leprol. 2012;78:560–8.
39. Paek SY, Lim HW. Chronic actinic dermatitis. Dermatol Clin. 2014;32:355–61.

Cosmetics

23

Vanessa Smith and S. Mark Wilkinson

Contents

V. Smith, MRCP • S.M. Wilkinson, MD, FRCP (✉)
Department of Dermatology, Leeds Teaching Hospitals NHS Trust, Chapeltown Road, Leeds LS7 4SA, UK
e-mail: vm.smith@nhs.net; mark.wilkinson15@nhs.net

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_23

23.1 What Is a Cosmetic?

A cosmetic is widely considered to be any preparation that is intended to be rubbed, poured, sprinkled or sprayed on, introduced into or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness or altering the physical appearance. Included within the definition of cosmetics are:

- Rinse off personal cleanliness products such as shower gel, shampoos, soaps and toothpastes
- Leave on products such as moisturisers, sunscreens and skin lightening creams
- Fragrance products such as perfumes, aftershaves and deodorants
- Make-ups such as foundations, eye shadows and lipsticks
- Hair care products including colourants and styling agents such as gels, waxes, sprays, shaving creams and hair removal creams
- Nail care products including nail varnishes, paint removers and acrylate nails

23.2 Epidemiology

Cosmetic products are used universally. About 8,000 substances are available to the cosmetic scientist for incorporation into cosmetics. It has been estimated that an average adult uses nine cosmetic products daily and more than 25 % of women use 15 or more. The precise incidence of cosmetic product allergy is unknown. Many people report a mild reaction to a cosmetic product but simply discontinue the offending product without pursuing further investigation. Studies have shown that when tested, the estimated incidence of allergy to a cosmetic or cosmetic ingredient is around 1–3 %, with an estimated 1 % being allergic to fragrance and 2–3 % being allergic to substances that may be present in cosmetics.

23.3 Clinical Features

23.3.1 Acute

A patient with an acute reaction to a cosmetic product may present to the general practitioner or the accident and emergency department with facial swelling and erythema. Particularly in the case of permanent hair dye allergy, a weeping vesicular dermatitis may be present. In such circumstances, the eruption is usually localised

to the hairline, nape of the neck and tops of the ears. In the acute setting, the diagnosis of an allergic contact dermatitis to a cosmetic product can often be mistaken for cellulitis, angio-oedema or more rarely autoimmune conditions such as lupus or dermatomyositis.

23.3.2 Chronic

More often, the dermatitis resulting from cosmetic allergy is milder and with erythema, scaling, oedema and papules often localised to the face and neck and sometimes the perianal region. The exact distribution is dependent on the causative product, but a typical pattern for an allergic reaction to a cosmetic would involve the face and particularly the eyelids. In these more chronic cases, the clinical appearances can be confused with irritation of sensitive skin or constitutional skin disease such as atopic eczema or seborrhoeic dermatitis. In darker-skinned individuals, patients may present with progressive facial hyperpigmentation. This is often the case when patients are allergic to fragrance.

23.4 Types of Product Causing Allergic Reactions

23.4.1 Rinse Off Personal Cleanliness Products Such as Shower Gels, Shampoos, Soaps and Shaving Creams

Skin and hair cleansing agents remain on the body for a very short period of time and rarely cause significant adverse reactions. Repeated application and cumulative exposure from other sources may result in an eliciting dose of allergen being applied. Possible sensitisers in rinse off products include fragrances, preservatives and antimicrobials such as triclosan and chlorhexidine.

23.4.2 Leave on Products Such as Moisturisers, Sunscreens and Skin Lightening Creams

These are a more common source of cosmetic allergy. Common sensitisers in such products include fragrances, preservatives (e.g. formaldehyde and releasers, isothiazolinones etc.), antioxidant (e.g. butylated hydroxyanisole (BHA), tocopherol), other excipients (e.g. propylene glycol) and surfactants.

UV filters: It is important to also remember that a lot of leave on skin care products contain UV filters, and therefore the associated allergens should also be considered in this category. Adverse effects to sunscreen agents include irritant, phototoxic and photoallergic reactions, and allergic reactions may be caused not only by UV filters but also by the additives such as fragrances and preservatives.

23.4.3 Fragrance Products Such as Perfumes, Aftershaves and Deodorants

Fragrance is the number one cause of skin allergic reactions to cosmetics. Fragrance also causes irritant, photosensitive and pigmented contact dermatitis and contact urticaria.

Deodorants: These not only contain fragrance which frequently causes ACD as seen in Fig. 23.1 but also contain preservatives, particularly antimicrobials as active antiperspirants (e.g. aluminium chloride hexahydrate which is a well-recognised irritant but can also be an allergen) as well as propellants (previously chlorofluorocarbons, now replaced by isobutene, butane and propane).

23.4.4 Make-Ups Such as Foundations, Eye Shadows and Lipsticks

Leave on skin care products are a common source of cosmetic allergy, and such products have already been discussed. However, it is worth noting that there are a few allergens specific to eye make-up and lip care products.

Eye make-ups: Mascara, eyeliner, eye shadow and eyebrow pencils are the most commonly used eye make-ups. Eye make-ups are usually unfragranced. Most associated allergies are due to preservatives. Parabens are often used as the preservatives for eye shadows. However, whilst parabens frequently induce an allergic response when used on inflamed skin, this does not appear to be the case when used on intact skin, even when the skin is as thin as it is on the eyelid. This is referred to as the 'paraben paradox'. Specific allergens to consider in cases of eyelid dermatitis include metals such as cobalt, chromate and nickel which are used to give colour to the make-ups. They are rarely reported to cause contact allergy in this context. Besides the use of eye make-up, nail varnish allergy should also be excluded in patients with periocular disease as tosyl amide formaldehyde resin in nail polish is a classic cause of eyelid dermatitis due to indirect contact. Acrylates

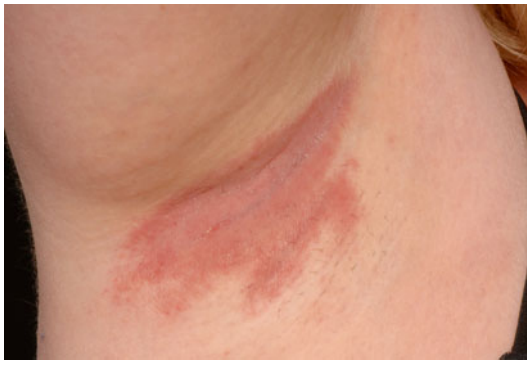


Fig. 23.1 Axillary dermatitis from the fragrance present in a deodorant

in artificial nails can also cause eyelid dermatitis. Rubber in make-up sponges and eyelash curlers may affect the eyelids. In addition to cosmetics, allergens in contact lens solutions or eye medicaments may also cause eyelid dermatitis. Despite the wide array of reported allergens, most cases of eyelid dermatitis are irritant in nature.

Lips: Specific allergens to consider include dyes in lipstick, emollients (e.g. lanolin), UV filters, preservatives and antioxidants (e.g. propyl gallate), excipients (e.g. propylene glycol) and fragrance. Although allergic reactions to lipstick are uncommon, it should be borne in mind even when the eruption has spread beyond the lips as the sensitising chemical may well be present in products other than the lipstick. Furthermore, perioral dermatitis may be the presentation of an allergy to toothpaste or a dietary ingredient. Figure 23.2 shows cheilitis caused by contact allergy to constituents of a lip balm.

23.4.5 Hair Care Products Including Colourants and Styling Agents Such as Gels, Sprays and Pressing Oils

There are a wide number of different hair products which are known to be able to provoke allergic reactions. In addition to shampoos, as discussed earlier in this chapter, hair care products which can cause allergy include permanent wave solutions, straighteners and hair colouring preparations.

23.4.6 Nail Care Products Including Nail Varnishes, Paint Removers and Acrylate Nails

Historically, a constituent of nail varnish (tosylamide formaldehyde resin) was the main contact allergen; however, with the use of acrylate nails, increasing this picture has changed. Trimetallic anhydride and acrylate copolymer have also been reported. Allergic contact dermatitis to acrylates can result in paronychia and nail dystrophy as seen in Fig. 23.3.

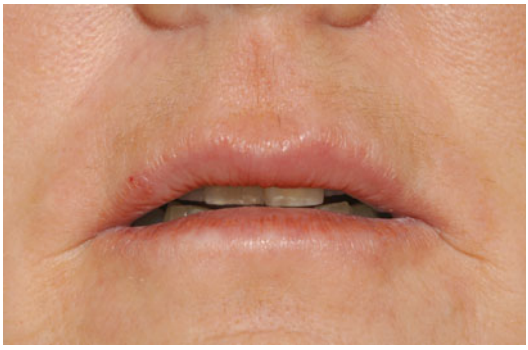


Fig. 23.2 Cheilitis caused by contact allergy to constituents of a lip balm

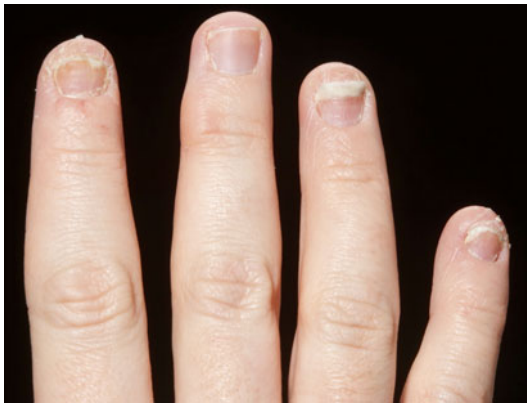


Fig. 23.3 Paronychia and nail dystrophy caused by allergy to acrylates in nail varnish

23.5 Ingredients That May Cause Allergy

Cosmetic ingredients can be classified into several categories: fragrances, preservatives (including antimicrobials and antioxidants), ultraviolet light absorbers, excipients (vehicles), emollients, surfactants (including detergents and emulsifiers), hair styling products and dyes, nail products and acrylates.

Preservatives and fragrances are the most frequently detected classes of allergens in those with an allergy to a cosmetic product. Other important allergens include the hair colour p-phenylenediamine, the nail lacquer resin tosylamide formaldehyde resin, UV filters and lanolin. A list of potential allergens to consider testing (other than fragrances, preservatives and dyes) can be found in Table 23.1.

23.5.1 Fragrance

Fragrances are covered in detail in Chap. 12**.**

Fragrance is a leading cause of allergic skin reactions to cosmetics. Contact dermatitis to fragrance usually causes dermatitis to the hands, face and axillae. Patients appear to become sensitised to fragrance from deodorant sprays and perfumes but then go on to develop reactions to the whole host of products which contain fragrance as a constituent.

23.5.2 Preservatives

Preservatives are covered in Chap. 13.

Preservatives are the second most common cosmetic contact allergens and can be divided into various groups.

23.5.2.1 Antimicrobials

These are added to a wide range of cosmetic products to inhibit the growth of bacteria, particularly *Staphylococcus aureus* and pseudomonas which can flourish in an

Table 23.1 Allergens to consider testing in patients with suspected cosmetic product allergy (excluding those allergens in the baseline series)

Group	Allergen	Test conc. and vehicle
Preservatives [3]	2-Bromo-2-nitropropane-1,3-diol	0.5 % pet
	Diazolidinyl urea	2 % pet
	Imidazolidinyl urea	2 % pet
	DMDM hydantoin	2 % aq
	Chlorocresol	1 % pet
	Sodium metabisulphite	1 % pet
	Iodopropynyl butylcarbamate	0.2 % pet
	Phenoxyethanol	1 % pet
Excipients	Propylene glycol	20 % aq
	Triethanolamine	2 % pet
	Benzyl alcohol	1 % pet
Emollients	Amerchol L 101	50 % pet
	Propolis	10 % pet
	Lanolin	As is
Emulsifiers and surfactants	Cocamidopropyl betaine	1 % aq
NB beware of irritancy and interpret with caution	Cocamide DEA	0.5 % pet
	Dimethylaminopropylamine	1 % pet
	Sorbitan sesquiolate	20 % pet
	Oleamidopropyl dimethylamine	0.1 % aq
	Decyl glucoside	10 %aq
	Lauryl glucoside	10 %aq
	Cetyl alcohol, stearyl alcohol	20 % pet
UV light absorbers (see Table 23.2)		
Hair products	Glycerol monothioglycolate	1 % pet
	Ammonium persulphate	2.5 % pet
	Ammonium thioglycolate	1 % pet
	o-Nitro-p-phenylenediamine	1 % pet
	p-Toluenediamine sulphate	1 % pet
	3-Aminophenol	1 % pet
	4-Aminophenol	1 % pet
Nail products (acrylates see Table 23.3)	Tosylamide formaldehyde resin	10 % pet
	Shellac	20 % EtOH

aqueous environment. This category includes formaldehyde, formaldehyde releasers and non-formaldehyde-releasing preservatives. Wet wipes frequently contain preservatives, and this was found to be the cause of the fingertip dermatitis illustrated in Fig. 23.4.

23.5.2.2 Antioxidants

Antioxidants are added to cosmetics to prevent the deterioration of unsaturated fatty acids and are occasionally a cause of cosmetic allergy. Antioxidants include the following:

- Butylated hydroxyanisole (BHA).
- Butylated hydroxytoluene (BHT).

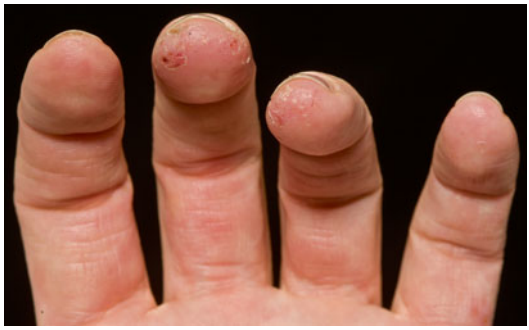


Fig. 23.4 Fingertip dermatitis due to contact allergy to preservative in a wet wipe

- Tocopherol (vitamin E) and its esters.
- t-Butylhydroquinone.
- Gallates (dodecyl, octyl, propyl): These may be found in antibiotic creams, lipsticks, moisturisers, topical steroids and eye cosmetics. Propyl gallate is particularly associated with lipsticks.

23.5.3 UV Sunscreen Allergens

Sunscreen allergens can be divided into the 'older' and the 'newer' generation of organic UV absorbers. Other topical preparations which cause a photoallergic contact dermatitis include topical NSAIDS and antihistamines. The UV absorbers can be divided into various classes: Para-aminobenzoic acid (PABA) and its esters, cinnamates, salicylates, thranilates, benzophenones and dibenzoylmethanes. Octocrylene (a cinnamate) is now the most common UV allergen, followed by benzophenone-3 and thirdly butyl methoxydibenzoylmethane. PABA and isopropyl dibenzoylmethane historically were frequently detected allergens, but numbers have fallen since these chemicals are no longer used in Europe. However, the most frequent adverse reaction to sunscreen is irritation, which occurs in 15 % of users. Currently recommended allergens for testing can be found in Table 23.2.

23.5.4 Excipients (Vehicles)

An excipient is an inactive substance that serves as the vehicle or medium. Its purpose is to bulk up formulations which contain potent active ingredients. The commonly used excipients are listed:

- Propylene glycol: This is an odourless, viscous liquid, readily miscible with water, acetone, chloroform and essential oils. It is a widely used vehicle for topical therapeutics and cosmetics. In some prescription products, the amount of propylene glycol may be as high as 70 %. It is sometimes used as the vehicle for deodorants. Propylene glycol can cause irritant reactions and allergic contact reactions are uncommon.

Table 23.2 Currently recommended cosmetic allergens for photopatch testing [4]

Agents recommended for the European photopatch test baseline series		
Type of agent	Allergen	Test conc. and vehicle
'Older' organic UV absorbers	Butyl methoxydibenzoylmethane	10 % pet
	Benzophenone-3	10 % pet
	Benzophenone-4	2 % pet
	Octocrylene	10 % pet
	4-Methylbenzylidene camphor	10 % pet
	Ethylhexyl methoxycinnamate	10 % pet
	Isoamyl-*p*-methoxycinnamate	10 % pet
	PABA	10 % pet
'Newer' organic UV absorbers	Methylene *bis*-benzotriazolyl tetramethylbutylphenol	10 % pet
	Bis-ethylhexyloxyphenol methoxyphenyl triazine	10 % pet
	Drometrizole trisiloxane	10 % pet
	Terephthalylidene dicamphor sulfonic acid	10 % aqua
	Diethylamino hydroxybenzoyl hexyl benzoate	10 % pet
	Ethylhexyl triazone	10 % pet
	Diethylhexyl butamido triazone	10 % pet

- Other glycols: These includes 1,3 butylene glycol, hexylene glycol and polyethene glycol.
- Glycerine: This is a rare sensitiser and does not irritate the skin; however, propylene glycol tends to be favoured over glycerine as a vehicle of choice as propylene glycol is more lipid soluble and as such permeates the stratum corneum more effectively. Propylene glycol is also cheaper.
- Petrolatum: Although allergy to petrolatum has been reported, it is incredibly rare.
- Triethanolamine: This is a widely used excipient found in hand and body lotions, shaving creams, soaps, shampoos, bath powders and occasionally pharmaceutical preparations.

23.5.5 Emollients

Emollients are incorporated into various cosmetic products. Of particular note are the following substances:

- Castor oil: This tends to be found in lipsticks, and most cases of allergy, although rare, have been related to lipstick use.
- Propolis (bee glue) and beeswax: Propolis is the dark yellow adhesive resin made by bees to cement together their hives. It is produced by the bees from various tree resins and cross-reaction with fragrances is sometimes seen. Propolis is found in many cosmetic products sold in health food shops. Beeswax is derived from the honeycomb and may be bleached or unbleached when used in cosmetic products.

- Lanolin (wool fat, wool grease, wool wax, wool alcohol and adeps lanae anhydrous) and its various esters, fatty acids and aliphatic alcohols are used in many topical medicaments and cosmetics. Lanolin contains sterols, fatty alcohols and fatty acids. The lanolin sterols (lanolin alcohols or wool alcohols) include principally cholesterol, lanosterol and agnesterol and are built from one or more benzene rings. Hydrogenated lanolin is often used in the cosmetic industry as it is colourless, odourless, less tacky and more hydrophilic than lanolin.

23.5.6 Surfactants

Surfactants are compounds that lower the surface tension between two liquids or between a liquid and a solid. Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents and dispersants.

- Sodium lauryl sulphate: This has been used in cosmetic products for many years and is a well-recognised irritant. It is most commonly used in shampoos and soapless cleansers.
- Cocamidopropyl betaine [1]: This has been used since the 1970s and is used in shampoos and cosmetics. Around 6 % of cosmetic products contain cocamidopropyl betaine. Most cases of allergy are related to shampoos. Prevalence rates of sensitisation to cocamidopropyl betaine range from 3.7 to 5 %. Although widely reported, patch test reactions to cocamidopropyl betaine are difficult to interpret due to frequent irritant reactions. Cocamidopropyl betaine itself is probably not the allergen. Allergic reactions, when they occur, seem to be caused by reactions to impurities particularly dimethylaminopropylamine.
- Cocamide DEA/lauramide DEA.
- Cetyl, stearyl, oleyl and myristyl alcohols.
- Glucosides: These are commonly used surfactant in wash off products and include caprylyl glucoside, decyl glucoside, lauryl glucoside, coco glucoside and cetaryl glucoside.
- Sorbitan sesquioleate: This is the emulsifier used in fragrance mix I. It was added to enhance stability, but rarely cases of presumed fragrance allergy have been in fact due to sorbitan sesquioleate.

23.5.7 Hair Styling Products and Dyes

Besides shampoos, hair care products which can cause allergy include permanent wave solutions, straighteners and hair colouring preparations.

23.5.7.1 Hair Colouring

Hair dyes are covered in more details in Chap. 16.

- Most hair dye allergy is due to permanent and semi-permanent hair dye ingredients.
- Temporary rinses: These coat the hair shaft and are easily washed off.
- Vegetable dyes: Natural henna rarely causes contact allergy.
- Metallic dyes: These contain lead acetate and sulphur and are combed through the hair to cover greys.

23.5.7.2 Permanent Waves

Permanent waves ('perms') alter the disulphide bonds of hair keratin so that hair fibre configuration can be changed. Initially, a waving solution is applied which breaks the disulphide bonds before the solution is neutralised, and new bonds are formed in a fixed position. The waving solutions are irritant but can also induce an allergic response.

- Glyceryl monothioglycolate is a major allergen amongst hairdressers as a result of these processes. It persists on permed hair for months and therefore re-exposes the hairdresser to the allergen even when the hair is just being cut. It is able to penetrate rubber gloves. The older perms contain thioglycolic acid combined with ammonia and are neutralised with hydrogen peroxide or sodium bromate. These older perms rarely cause a contact allergy.

23.5.7.3 Straighteners

Historically, the hair was straightened with hot combs. Mixtures of petrolatum, oils and waxes were used to help conduct the heat and reduce friction. However, over time, this process damages the hair and chemical straighteners have since been introduced. Various chemical straighteners are available:

- Sodium hydroxide
- Sulphite straighteners
- Ammonium thioglycolate and a bromate or peroxide neutraliser

Follow-up care often involves the application of oils and moisturisers which may contain fragrance, preservatives and propylene glycol.

23.5.7.4 Bleaching Agents

The active ingredients in hair bleaches are hydrogen peroxide solutions that oxidise melanin to a lighter colour. They may be supplemented with persulfate boosters.

23.5.8 Nail Products and Acrylates

23.5.8.1 Nail Enamels

These, including base coats and top coats, have similar components and are comprised of the following:

- Film former: nitrocellulose
- Resins: tosylamide formaldehyde resin, alkyd resins, acrylates, vinyls or polyesters

- Plasticisers: camphor, dibutyl phthalate, dioctyl phthalate and tricresyl phosphate
- Solvents: alcohol, toluene, ethyl acetate and butyl acetate
- Colourants
- Pearlizers: guanine and bismuth oxychloride

Tosylamide formaldehyde resin is responsible for almost all the allergic reactions. Of all cosmetic allergens, tosylamide formaldehyde resin is ranked very highly in terms of prevalence, accounting for around 10 %, or reactions and ranked behind only preservative, fragrances and emulsifiers.

23.5.8.2 Nail Enamel Removers

These are a mixture of solvents such as acetones and amyl, butyl or ethyl acetate to which fatty materials and fragrance may be added. ICD is more likely to occur than ACD.

23.5.8.3 Artificial Nails and Acrylates

Sculptured nails can be applied in a salon or kits are available for home use [2]. The kits consist of a powdered methacrylate polymer, with benzoyl peroxide as an initiator, and a liquid methacrylate ester. When the components are mixed, polymerisation occurs and an artificial nail extension can be formed. Photobonding of acrylate nail extenders using UV light is a newer method of application. Reactions to this process occur just as with non-UV requiring products. Screening for acrylate allergy can be undertaken with the allergens listed in Table 23.3.

Table 23.3 Recommended allergens for acrylate allergy testing [5]

Allergen	Test conc. and vehicle
Ethyl acrylate	0.1 % pet
Butyl acrylate	0.1 % pet
2-Hydroxyethyl acrylate	0.1 % pet
Methyl methacrylate	2.0 % pet
Ethyl methacrylate	2.0 % pet
n-Butyl methacrylate	2.0 % pet
2-Hydroxyethyl methacrylate	2.0 % pet
2-Hydroxypropyl methacrylate	2.0 % pet
Ethylene glycol dimethacrylate	2.0 % pet
Triethylene glycol dimethacrylate	2.0 % pet
Trimethylolpropane triacrylate	0.1 % pet
Triethylene glycol diacrylate	0.1 % pet
1,6-Hexanediol diacrylate	0.1 % pet
Ethyl cyanoacrylate	10.0 % pet
Tetrahydrofurfuryl methacrylate	2.0 % pet
Screening with ethylene glycol dimethacrylate, 2-hydroxyethyl methacrylate and triethylene glycol diacrylate alone has also been proposed	

23.6 How and What to Test

23.6.1 Patch Testing

All patients being investigated for a suspected cosmetic contact allergy should undergo the baseline series of patch tests as recommended locally. This normally covers a large number of the fragrances and preservatives which are the leading causes of contact allergy in patients with a suspected cosmetic allergy. Additional series will be determined by the specifics of the history, but additional series to consider may include:

- Facial/cosmetic series: This may include additional preservatives, excipients and nail varnish compounds not covered in the baseline series.
- Photopatch test series: This should be considered in cases of facial dermatitis when the suspected cosmetic contains UV filters especially when dermatitis develops on holiday. Irradiation is typically performed on day 2 of investigation using 5 J UVA.
- Acrylate series: In patients who give a history of acrylate nail use.
- Fragrance series: Although the baseline series detects a large proportion of fragrance allergy as a multitude of fragrances are used in different cosmetic products, it may be well worth testing the patient to additional allergens outside of the baseline series of fragrance screening chemicals (Table 23.4).
- Dental and food flavour and preservative allergens should be considered in those with perioral dermatitic eruptions.

Since 1997, the European Union legislated that all cosmetic products should display their ingredients on the outer packaging or in some cases the accompanying leaflet. For this purpose, companies must use the INCI (International Nomenclature of Cosmetic Ingredients) for ingredient listings. This was based on the American Cosmetic, Toiletry and Fragrance Association (CTFA) system which was introduced some years earlier. These systems make it easier for clinicians and patients to identify cosmetics containing specific ingredients as the use of brand names for these purposes has been restricted.

23.6.2 Patch Testing to Own Products

Patch testing to own products is covered in more details in Chap. 4.

It is important to test a patient to their own products to reduce the chance of a contact allergen being overlooked. With many products, it may also be wise to phototest as well. As a general rule, leave on products are safe for closed patch testing, whereas rinse off products may irritate and open patch testing performed or the substance diluted.

Table 23.4 Additional fragrance allergens that when tested individually may increase the sensitivity to detect fragrance allergy [6]

	Allergen	Test conc. and vehicle
Ingredients of fragrance mix I	Cinnamyl alcohol	2 % pet
	Cinnamal	1 % pet
	Eugenol	2 % pet
	Amyl cinnamal	2 % pet
	Hydroxycitronellal	2 % pet
	Geraniol	2 % pet
	Isoeugenol	2 % pet
	Evernia prunastri	2 % pet
Ingredients of fragrance mix II	Citral	2 % pet
	Citronellal	1 % pet
	Farnesol	5 % pet
	Coumarin	5 % pet
	Hexyl cinnamic aldehyde	10 % pet
	Hydroxymethylpentylcyclohexenecarboxaldehyde	5 % pet
Oxidised fragrance allergens	Limonene hydroperoxide	0.3 % pet
NB irritancy: use dilution series	Linalool hydroperoxide	1 % pet
Plant extracts	*Cananga odorata*	2 % pet
	Evernia furfuracea	1 % pet
	Jasminium officinale	2 % pet
	Lavandula angustifolia	2 % pet
	Melaleuca alternifolia (oxidised)	5 % pet
	Mentha piperita	2 % pet
	Santalum album	2 % pet
Other fragrance chemicals	Anise alcohol	10 % pet
	Benzyl alcohol	1 % pet
	Benzyl benzoate	10 % pet
	Benzyl cinnamate	5 % pet
	Benzyl salicylate	2 % pet
	Majantole	5 % pet
	Vanillin	10 % pet

23.7 What to Tell the Patient

23.7.1 If They Have a Positive Result

Initially, the relevance of the positive result must be established (see Chap. 5). If the reaction is relevant, the patient should be provided with all the necessary information to allow them to ensure that they do not come into contact with the allergen in question. In many cases, this can be achieved by simply checking the labelling of all cosmetic products. However, in some circumstances, such as that of a fragrance

allergy, it may be preferable for a patient to avoid all fragrances rather than to try and cut out the particular fragrance in question (see Chap. 12). Patients should be made aware that chronic eczematous changes may take several weeks to settle after avoidance of the allergen is initiated.

23.7.2 If They Have a Negative Result

If a patient has a negative result, they can be reassured that it is unlikely that they have an allergic contact dermatitis. Other diagnoses at this stage should be explored such as irritant contact dermatitis and endogenous disease. Figure 23.5 shows an individual who developed cold injury from prolonged use of a spray.

Some individuals with sensitive skin, such as those with atopic dermatitis, may be more likely to develop irritant reactions. Products formulated for sensitive skin will typically have undergone testing by the manufacturer to substantiate the marketing claim. Whilst there is no agreed definition of sensitive skin, such products may form a starting point for individuals in choosing products that they are able to tolerate. Individuals need to be warned, however, that it is often a matter of trial and error and that once identified they should stick to a limited range that they establish as safe.

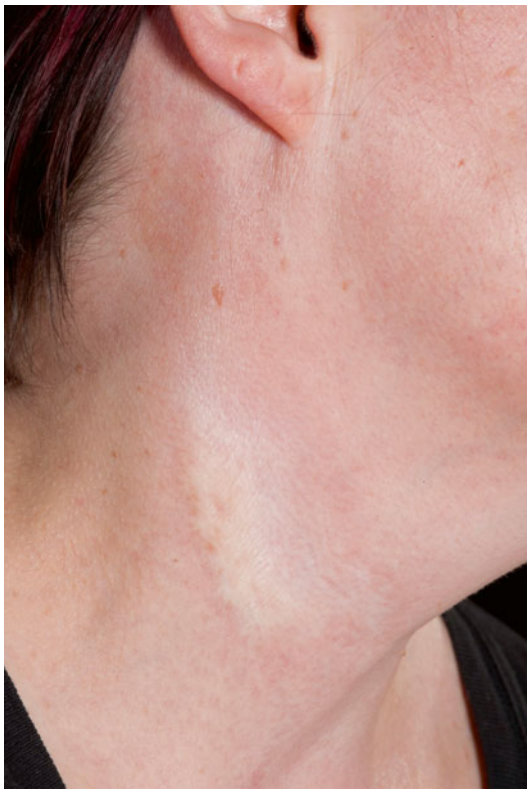


Fig. 23.5 A scar from prolonged exposure to a perfumed spray resulting in cold injury

If however there is a history suggestive of a contact allergy but the tests have been negative, it is possible that a false-negative reaction may have occurred. The concentrations of an allergen in a cosmetic product may be great enough to produce dermatitis after repeated application on sensitive skin but may be too low to produce a positive patch test on the back. This is especially true in fragrances and preservatives. A negative reaction to a cosmetic, therefore, does not rule out an allergy to a component of the product. If an adverse reaction to a product is suspected despite a negative patch test to the product and the constituent parts then, it may be advised that a usage test is performed to the forearm before further use. This testing to the forearm should consist of twice daily application for 2 weeks.

23.8 Checklist of What to Think About/Action Points

Take a clear history; ask about:

- Specific body site involved.
- Duration of the problem.
- Background of atopy.
- Products used on the skin (previous as well as current): Patients often dismiss regularly used products which may be relevant, and most people use numerous products.
- Specifically ask about nail varnish use and hair dye/hair care products.

Test patients to:

- Baseline series
- Any other relevant series including cosmetic/the face, acrylate, photopatch, fragrance, dental, hair, food-related flavours and preservatives
- Own products

Carefully consider the history and clinical features when interpreting the results.

References

1. Suuronen K, Pesonen M, Aalto-Korte K. Occupational contact allergy to cocamidopropyl betaine and its impurities. Contact Dermatitis. 2012;66:286–92.
2. Kwok C, Money A, Carder M, et al. Cases of occupational dermatitis and asthma in beauticians that were reported to The Health and Occupation Research (THOR) network from 1996 to 2011. Clin Exp Dermatol. 2014;35:590–5.
3. de Groot AC, White IR, Flyvholm MA, et al. Formaldehyde-releasers in cosmetics: relationship to formaldehyde contact allergy. Part 1. Characterization, frequency and relevance of sensitization, and frequency of use in cosmetics. Contact Dermatitis. 2010;62:2–17.

4. Goncalo M, Ferguson J, Bonevalle A, et al. Photopatch testing: recommendations for a European photopatch test baseline series. Contact Dermatitis. 2013;68:239–43.
5. Goon AT, Bruze M, Zimerson E, et al. Contact allergy to acrylates/methacrylates in the nail and acrylate series in southern Sweden. Contact Dermatitis. 2007;57:21–7.
6. Karlberg AT, Börje A, Duus Johansen J, et al. Activation of non-sensitizing or low-sensitizing fragrance substances into potent sensitizers – prehaptens and prohaptens. Contact Dermatitis. 2013;69:323–34.

Worker's Protection: Gloves and Creams

24

Britta Wulfhorst, Swen Malte John, and Meike Strunk

Contents

24.1 Systematic Skin Protection

Contact dermatitis (CD) often appears as hand eczema and hand eczema is often occupationally induced [7]. Occupational skin diseases impose by about 90 % as hand eczema and are the most frequent occupational diseases in industrialized

B. Wulfhorst (✉)
Faculty of Human Sciences, Medical School Hamburg, Hamburg 20457, Germany
e-mail: britta.wulfhorst@medicalschool-hamburg.de

S. Malte John, MD, PhD
Department of Dermatology, Environmental Medicine and Health Theory, Lower Saxonian Institute of Occupational Dermatology (NIB), University of Osnabrueck, Osnabrück, Germany

M. Strunk
Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrueck, Osnabrueck, Germany
e-mail: meike.strunk@uos.de

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_24

Fig. 24.1 Hierarchical skin protection strategy

countries [1, 3, 26, 35]. But also, private contacts to irritants and allergens (i.e., water, cleaning substances, etc.) can induce hand eczema. The following contents on how to protect the patient are regardless if the eczema is induced by occupational or private contacts to harmful substances. Skin protection for persons at risk (occupational and private risks) should start with primary prevention. Before workers are committed to use personal protective measures, a hierarchy of risk management has to be taken in consideration, following the STOP concept [14, 27]. S in STOP means prevention from the source, for example, due to elimination or substitution of harmful substances. So it has to be proved if the harmful exposure to irritants (inclusive frequent contact to sub-toxic irritants, i.e., water) and allergens could be avoided by elimination or substitution. T in STOP means technical measures, for example, using "no touch techniques." O in STOP means organizational measures, for example, to implement rotating systems for wet work duties to reduce the individual load. P in STOP means personal protection of workers on which prevention should focus after the hierarchically higher standing steps are implemented (see Fig. 24.1).

Worker-related strategies, for example, skin protection, should be optimized by choice of adequate gloves, barrier creams, emollients, and skin cleaning products and by workers education to improve their motivation to practice skin protection and to avoid application errors [32, 44]. It is also recommended to summarize all skin protective measures in a skin protection plan that includes handwashing, skin protection (gloves and barrier creams), and skin care.

Personal skin protection is intended to protect the skin from harmful substances, and systematic skin protection is based on three basic components: (1) skin protection, (2) skin cleansing, and (3) skin care [19, 42]. For all dimensions of personal skin protection, a careful selection of products is needed as well as a thorough instruction of the persons who are to apply the skin protection measures. In the use of skin protection, a careful selection along standardized criteria (if available) is needed in all types of protective measures.

24.2 Chemical Protective Gloves

Gloves are the most important and most effective option of skin protection [29]. There is a big range of different glove materials (e.g., nitrile, neoprene, natural rubber latex, PVC, PVA, laminated film, vinyl, butyl, or Viton®/butyl gloves) and properties of different types of gloves (e.g., disposable gloves, single-use gloves, see Fig. 24.2). There is no universally suitable glove for all chemicals and for all

Fig. 24.2 Wide range of glove materials and product types

application situations. Important factors for providing protection are the penetration capacity for water and permeability to chemicals. The amount of protection provided by PPE is material-hazard specific. That is, protective equipment materials will protect well against some hazardous substances and poorly, or not at all, against others. In addition, undesirable effects of glove wearing must be taken into account and avoided (e.g., occlusion effect, latex and contact allergy due to ingredients of glove materials, see Wulfhorst et al. [44]). As mentioned above, application errors are common and cause the desired effect of protecting ad absurdum (see below).

OSHA's personal protective equipment standard (29 CFR 1910.138) specifically addresses the need for hand protection or chemical protective gloves [38]:

(a) Appropriate hand protection must be worn when the hands are exposed to hazards such as skin absorption of harmful substances, severe cuts, lacerations or abrasions, punctures, chemical or thermal burns, and harmful temperature extremes.
(b) Employers must base the selection of appropriate hand protection on an evaluation of the performance characteristics of the hand protection relative to the task(s) to be performed, conditions present, duration of use, and the hazards and potential hazards identified.

This rule makes it mandatory to match the right glove material with each application or task. This includes assessing the job for chemical exposures and then selecting the appropriate, chemical protective glove based on material, thickness, length, and other traits.

By the Health and Safety Executive [13], five factors are named that has to be taken into consideration to choose an appropriate glove:

- Identify the substances handled.
- Identify all other hazards.
- Consider the type and duration of contact.
- Consider the user size and comfort.
- Consider the task.

Core Message

- Inappropriately selected or misapplied gloves may increase the risk for contact dermatitis due to the following:
- Contamination of the inside glove could increase exposure to hazardous substances in comparison to no glove wearing.
- The occlusion effect due to extended wearing times that can lead to an excessive moisturizing of the horny layer.
- Allergens that are ingredients of glove material [44].

24.2.1 Requirements and Standards

In many countries, requirements for gloves are standardized due to regulations [5, 6]. In Europe, gloves are covered by the PPE Directive 89/686/EEC "Gloves intended for protection"; the comparable US standard is fixed in the Occupational Safety and Health Standards 1919: Personal Protective Equipment/Hand Protection, 1910.138 [15, 38].

The European Directive is based upon the existence of European standards to define specifications or performance levels for the products.

Under European regulations, three levels of risk and seriousness of the potential injury have to be distinguished, and the protective gloves are to label into three categories that require different amounts of quality proofs:

Category I: Gloves of simple design – suitable for minimum risk.
Category II: Gloves of intermediate design – for intermediate risk.
Category III: Gloves of complex design – for protection against high risks, i.e., where skin exposure would result in irreversible damage to health or possibly death.

Referring to Tab. 1 only for category III (protection against high risks), gloves have to be labeled with the number of a certified testing institute, according to the results of testing penetration and permeation properties of the gloves, and different pictograms have to be marked on each glove, see Table 24.1 [Directive 89/689/EEC].

Penetration refers to the passage of chemicals through macroscopic holes or pores. Penetrability can result from a manufacturing process (a material defect) or from faulty or lengthy storage.

The results of an air or water leakage test are described as acceptance quality level (AQL) which names the number of leaking gloves according to EN 374-2 (see Fig. 24.3).

Permeation refers to the migration of chemicals through the protective glove material on a molecular level. The results of determination of the breakthrough time in minutes are described in six classes according to EN 374-3 (see Fig. 24.4).

Table 24.1 Identification of gloves according to European regulations

	Indication of conformity with the fundamental requirements according to the European Directive 89/686/EC, the manufacturer is obliged to affix the CE marking on the gloves/the glove packaging. The 4-digit number refers to a certified test institute which has done the tests according to DIN EN 374 and to other regulations
	Chemical resistant glove accompanied by a 3-digit code referring to the code letters of three chemicals from a list of 12 standard defined chemicals, for which a breakthrough time of at least 30 min has been obtained in the permeation test according to DIN EN 374
	Low chemical resistant or "waterproof" glove which complies with the penetration test (AQL) according to DIN EN 374. These gloves normally have not achieved a breakthrough time of at least 30 min against at least three chemicals from the defined list or were not tested for permeability
	"Microorganism" resistant glove, glove has to conform to at least the performance level 2 (AQL) for the penetration test according to the DIN EN 374
	This pictogram means that further information/instructions are to be obtained by the manufacturer

24.2.2 Choosing the Right Chemical Protective Gloves

As mentioned above, it is very important to match the right glove material with each application of chemicals. Mellström and Bowman [24] presented a detailed description of the materials used for gloves. In Table 24.2, some glove material and applications are listed according to the American National Standard for Hand Protection Selection Criteria [2].

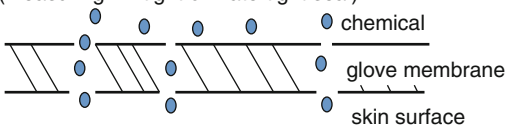
By regarding lists of glove materials with their general applications, it has to be taken into account that the protective effect of different glove materials against hazardous substances depends on the one hand on the type and composition of the material but on the other hand, the protective effect of the same material can differ due to manufacturing processes. In addition, the protective effect depends on the thickness of the glove material [25].

To help in the selection of appropriate gloves, manufacturers of gloves provide charts and computer software. Some general databases can be referred to get informations about selected chemicals (e.g., see [4]).

In Europe, it is in the responsibility of the manufacturer who puts a chemical on the market to investigate and document efficient gloves to protect the user of the hazardous chemicals. Minimum standards of effective protective glove or product names of effective gloves are documented in the safety data sheets [21].

Penetration according to EN 374, part 2

(Measuring: Airtight or watertight seal)

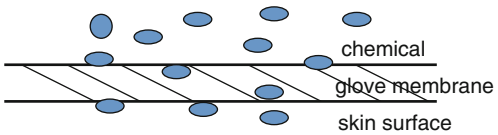


Protection Index	AQL (max. number of leaking gloves %)
3	0.65
2	1.5
1	4.0

Fig. 24.3 Penetration of gloves: acceptance quality levels (Adapted from Wulfhorst et al. [44], 983–1016)

Permeation according EN 374, part 3

(Measuring: Permeation test-cell)



Protection Index	Breakthrough time (min)
6	> 480
5	> 240
4	> 120
3	> 60
2	> 30
1	> 10

Fig. 24.4 Permeation of gloves: Breakthrough time and protection index (Adapted from Wulfhorst et al. [44], 983–1016)

24.3 Barrier Creams

The effectiveness of barrier creams is of conflicting evidence [19, 20]. The idea of the mechanism of action of barrier creams during the recent years has been that they are effective in a physical way because due to their composition, a diffusion barrier against the offending irritant is built up. According to this idea, hazardous substances of similar physicochemical properties are grouped (e.g., water miscible or non-water miscible) to simplify the product recommendation [18]. However, the theory that the product only builds up a physical barrier between the skin and the irritant and the formulation remains unchanged after the product has been applied to the skin could not be validated [12]. Rather, it should be taken in consideration that in many workplaces, skin contact to both water-miscible and non-water-miscible irritants takes place in exchange. Moreover, it has to be considered that skin protection products cannot offer protection comparable with gloves, marketing promises like "the barrier creams is an invisible glove" may feign a seeming protection, but barrier creams do not act as the protective shield which may be claimed, and other protective measures, such as wearing gloves, will still be required. On the other hand, barrier creams are often the only realizable preventive measure in the case of occupations with an increased requirement for sense of touch and finger

Table 24.2 Glove material and applications. Source: ANSI/ISEA 105-2011, American National Standard for Hand Protection Selection Criteria

Glove material	Applications
Butyl	A synthetic rubber material that offers the highest permeation resistance to gas and water vapors. Especially suited for use with esters and ketones
Neoprene	A synthetic rubber material that provides excellent tensile strength and heat resistance. Neoprene is compatible with some acids and caustics. It has moderate abrasion resistance
Nitrile	A synthetic rubber material that offers chemical and abrasion resistance, a very good general duty glove. Nitrile also provides protection from oils, greases, petroleum products, and some acids and caustics
PVC (polyvinyl chloride)	A synthetic thermoplastic polymer that provides excellent resistance to most acids, fats, and petroleum hydrocarbons. Good abrasion resistance
PVA™ (polyvinyl alcohol)	A water-soluble synthetic material that is highly impermeable to gases. Excellent chemical resistance to aromatic and chlorinated solvents. The glove cannot be used in water or water-based solutions
Viton®	A fluoroelastomer material that provides exceptional resistance to chlorinated and aromatic solvents. Viton is very flexible but has minimal resistance to cuts and abrasions
Silver Shield®/4H	A lightweight, flexible laminated material that resists permeation from a wide range of toxic and hazardous chemicals. It offers the highest level of overall chemical resistance but has virtually not cut resistance

mobility or when working at rotating machines [44]. So applying barrier cream before work can make cleaning the skin easier, for example, after working with grease or oil, see Fig. 24.5 ([28], Kütting).

24.3.1 Requirements and Standards

The German Task Force on Occupational and Environmental Dermatology (ABD) has recently reviewed the current literature and gives recommendations for the selection of test models and study designs and discusses their values and limitations [8]. Repetitive irritation tests in humans are more related to the workplace situation and should be performed with relevant irritants. Most repetitive test designs are based on the standardized repeated irritation test (RIT) in humans using a set of four relevant irritants [11]. With the RIT, different formulations could be compared to the control field, which receives the irritant only, without barrier cream application. A standard similar to the abovementioned glove standards for testing barrier creams does not exist. It has to be taken in consideration that in some studies after the application of barrier creams, no protection from or even aggravation of irritant contact dermatitis was found [10, 41]. Barrier creams may in dependence of their galenic composition and their interaction with the irritant induce either a protective or an irritant effect, and even a better penetration of the irritant as an effect of barrier creams may appear [45].

In some situations, use of specific barrier creams is not necessary, and a moisturizing cream may have a similar effect. Again, there is most research available which suggests that after-work moisturizing is the most important.

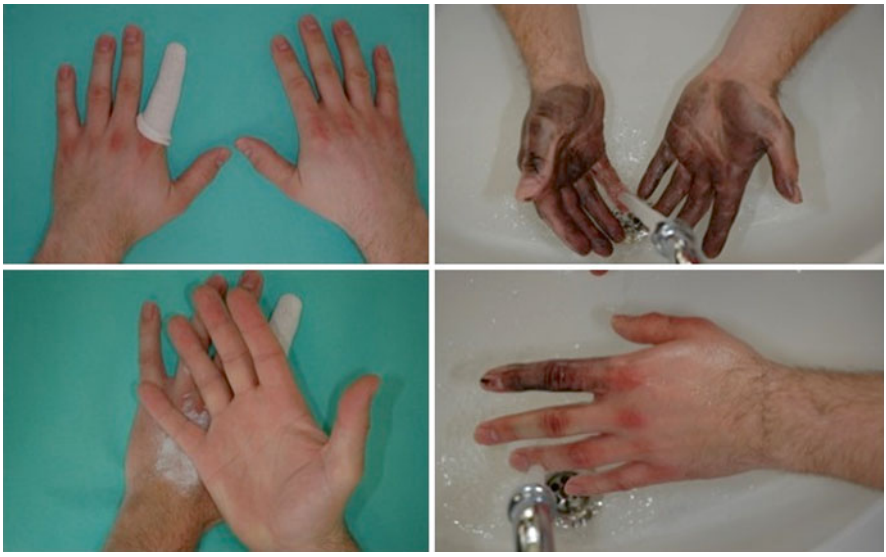


Fig. 24.5 Easier cleaning of the skin after applying barrier cream before work with grease or oil. Experiment to demonstrate this effect: Apply barrier cream (one finger is omitted) and use oily "standard" dirt; the dirt can be rinsed off easily without rubbing or using soap, and only the omitted finger remains dirty

Core Message
Whenever protection against an individual substance, groups of working materials, or other skin hazardous is claimed, it has to be proven that the skin protection was examined against these substances.

24.3.2 Right Application of Barrier Creams

Application errors by using barrier creams are common. Barrier creams have to be applied before contact to irritants, this includes a reapplication after every break or a certain period, and manufacturers often recommend to reapplicate barrier cream after half a work shift. Barrier cream has to be applied on clean and dry skin to avoid increased penetration of remaining irritants on the skin surface [18]. The application of the barrier cream itself is of most importance and influences the effectiveness significantly. It has to be applied frequently enough and in adequate amounts to all skin areas. As shown in Fig. 24.6 in studies, fluworescent-marked barrier creams indicated that the application was mostly incomplete especially in the dorsum of the hands and the interdigital spaces [39]. One aim of worker education is therefore to make individuals aware of the most commonly missed regions to ensure complete skin protection, and a fluorescence method may be useful to do this [39, 40].

Fig. 24.6 Fluorescence method for visualization of applied barrier cream

24.4 Skin Cleaning

"As little as possible, as often as needed" is the most important rule for skin cleaning. The hands need not be cleaned with skin cleansers, if not dirty, discolored, or contaminated with bacteria, such as after wearing gloves. When using skin cleansers, the following points should be observed:

- For maintaining the acid protection layer of the skin, the pH value should be neutral to the skin approx. pH 5.5 – [34].
- The product should be free of dyes, perfumes, and preservatives (potential allergens).
- The product should contain mild tensides.
- The product should be free of solvents [17].
- The product should be free of abrasives [23].
- Lukewarm water should be used.
- After washing, the hands should be carefully patted dry with single-use paper towels as soft and gentle as possible.

24.5 Skin Care

Skin care products are one effective module in preventing contact eczema. In the abovementioned discussion on the effectiveness of barrier creams, not only it has been debated whether a strict distinction between skin care products used before and after work is justified, since emollients alone have been shown to treat and prevent irritant contact dermatitis [31]. After work, appropriate skin care products should be used for regeneration of the skin. When needed, lotion can be generously applied to the hands and covered in cotton gloves overnight to promote healing [36].

Moisturizing creams which are used regularly can repair and maintain moisture in the skin. They may prevent dry skin from becoming inflamed and turning into dermatitis.

When selecting a moisturizer, there are several things to consider:

- A greasy ointment (they are usually thick and clear, like Vaseline) is most effective for healing damaged skin, but not always practical for day use. Ideally, it should be used when you get home and before bed. If an ointment can't be used, a less greasy cream purchased in a tub or tube is next best.
- Moisturizing lotions are also available. A lotion is a thin and watery substance often purchased in a pump pack. Pump packs of sorbolene lotion are convenient and useful for moisturizing during the day but are not generally as effective moisturizers as an ointment or cream.
- Some oil-based moisturizers may not be suitable for use under some gloves, as these moisturizers can damage the protective functions of the gloves. Generally, we do not recommend the use of moisturizers under occlusive (tight fitting, waterproof type) gloves. However, at night, creams may be applied under cotton gloves [28].

24.6 Workers' Education

Tucker [37] stated: "even if a glove is capable of preventing contact between a chemical and the skin, it must be worn to accomplish this preventive effect." In the prevention of occupational contact dermatitis, educational measures (primary prevention) and patient education (secondary and tertiary prevention) are components of skin protection programs. A skin protection program is defined as "a series of practical instructions about skin care aimed at a well-defined group of people (…) or at a certain workplace. It is necessary that the skin protection programme is an integrated part of an educational programme, which should provide information on healthy and diseased skin, lead to early recognition of skin symptoms, and give the employees prerequisites to understand evidence-based recommendations regarding skin protective procedures. Ideally, an educational programme should improve knowledge about skin care, followed by a change in behaviour of skin protection and a decrease in clinical symptoms. Recommendations given in a skin protection programme should be evidence-based, as far as this is available" [1, p. 254].

Some kind of specific aims for patient educational programs are summarized as follows: change behavior and decrease skin symptoms in wet occupations; improve the compliance; improve the level of knowledge; inform adolescents about potentially dangerous occupations, risk groups, and preventive measures before they started apprenticeships in order to minimize the risk of occupational allergies or skin diseases; improve the health-related quality of life; and acquire problem-solving skills associated with acting or participating in authentic situations [1, 16, 22, 30, 43, 44]. Flyvholm and Rrydendall Jepsen [9] stated that educational activities include lectures, discussions, reflection, homework, and feedback [9]. A variety of educational tools, including instructional pamphlets, videotapes, and lectures, can be found at the website of different institutions [3, 28, 33].

References

1. Agner T, Held E. Skin protection programs. Contact Dermatitis. 2002;47:253–6.
2. ANSI/ISEA 105-2011, American National Standard for Hand Protection Selection Criteria. [https://www.safetyequipment.org/c/std105-2011.cfm].
3. Brown T. Strategies for prevention: occupational contact dermatitis. Occup Med (Lond). 2004;54(7):450–7.
4. CCOHS. Canadian Centre for Occupational Health and Safety. 2014. http://www.ccohs.ca/oshanswers/prevention/ppe/gloves.html.
5. CEN. EN374-2:2003, Protective gloves against chemicals and micro-organisms. Part 2: determination of resistance to penetration. Brussels: Comité Européen de Normalisation; 2003.
6. Council Directive of 21 December 1989 on the approximation of the laws of the Member States relating to personal protective equipment: 89/686/EEC.
7. English JSC. Current concepts of irritant contact dermatitis. Occup Environ Med. 2004;61:722–6.
8. Fartasch M, Diepgen TL, Drexler H, Elsner P, Fluhr JW, John SM, Kresken J, Wigger-Alberti W. Berufliche Hautmittel (ICD-10:L23, L24) S1-Leitlinie der Arbeitsgemeinschaft für Berufs- und Umweltdermatologie (ABD) in der Deutschen Dermatologischen Gesellschaft (DDG). Arbeitsmed Sozialmed Umweltmed. 2009;44:53–67.
9. Flyvolm MA, Rrydendall Jepsen K. Experiences with implementation of evidence-based prevention programs to prevent occupational skin diseases in different occupations. GITAL Dermatol Venereol. 2008;143(1):71–8.
10. Frosch P, Schulze-Dirks A, Hoffmann M, Axthelm I. Efficacy of skin barrier creams (II). Ineffectiveness of a popular "skin protector" against various irritants in the repetitive irritation test in the guinea pig. Contact Dermatitis. 1993;29:74–7.
11. Frosch PJ, Kurte A. Efficacy of skin barrier creams (IV). The repetitive irritation test (RIT) with a set of 4 standard irritants. Contact Dermatitis. 1994;31(3):161–8.
12. Frosch PJ, Peiler D, Grunert V, Grunenberg B. Efficacy of barrier creams in comparison to skin care products in dental laboratory technicians – a controlled trial. JDDG. 2003;1(7):547–57.
13. Health & Safety Executive. Choosing the right gloves to protect skin. 2009. [www.hse.gov.uk/skin/employ/gloves.htm].
14. Heederik D, Henneberger PK, Redlich CA. Primary prevention: exposure reduction, skin exposure and respiratory protection. Eur Respir Rev. 2012;21:112–24.
15. Henry NW. U.S. rules, regulations and standards for protective gloves for occupational use. In: Boman A, Estlander T, Wahlberg JE, Maibach HI, editors. Protective gloves for occupational use. 2nd ed. Boca Raton: CRC Press; 2005. p. 35–42.
16. Kalimo K, Kautiainen H, Niskanen T, Niemi L. 'Eczema school' to improve compliance in an occupational dermatology clinic. Contact Dermatitis. 1999;41:315–9.
17. Klotz A, Thörner B, Veeger M, zur Mühlen A. Skin cleaners for removing heavy-duty contamination: testing efficacy and compatibility. SÖFW-J. 2002;128:14–21.
18. Kresken J, Klotz A. Occupational skin-protection products – a review. Int Arch Occup Environ Health. 2003;76:355–8.
19. Kütting B, Baumeister T, Weistenhöfer W, Pfahlberg A, Uter W, Drexler H. Effectiveness of skin protection measures in prevention of occupational hand eczema: results of a prospective randomized controlled trial over a follow-up period of 1 year. Br J Dermatol. 2010;162:362–70.
20. Kütting B, Drexler H. The three-step programme of skin protection. A useful instrument of primary prevention or more effective in secondary prevention? Dtsch Med Wochenschr. 2008;133:201–5.
21. Leuchtenberg-Auffahrt E, Rühl R. Safety of gloves for chemical protection. Ann Occup Hyg. 2007;51(8):739–40.
22. Löffler H, Bruckner T, Diepgen TL, Effendy I. Primary prevention in health care employees: a prospective intervention study with a 3-year training period. Contact Dermatitis. 2006;54:202–9.
23. Löffler H, Effendy I, Happle R. Die irritative Kontaktdermatitis. Hautarzt. 2000;51:203–18.

24. Mellström GA, Boman A. Gloves: types, materials, and manufacturing. In: Boman A, Estlander T, Wahlberg JE, Maibach HI, editors. Protective gloves for occupational use. 2nd ed. Boca Raton: CRC Press; 2005. p. 15–28.
25. Mellström GA, Boman A. Protective gloves. In: Chew A-L, Maibach HI, editors. Irritant dermatitis. Berlin: Springer; 2006. p. 409–19.
26. Moberg C, Alderling M, Meding B. Hand eczema and quality of life: a population-based study. Br J Dermatol. 2009;161:397–403.
27. Nicholson PJ. Evidence-based guidelines: occupational contact dermatitis and urticaria. Occup Med. 2010;60:502–6.
28. Occupational Research and Education Centre. Skin care. 2010. [http://www.occderm.asn.au/skin-care.html].
29. Packham CL. Gloves as chemical protection – can they really work? Ann Occup Hyg. 2006;50(6):545–8.
30. Radulescu M, Bock M, Bruckner T, Ellsäßer G, Fels H, Diepgen TL. Health education on occupational allergies and dermatoses for adolescents. JDDG. 2007;7:576–82.
31. Ramsing DW, Agner T. Preventive and therapeutic effects of a moisturizer. An experimental study of human skin. Acta Derm Venereol (Stockh). 1997;77:335–7.
32. Saary J, Qureshi R, Palda V, et al. A systematic review of contact dermatitis treatment and prevention. J Am Acad Dermatol. 2005;53:845–55.
33. SafeHair. Common Health and safety development in professional hairdressing in Europe. EU-Project. 2012. [http://safehair.loungemedia.de/safehair/homepage.html].
34. Schmid MH, Korting HC. The concept of the acid mantle of the skin. Its relevance for the choice of skin cleansers. Dermatology. 1995;151:276–80.
35. Skudlik C, Wulfhorst B, Gediga G, Bock M, Allmers H, John SM. Tertiary individual prevention of occupational skin diseases: a decade's experience with recalcitrant occupational dermatitis. Int Arch Occup Environ Health. 2008;81:1059–64.
36. Sonsmann F, Braumann, A, Wilke A, John SM, Wulfhorst B. EU Project SafeHair 2.0: Medical Reference Document for Occupational Skin Diseases in the Hairdressing Trade in Europe VP/2011/0123. 2012. [http://safehair.loungemedia.de/fileadmin/user_upload/documents/Documents/Grundlagendokument/Occupational_Skin_Diseases_in_hairdressing_EN.pdf].
37. Tucker SB. Prevention of occupational skin disease. Dermatol Clin. 1988;6:87–96.
38. US Department of Labor. Occupational and Health Standards 1919, Personal Protective Equipment/Hand Protection, 1910.138. 1994. [https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9788].
39. Wigger-Alberti W, Maraffio B, Elsner P. Training workers at risk for occupational contact dermatitis in the application of protective creams: efficacy of a fluorescence technique. Dermatology. 1997;195:129–33.
40. Wigger-Alberti W, Maraffio B, Wernli M, Elsner P. Self-application of a protective cream: pitfalls of occupational skin protection. Arch Dermatol. 1997;133:861–4.
41. Wigger-Alberti W, Rougier A, Richard A, Elsner P. Efficacy of protective creams in a modified repeated irritation test (RIT): methodological aspects. Acta Derm Venereol (Stockh). 1998;78:270–3.
42. Winkler R, Salameh B, Stolkovich S, Nikl M, Barth A, Ponocny E, Drexler H, Tappeiner G. Effectiveness of skin protection creams in the prevention of occupational dermatitis: results of a randomized, controlled trial. Int Arch Occup Environ Health. 2009;82:653–62.
43. Wulfhorst B, Bock M, John SM. Worker's education and teaching programmes: the German experience. In: Frosch PJ, Menné, Lepoittevin JP, editors. Textbook of contact dermatitis. 4th ed. Berlin: Springer; 2006.
44. Wulfhorst B, Bock M, Skudlik C, Wigger-Alberti W, John SM. Prevention of hand eczema: gloves, barrier creams and workers' education. In: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. Contact dermatitis. Berlin: Springer; 2011. p. 985–1011.
45. Xhauflaire-Uhoda E, Macarenko E, Denooz R, Charlier C, Piérard GE. Skin protection creams in medical settings: successful or evil? J Occup Med Toxicol. 2008;25:3–15.

Overview of Allergens Present in the European, North American, and Chinese Baseline Series

25

Jean-Pierre Lepoittevin and Christophe J. Le Coz

Contents

J.-P. Lepoittevin, DSc (✉) • C.J. Le Coz, MD
Laboratoire de Dermatochimie, University of Strasbourg, ILB,
4, rue Blaise Pascal, Strasbourg 67081, France
e-mail: jplepoit@unistra.fr; Christophe.lecoz@wanadoo.fr

J.D. Johansen et al. (eds.), *Quick Guide to Contact Dermatitis*,
DOI 10.1007/978-3-662-47714-4_25

25.1 Introduction

This chapter has been written in order to familiarize the reader with the structure of the main chemicals involved in contact dermatitis and therefore included in the European Baseline Series (EBS), the North American Core Series (NACS), and the Chinese Baseline Series (CBS). For each chemical, the principal name is used for classification, but also listed are the most important synonym(s), the Chemical

Abstracts Service (CAS) Registry Number that characterizes the substance, and its chemical structure. The reader will also find one literature reference. For botanical natural mixtures, only the main chemicals that have been shown, or suspected, to be associated with skin allergy are listed, and the reader should never forget that some other minor chemicals could also be relevant to some patients.

25.2 Amerchol L101 (NACS, CBS)

CAS Registry Number [9029–05–8]

Amerchol L101 is a concentrated absorption base composed of lanolin alcohols and mineral oil. It is found in cosmetics, pharmaceuticals, and topical drugs, but also in cutting oils, metal corrosion prevention products, etc.

Suggested Reading

Lee B, Warshaw E. Lanolin allergy: history, epidemiology, responsible allergens and management. Dermatitis. 2008;19:63–72.

25.3 Bacitracin (NACS) (Fig. 25.1)

CAS Registry Number [1405–87–4]

Bacitracin is a mixture of related cyclic polypeptides produced by organisms of the *licheniformis* group of *Bacillus subtilis* var. Tracy. It is used as a topical preparation and was voted Allergen of the Year in 2003 by the NACDG.

Suggested Reading

Zug KA et al. Patch-test results of the North American Contact Dermatitis Group 2005–2006. Dermatitis. 2009;20:149–60.

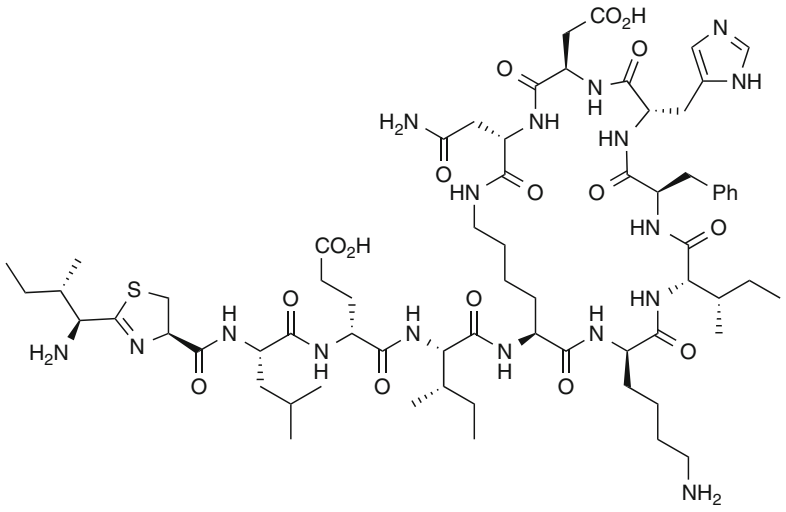


Fig. 25.1 Bacitracin (NACS)

25.4 Benzocaine (EBS, NACS) (Fig. 25.2)

Ethyl 4-aminobenzoate

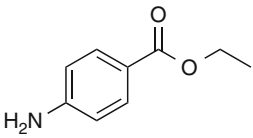
CAS Registry Number [94–09–7]

Benzocaine is a local anesthetic derived from *p*-aminobenzoic acid. Cross-reactions with other *p*-amino compounds such as PPD have been reported.

Suggested Reading

Gail H et al. Adverse reactions to local anesthetics: analysis of 197 cases. J Allergy Clin Immunol. 1996;97:933–7.

Fig. 25.2 Benzocaine (EBS, NACS)



25.5 Benzophenone-3 (NACS, CBS) (Fig. 25.3)

Oxybenzone

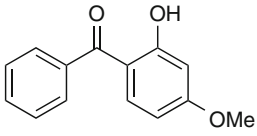
CAS Registry Number [131–57–7]

Benzophenones (BZPs), and substituted BZP numbered 1–12, are photo-screen agents widely used in sunscreens and in cosmetics, such as "antiaging" creams and hair sprays and shampoos, but also in paints and plastics. BZP-3 is used as a direct sunscreen agent and in antiaging creams. Cross-reactivity is expected in an average of one in four patients photoallergic to ketoprofen.

Suggested Reading

Matthieu L et al. Contact and photocontact allergy to ketoprofen. The Belgian experience. Contact Dermatitis. 2004;50:238–41.

Fig. 25.3 Benzophenone-3 (NACS, CBS)



25.6 Benzoyl Peroxide (CBS) (Fig. 25.4)

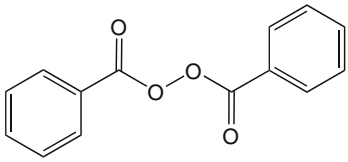
CAS Registry Number [94–36–0]

Benzoyl peroxide is an oxidizing agent widely used in acne topical therapy. It is also used as a polymerization catalyst of dental or industrial plastics, as a bleaching agent of flours, oils, fats, and waxes. Irritant or allergic dermatitis may affect workers in the electronics and plastics (epoxy resins and catalysts) industries, electricians, ceramic workers, dentists and dental technicians, laboratory technicians, bakers, and acne patients.

Suggested Reading

Rustemeyer T, Frosch PJ. Occupational skin diseases in dental laboratory technicians. (I). Clinical picture and causative factors. Contact Dermatitis. 1996;34:125–33.

Fig. 25.4 Benzoyl peroxide (CBS)



25.7 Benzyl Salicylate (CBS) (Fig. 25.5)

Benzyl-*o*-hydroxybenzoate, 2-hydroxybenzoic acid phenylmethyl ester

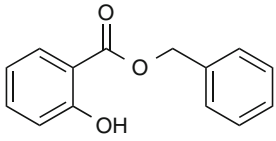
CAS Registry Number [118–58–1]

Benzyl salicylate is used in perfumery and in sunscreen preparations as a fixative agent. As a fragrance sensitizer, it has to be listed by name in cosmetic preparations in the EU.

Suggested Reading

Larsen W et al. Fragrance contact dermatitis: a worldwide multicenter investigation (Part I). Am J Contact Dermatitis. 1996;7:77–83.

Fig. 25.5 Benzyl salicylate (CBS)



25.8 2-Bromo-2-nitropropane-1,3-diol (NACS, CBS) (Fig. 25.6)

Bronopol

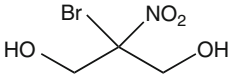
CAS Registry Number [52–51–7]

Bronopol is a preservative sometimes considered as a formaldehyde releaser. It was reported to be an allergen in cosmetics and cleaning agents, in dairy workers and in a gel used for ultrasound examination.

Suggested Reading

Wilson CL, Powell SM. An unusual cause of allergic contact dermatitis in a veterinary surgeon. Contact Dermatitis. 1990;23:42–3.

Fig. 25.6 2-Bromo-2-nitropropane-1,3-diol (NACS, CBS)



25.9 Budesonide (EBS, NACS) (Fig. 25.7)

CAS Registry Number [51333–22–3]

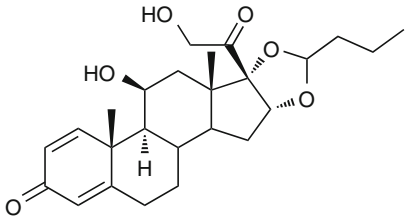
(R)-Budesonide/CAS Registry Number [51372–29–3]; *(S)*-Budesonide/CAS Registry Number [51372–28–2]

Budesonide is a mix of two diastereoisomers. The *(R)*-budesonide is considered to be a marker of the B group of corticosteroids (amcinonide, budesonide, desonide or prednacinolone, flunisolide, fluocinolone and its acetonide, fluocinonide, fluclorolone and its acetonide, halcinonide, and acetonide, benetonide, diacetate, and hexacetonide of triamcinolone). The *(S)*-budesonide is considered to be a marker of the D2 group of corticosteroids (hydrocortisone 17-butyrate, hydrocortisone 17-valerate, hydrocortisone aceponate, methylprednisolone aceponate, and prednicarbate).

Suggested Reading

Lepoittevin JP, Drieghe J, Dooms-Goossens A. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. Arch Dermatol. 1995;131:31–7.

Fig. 25.7 Budesonide (EBS, NACS)



25.10 2-tert-Butyl-4-methoxyphenol/BHA (CBS) (Fig. 25.8)

Butylated hydroxyanisole

CAS Registry Number [25013–16–5]

BHA is an antioxidant widely used in cosmetics and food. It was also reported to induce sensitization in caterers.

Suggested Reading

Acciai MC et al. Allergic contact dermatitis in caterers. Contact Dermatitis. 1993;28:48.

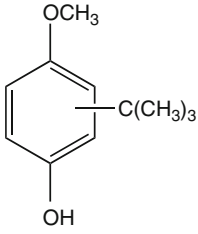


Fig. 25.8 2-tert-Butyl-4-methoxyphenol/BHA (CBS)

25.11 4-tert-Butylphenol formaldehyde Resin/PTBP (EBS, NACS, CBS) (Fig. 25.9)

para-tert-Butylphenol

CAS Registry Number [98–54–4]

The polycondensate *p-tert*-butylphenol formaldehyde resin (PTBPFR) is obtained by reaction of *p-tert*-butylphenol with formaldehyde. Major occupational sources are neoprene glues and adhesives in industry, in the shoemaking and leather industries, or in car production. It is also used as a preservative in box and furniture manufacture and in the production of casting molds, car brake linings, insulated electrical cables, adhesives, printing inks, and paper laminates. *p-tert*-Butylphenol seems to be the main sensitizer.

Suggested Reading

Tarvainen K. Analysis of patients with allergic patch test reactions to a plastics and glue series. Contact Dermatitis. 1995;32:346–51.

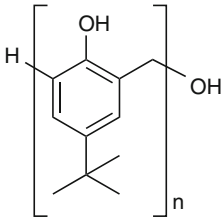


Fig. 25.9 4-tert-Butylphenol formaldehyde resin/PTBP (EBS, NACS, CBS)

25.12 *Cananga odorata* Oil

Ylang-ylang oil

CAS Registry Number [8006–81–3]

This essential oil is obtained from flowers of *Cananga odorata* Hook. F. and Thoms. It is mainly used as a fragrance material in fine perfumes but also in aromatherapy and can therefore induce occupational contact dermatitis. The oil contains several potential allergens such as isoeugenol and derivatives of geraniol and linalool (see FMI).

Suggested Reading

Romaguera C, Vilaplana J. Occupational contact dermatitis from ylang-ylang oil. Contact Dermatitis. 2000;43:251.

25.13 Carba Mix (NACS, CBS) (Fig. 25.10)

This mix contains the following three allergens: diphenylguanidine, zinc dibutyldithiocarbamate, and zinc diethyldithiocarbamate. These chemicals are used as fungicides and pesticides and also in the manufacture of many rubber products. One can

get in contact with these substances when using, wearing, or handling rubber products at work or at home.

(a) 1,3-Diphenylguanidine/CAS Registry Number [102–06–7]
Diphenylguanidine is a rubber sensitizer that can induce both immediate- and delayed-type contact allergy. Occupational exposure concerns finished rubber items and the rubber manufacturing industry. The most frequent occupational categories are metal industry, homemakers, health services and laboratories, and the building industry.

(b) Zinc bis-Dibutyldithiocarbamate/CAS Registry Number [136–23–2]
It is used as a vulcanization accelerator; it can also be contained in paints, glue removers, and anticorrosive products.

(c) Zinc *bis*-Diethyldithiocarbamate/CAS Registry Number [14324–55–1]
It is a rubber component used as a vulcanization accelerator. Oxidation of this carbamate derivative leads to tetraethylthiuram disulfide.

Suggested Reading

Condé-Salazar L et al. Type IV allergy to rubber additives: a 10-year study of 686 cases. J Am Acad Dermatol. 1993;29:176–80.

Chipinda I et al. Zinc diethyldithiocarbamate allergenicity: potential haptenation mechanisms. Contact Dermatitis. 2008;59:79–89.

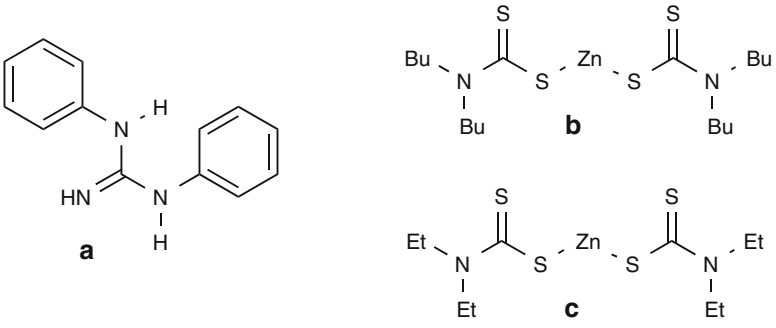


Fig. 25.10 Carba mix (NACS, CBS)

25.14 Chloroxylenol/PCMX (NACS, CBS) (Fig. 25.11)

4-Chloro-3,5-dimethylphenol

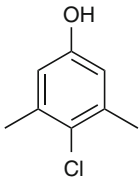
CAS Registry Number [88–04–0]

Chloroxylenol is a broad-spectrum antimicrobial chemical compound used to control bacteria, algae, fungi, and viruses. It is primarily used in household products and topical medicine.

Suggested Reading

Berthelot C, Zirwas MJ. Allergic contact dermatitis to chloroxylenol. Dermatitis. 2006;17:156–9.

Fig. 25.11 Chloroxylenol/PCMX (NACS, CBS)



25.15 Cinnamal (NACS, CBS) (Fig. 25.12)

Cinnamic aldehyde, cinnamaldehyde, 3-phenyl-2-propenal

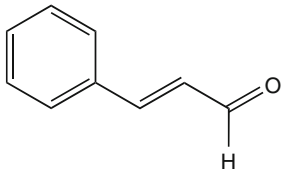
CAS Registry Number [104–55–2]

This chemical is used as a fragrance in perfumes and as a flavoring agent in soft drinks, ice creams, toothpastes, pastries, chewing gum, etc. It can induce both contact urticaria and delayed-type reactions. It can be responsible for dermatitis in the perfume industry or in food handlers. Cinnamic aldehyde is contained in "fragrance mix I" and has to be mentioned by name in cosmetics within the EU.

Suggested Reading

Seite-Bellezza D et al. Contact urticaria from cinnamic aldehyde and benzaldehyde in a confectioner. Contact Dermatitis. 1994;31:272–3.

Fig. 25.12 Cinnamal (NACS, CBS)



25.16 Clioquinol (EBS) (Fig. 25.13)

Chloroiodoquine, 5-chloro-7-iodoquinolin-8-ol

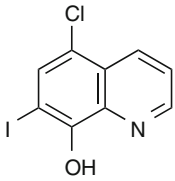
CAS Registry Number [130–26–7]

Clioquinol is an antifungal and antiprotozoal drug. It can be incorporated in many topical creams and ointments to treat skin conditions in which an anti-infective agent is required. The oral administration of clioquinol has resulted in a generalized eruption in individuals allergic to this chemical.

Suggested Reading

Morris SD et al. Comparative frequency of patch test reactions to topical antibiotics. Br J Dermatol. 2002;146:1047–51.

Fig. 25.13 Clioquinol (EBS)



25.17 Cocamide DEA (CBS) (Fig. 25.14)

Coconut diethanolamide, coconut oil fatty acid diethanolamide, *N*,*N*-bis(2-hydroxyethyl)coco fatty acid diethanolamide, cocoyl diethanolamide

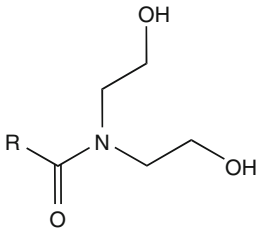
CAS Registry Number [68603–42–9]

Cocamide DEA, manufactured from coconut oil, is widely used in industry and at home as a surface-active agent. It is contained in hand gels, handwashing soaps, shampoos, and dishwashing liquids for its foam-producing and stabilizing properties and in metalworking fluids and polishing agents as an anticorrosion inhibitor.

Suggested Reading

Fowler JF Jr. Allergy to cocamide DEA. Am J Contact Dermatitis. 1998;9:40–1.

Fig. 25.14 Cocamide DEA (CBS)



25.18 Cocamidopropyl Betaine (NACS) (Fig. 25.15)

Cocoamphodipropionate, cocamidopropyl dimethyl glycine, cocoamphocarboxypropionate, cocoyl amide propylbetaine

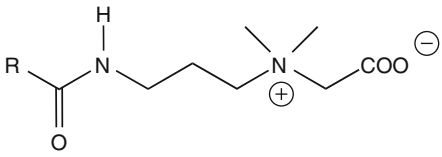
CAS Registry Numbers [61789–40–0], [83138–08–3], [86438–79–1]

Cocamidopropyl betaine is a pseudo-amphoteric zwitterion detergent derived from long-chain alkyl betaines. It is available from many suppliers under more than 50 trade names. Exposure occurs via rinse-off products such as liquid soaps, shampoos, and shower gels but also via leave-on products such as roll-on deodorants. Occupational sources are mainly in hairdressing. The first synthesis step consists of the reaction of coconut fatty acids with 3-dimethylaminopropylamine, giving cocamidopropyl dimethylamine. This amidoamine is converted into cocamidopropyl betaine by reaction with sodium monochloroacetate. Both dimethylaminopropylamine and cocamidopropyl dimethylamine are thought to be the sensitizers.

Suggested Reading

McFadden JP et al. Clinical allergy to cocamidopropyl betaine: reactivity to cocamidopropylamine and lack of reactivity to 3-dimethylaminopropylamine. Contact Dermatitis. 2001;45:72–4.

Fig. 25.15 Cocamidopropyl betaine (NACS)



25.19 Colophonium (EBS, NACS, CBS) (Fig. 25.16)

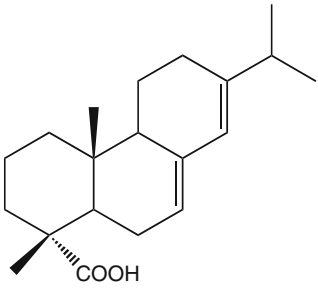
Abietic acid/CAS Registry Number [514–10–3]

Abietic acid is probably the major source of allergens in colophony or rosin by way of air oxidation. The formation of highly sensitizing hydroperoxides has been demonstrated, and therefore the detection of abietic acid in a material indicates that allergenic components of colophony are present.

Suggested Reading

Karlberg AT et al. Is abietic acid the allergenic component of colophony? Contact Dermatitis. 1985;13:209–15.

Fig. 25.16 Colophonium (EBS, NACS, CBS)



25.20 Compositae Mix II (NACS) (Fig. 25.17)

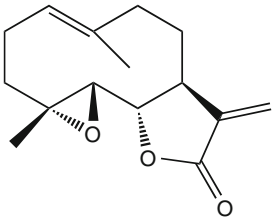
This mix was introduced as a complement of the sesquiterpene lactone mix for the detection of Compositae dermatitis. It is made of parthenolide and a sesquiterpene lactone and of five natural extracts: *Tanacetum vulgare* L., *Arnica montana* L., *Chamomilla romana* (*Anthemis nobilis* L.), *Matricaria chamomilla* L., and *Tanacetum millefolium* (L.) Tzvelev.

- Parthenolide/CAS Registry Number [20554–84–1]
- Parthenolide is a sesquiterpene lactone found in Asteraceae/Compositae such as feverfew (*Tanacetum parthenium* Schultz-Bip.) or congress grass (*Parthenium hysterophorus* L.).

Suggested Reading

Paulsen E et al. Compositae dermatitis in a Danish dermatology department in one year (I). Contact Dermatitis. 1993;29:6–10.

Fig. 25.17 Parthenolide (NACS)



25.21 Decyl Glucoside (CBS) (Fig. 25.18)

Decyl D-glucoside, decyl-beta-D-glucopyranoside

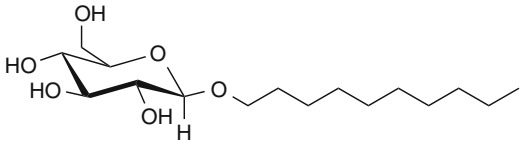
CAS Registry Number [58846–77–8]

Decyl glucoside belongs to the alkyl glucoside family and is obtained by condensation of the fatty alcohol decyl alcohol and a D-glucose polymer. This nonionic surfactant and cleansing agent has been widely used for several years in rinse-off products such as shampoos, hair dyes and colors, and soaps due to its foaming power and good tolerance. Decyl glucoside is also employed in leave-on products such as no-rinse cleansing milks, lotions, and several sunscreen agents.

Suggested Reading

Goossens A et al. Glucosides as unexpected allergens in cosmetics. Contact Dermatitis. 2003;48:164–6.

Fig. 25.18 Decyl glucoside (CBS)



25.22 Diazolidinyl Urea (NACS, CBS) (Fig. 25.19)

Germall II

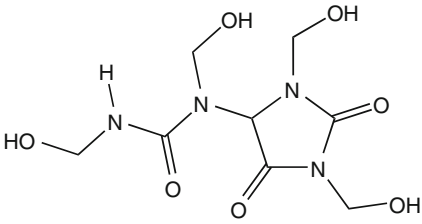
CAS Registry Number [78491–02–8]

Diazolidinyl urea, a formaldehyde releaser, is contained mainly in cosmetics and toiletries, but can also be found in barrier creams.

Suggested Reading

Van Hecke E, Suys E. Where next to look for formaldehyde? Contact Dermatitis. 1994;31:268.

Fig. 25.19 Diazolidinyl urea (NACS, CBS)



25.23 Dimethylol Dihydroxy Ethylene Urea (NACS) (Fig. 25.20)

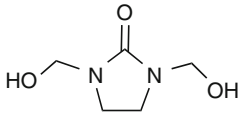
CAS Registry Number [136–84–5]

Dimethylol ethylene urea is an organic compound derived from formaldehyde and urea. It is used for treating cellulose-based fabrics to avoid wrinkle formation. The chemical can release formaldehyde.

Suggested Reading

Metzler-Brenckle L. Rietschel RL. Patch testing for permanent-press allergic contact dermatitis. Contact Dermatitis. 2002;46:33–7.

Fig. 25.20 Dimethylol dihydroxy ethylene urea (NACS)



25.24 Disperse Blue Mix (NACS, CBS) (Fig. 25.21)

This mix contains two of the most often incriminated disperse textile dyes: disperse blue 106 and 124. Concomitant reactions between these dyes are due to their chemical similarities. Both are used in synthetic fibers.

(a) Disperse blue 106/CAS Registry Number [74339–69–8]
(b) Disperse blue 124/CAS Registry Number [15141–18–1]

They are used in synthetic fibers.

Suggested Reading

Mota F et al. An outbreak of occupational textile dye dermatitis from Disperse Blue 106. Contact Dermatitis. 2000;43:235–6.

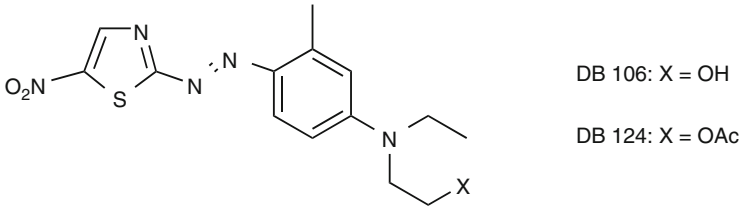


Fig. 25.21 Disperse blue mix (NACS, CBS)

25.25 Disperse Orange 3 (CBS) (Fig. 25.22)

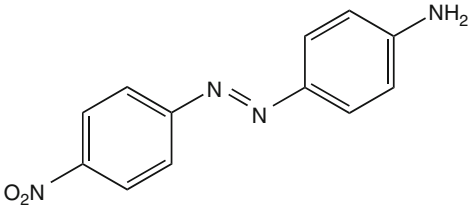
CAS Registry Number [730–40–5]

Disperse orange 3 is an azo dye reported to induce contact dermatitis in the textile industry. It is positive in a great majority of PPD-positive individuals, because of metabolism in the skin into PPD. Disperse orange 3 can also be found in some semipermanent hair dyes.

Suggested Reading

Soni BP, Sherertz EF. Contact dermatitis in the textile industry: a review of 72 patients. Am J Contact Dermatitis. 1996;7:226–30.

Fig. 25.22 Disperse orange 3 (CBS)



25.26 Disperse Yellow 3 (CBS) (Fig. 25.23)

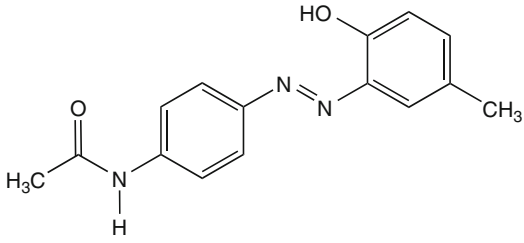
CAS Registry Number [2832–40–8]

This azo dye is responsible for textile dermatitis from stockings and occupational contact dermatitis in the textile industry. It can be found in some semipermanent hair dyes.

Suggested Reading

Condé-Salazar L et al. Contact dermatitis in hairdressers: patch test results in 379 hairdressers (1980–1993). Am J Contact Dermatitis. 1995;6:19–23.

Fig. 25.23 Disperse yellow 3 (CBS)



25.27 DMDM Hydantoin (NACS, CBS) (Fig. 25.24)

1,3-Dimethylol-5,5-dimethylhydantoin, Glydant™

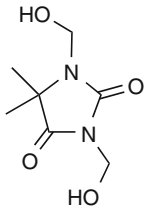
CAS Registry Number [6440–58–0]

DMDM hydantoin is an antimicrobial formaldehyde releaser preservative belonging to a class of compounds known as hydantoins. It is used in the cosmetics industry and found in products like shampoos, hair conditioners, hair gels, and skin care products.

Suggested Reading

de Groot AC et al. Patch test reactivity to DMDM hydantoin. Relationship to formaldehyde allergy. Contact Dermatitis. 1988;18:197–201.

Fig. 25.24 DMDM hydantoin (NACS, CBS)



25.28 Ethyl Acrylate (NACS, CBS) (Fig. 25.25)

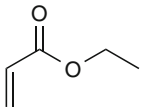
CAS Registry Number [140–88–5]

Acrylates are esters of acrylic acid, and occupational contact allergies from acrylates have frequently been reported in workers exposed to the glues, as well as dental workers and beauticians.

Suggested Reading

Rustemeyer T, Frosch PJ. Occupational skin diseases in dental laboratory technicians. (I). Clinical picture and causative factors. Contact Dermatitis. 1996;34:125–33.

Fig. 25.25 Ethyl acrylate (NACS, CBS)



25.29 Ethylenediamine (NACS, CBS) (Fig. 25.26)

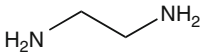
CAS Registry Number [107–15–3]

Ethylenediamine is used in numerous industrial processes as a solvent for casein or albumin, as a stabilizer in rubber latex, and as a textile lubricant. It can be found in epoxy resin hardeners, cooling oils, fungicides, and waxes. Contact dermatitis from ethylenediamine is almost exclusively due to topical drugs. Ethylenediamine can cross-react with triethylenetetramine and diethylenetriamine.

Suggested Reading

Sasseville D, Al-Khenaizan S. Occupational contact dermatitis from ethylenediamine in a wire-drawing lubricant. Contact Dermatitis. 1997;3:228–9.

Fig. 25.26 Ethylenediamine (NACS, CBS)



25.30 Epoxy Resins of the Bisphenol A Type (EBS, NACS, CBS) (Fig. 25.27)

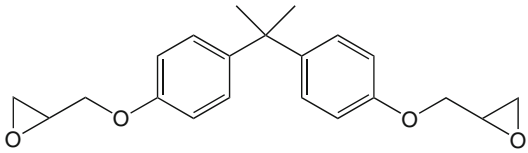
These resins are synthesized from bisphenol A and epichlorhydrin. Hardeners are added, such as amines (ethylenediamine, diethylenetriamine, triethylenetetramine, isophoronediamine, triethylenetriamine, and 4,4-diaminodiphenylmethane) and acid anhydrides (phthalic anhydride). Reactive diluents may be added, such as allyl glycidyl ether, butanediol diglycidyl ether, *n*-butyl glycidyl ether, *o*-cresyl glycidyl ether, hexanediol diglycidyl ether, neopentyl glycol diglycidyl ether, phenyl glycidyl ether, glycidyl ester of synthetic fatty acids, and glycidyl ether of aliphatic alcohols.

- Bisphenol A Diglycidyl Ether (DGEBA)/CAS Registry Number [1675–54–3]
- Most epoxy resins result from polymerization of bisphenol A diglycidyl ether (BADGE). Delayed hypersensitivity is caused by the low-molecular-weight monomer BADGE (Mol. Wt. 340 g/mol), the dimer having much a lower sensitization power.
- Phenyl Glycidyl Ether/CAS Registry Numbers [122–60–1], [66527–93–3]
- This monoglycidyl derivative is a reactive diluent in epoxy resin bisphenol A type. It is a component of epoxy paints, epoxy glues, and epoxy resins. Sensitization has been observed in many professions, such as in construction workers, marble workers, ceramic workers, and shoemakers.

Suggested Reading

Tarvainen K. Analysis of patients with allergic patch test reactions to a plastic and glues series. Contact Dermatitis. 1995;32:346–51.

Fig. 25.27 Epoxy resins of the bisphenol A type (EBS, NACS, CBS)



25.31 Ethylene Urea-Melamine-Formaldehyde Mix (NACS, CBS) (Fig. 25.28)

Mixture of ethylene urea and melamine-formaldehyde resin. Both chemicals are found in finishing agents for textile and leather. Melamine-formaldehyde resin (MFR) results from condensation of melamine and formaldehyde. It is an active ingredient of strong (reinforced) plasters, such as industrial or some dental plasters

used for molding. It is also used as a textile finish resin. MFR acts as an allergen generally because of formaldehyde releasing

- Ethylene Urea/CAS Registry Number [120–93–4]
- This chemical is used in the manufacturing of polymers and as a finishing agent for textiles and leather.
- Melamine (2,4,6-Triaminotriazine)/CAS Registry Number [108–78–1]

Suggested Reading

Aalto-Korte K et al. Formaldehyde-negative allergic contact dermatitis from melamine-formaldehyde resin. Contact Dermatitis. 2003;49:194–6.

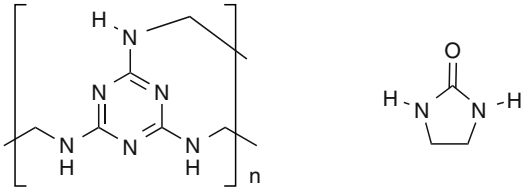


Fig. 25.28 Ethylene urea-melamine-formaldehyde mix (NACS, CBS)

25.32 Formaldehyde (EBS, NACS, CBS) (Fig. 25.29)

Methanal, formalin

CAS Registry Number [50–00–0]

Sources and uses of formaldehyde are numerous. Exposed people are mainly health workers, cleaners, painters, and metalworkers, but also photographers (color developers) and carbonless copy paper users. Formaldehyde can induce contact urticaria. Formaldehyde may be the cause of sensitization to formaldehyde releasers: benzylhemiformal, bromonitrodioxane, bromonitropropanediol, chloroallylhexaminium chloride or quaternium-15, diazolidinyl urea, dimethylol urea, dimethyloldimethylhydantoin or DMDM hydantoin, hexamethylenetetramine or methenamine, imidazolidinyl urea, monomethyloldimethylhydantoin or MDM hydantoin, *N*-methylolchloroacetamide, paraformaldehyde, and trihydroxyethylhexahydrotriazine or Grotan BK. Formaldehyde is used for the synthesis of many resins. Some of them, such as formaldehyde-urea and melamine-formaldehyde resins, can be used in textiles and secondarily release free formaldehyde.

Other resins, such as *p-tert*-butylphenol formaldehyde resin or tosylamide-formaldehyde resin, do not release formaldehyde.

Suggested Reading

Flyvholm MA, Menné T. Allergic contact dermatitis from formaldehyde. A case study focussing on sources of formaldehyde exposure. Contact Dermatitis. 1992;27:27–36.

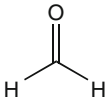


Fig. 25.29 Formaldehyde (EBS, NACS, CBS)

25.33 Fragrance Mix I (EBS, NACS, CBS) (Fig. 25.30)

This mix is aimed at the detection of fragrance allergy and contains seven individual chemicals (α-amylcinnamaldehyde, cinnamaldehyde, cinnamic alcohol, hydroxycitronellal, eugenol, isoeugenol, and geraniol as well as a natural extract and oakmoss absolute). All these chemicals have to be mentioned by name in cosmetics within the EU.

(a) α-Amylcinnamaldehyde/CAS Registry Number [122–40–7]

α-Amyl cinnamic aldehyde, amyl cinnamal, 2-benzylideneheptanal, 2-pentylcinnamaldehyde, jasminal

α-Amyl cinnamic aldehyde is the oxidation product of α-amylcinnamic alcohol, a fragrance sensitizer. It was also reported to be a sensitizer in bakers.

(b) Cinnamal/CAS Registry Number [104–55–2]

Cinnamic aldehyde, cinnamaldehyde, 3-phenyl-2-propenal

This is used as a fragrance material and as a flavoring agent in soft drinks, ice creams, toothpastes, pastries, chewing gum, etc. It can induce both contact urticaria and delayed-type reactions.

(c) Cinnamyl Alcohol/CAS Registry Number [104–54–1]

Cinnamic alcohol, 3-phenyl-2-propenol

Cinnamyl alcohol is present as esters in storax, *Myroxylon pereirae*, cinnamon leaves, and hyacinth oil. Occupational cases of contact dermatitis were reported in the perfume industry and in food handlers.

(d) Hydroxycitronellal/CAS Registry Number [107–75–5]

7-Hydroxycitronellal, citronellal hydrate, laurine, muguet synthetic

Hydroxycitronellal is a classical fragrance allergen, found in many products.

(e) Eugenol/CAS Registry Number [97–53–0]

Occupational sensitization to eugenol may occur in dental profession workers.

(f) Isoeugenol/CAS Registry Number [97–54–1]

cis-Isoeugenol/CAS Registry Number [5912–86–7]; *trans*-Isoeugenol/CAS Registry Number [5932–68–3]

Isoeugenol is a mixture of *cis* and *trans* isomers and occurs in ylang-ylang and other essential oils. It is a common allergen of perfumes and cosmetics such as deodorants. Substitution by esters such as isoeugenyl acetate (not labeled) does not always resolve the allergenic problem, because of the in vivo hydrolysis of the substitute into isoeugenol.

(g) Geraniol/CAS Registry Number [106–24–1]

3,7-Dimethyl-2,6-octadien-1-ol

cis-Geraniol (Nerol)/CAS Registry Number [106–25–2]; *trans*-Geraniol (Citrol)/CAS Registry Number [624–15–7]

Geraniol is an olefinic terpene, constituting the chief part of rose oil and oil of palmarosa. It is also found in many other essential oils such as citronella, lemongrass, or ylang-ylang (*Cananga odorata* Hook. F. and Thoms.) and is contained in most fine fragrances.

– Oakmoss Absolute

Oakmoss absolute is a natural extract of *Evernia prunastri* (L.) Ach. and is used in many fragrances due to its woody odor. Oakmoss has been shown to contain many different sensitizers, two of them being atranol and chloroatranol.

(h) Atranol/CAS Registry number [526–37–4]

2,6-Dihydroxy-4-methyl-benzaldehyde

(i) Chloroatranol/CAS Registry Number [57074–21–2]

This potent allergen gives reactions with concentrations down to 5 ppm in sensitized patients.

Suggested Reading

Rastogi SC et al. Deodorants on the European market: quantitative chemical analysis of 21 fragrances. Contact Dermatitis. 1998;38:29–35.

Tanaka S et al. Contact allergy to isoeugenol and its derivatives: problems with allergen substitution. Contact Dermatitis. 2004;51:288–91.

Johansen JD et al. Chloroatranol, an extremely potent allergen hidden in perfumes: a dose response elicitation study. Contact Dermatitis. 2003;49:180–4.

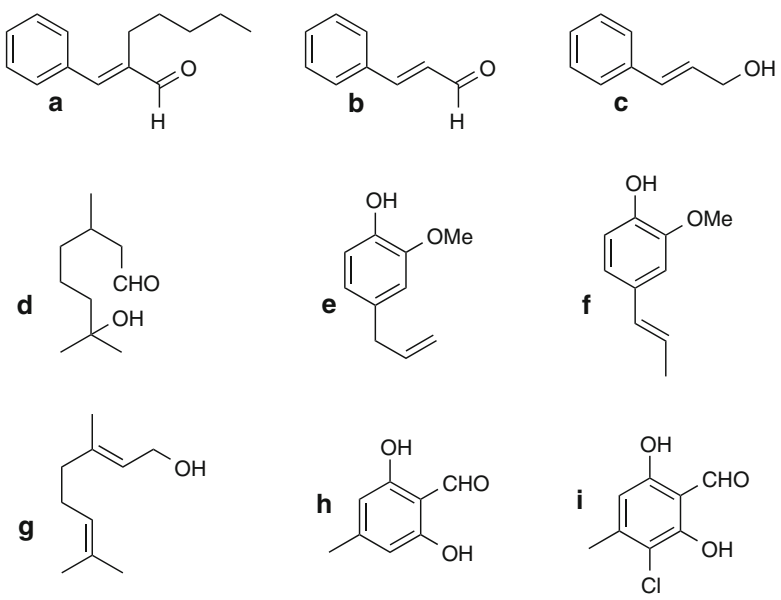


Fig. 25.30 Fragrance mix I (EBS, NACS, CBS)

25.34 Fragrance Mix II (EBS, NACS, CBS) (Fig. 25.31)

This mix aimed at the detection of fragrance allergy in addition to fragrance mix I contains six individual chemicals (α-hexylcinnamaldehyde, farnesol, coumarin, Lyral, citral, and citronellol). All these chemicals have to be mentioned by name in cosmetics within the EU.

(a) Hexyl Cinnamic Aldehyde/CAS Registry Number [101–86–0]

Hexyl cinnamaldehyde, α-hexylcinnamaldehyde, 2-(phenylmethylene) octanal, 2-benzylideneoctanal

(b) Farnesol/CAS Registry Number [4602–84–0] for the mixture of isomers

3,7,11-Trimethyldodeca-2,6,10-trienol (four isomers)

CAS Registry Numbers are [106–28–5] for the *trans/trans*, [3790–71–4] for the *cis/trans*, [3879–60–5] for the *trans/cis*, and [16106–95–9] for the *cis/cis* isomers, respectively.

Farnesol is one of the most frequent contact allergens in perfumes. It is contained in small amounts in *Myroxylon pereirae* and in poplar buds. It is a mix of four diastereoisomers *trans*/*cis*.

(c) Coumarin/CAS Registry Number [91–64–5]

1-Benzopyran-2-one, *cis*-*o*-coumarinic acid lactone

Coumarin is an aromatic lactone naturally occurring in tonka beans and other plants.

(d) Hydroxymethylpentacyclohexenecarboxaldehyde/CAS Registry Number [31906–04–4]

Lyral®, hydroxyisohexyl 3-cyclohexene carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)cyclohex-3-ene-carbaldehyde

Lyral® is a synthetic mixture of two isomers and one of the most frequently encountered allergens in perfumes.

(e) Citral/CAS Registry Number [5392–40–5]

3,7-Dimethyl-2,6-octadien-1-al, blend of neral and geranial, blend of (*Z*)-3,7-dimethyl-2,6-octadienal and (*E*)-3,7-dimethyl-2,6-octadienal (CAS Registry Number [141–27–5] + CAS Registry Number [106–26–3])

Citral is an aldehyde fragrance and flavoring ingredient and present as a mix of two isomers: *cis* (neral) and *trans* (geranial).

(f) Citronellol/CAS Registry Numbers [106–22–9] and [26489–01–0]

3,7-Dimethyl-6-octen-1-ol, cephrol

l-Citronellol is a constituent of rose and geranium oils, while *d*-citronellol occurs in Ceylon and Java citronella oils.

Suggested Reading

Frosch PJ et al. Further important sensitizers in patients sensitive to fragrances. Contact Dermatitis. 2002;47:78–85.

Johansen JD et al. Hydroxyisohexyl 3-cyclohexene carboxaldehyde – known as Lyral: quantitative aspects and risk assessment of an important fragrance allergen. Contact Dermatitis. 2003;48:310–6.

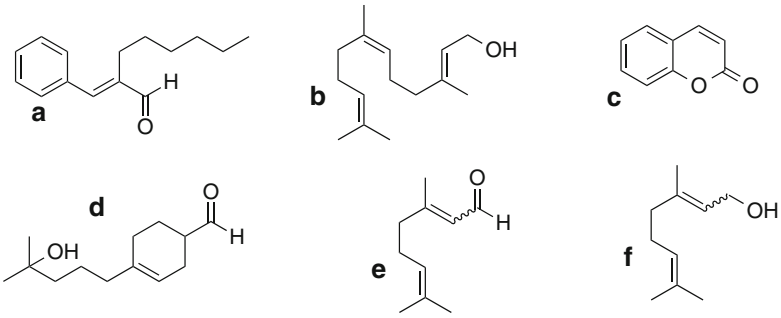


Fig. 25.31 Fragrance mix II (EBS, NACS, CBS)

25.35 Glutaraldehyde (NACS, CBS) (Fig. 25.32)

Glutaral, pentanedial, glutaric dialdehyde

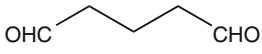
CAS Registry Number [111–30–8]

Glutaraldehyde is a well-known sensitizer in cleaners and health workers.

Suggested Reading

Stingeni L et al. Occupational hand dermatitis in hospital environments. Contact Dermatitis. 1995;33:172–6.

Fig. 25.32 Glutaraldehyde (NACS, CBS)



25.36 Glyceryl Thioglycolate (NACS, CBS) (Fig. 25.33)

Glyceryl monothioglycolate, glycerol monomercaptoacetate

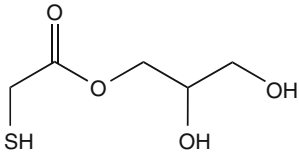
CAS Registry Number [30618–84–9]

It is an acid permanent wave ingredient, which induces contact dermatitis in hairdressers.

Suggested Reading

Frosch PJ et al. Allergic reactions to a hairdresser's series: results from 9 European centres. Contact Dermatitis. 1993;28:180–3.

Fig. 25.33 Glyceryl thioglycolate (NACS, CBS)



25.37 Hydrocortisone 17-Butyrate (NACS) (Fig. 25.34)

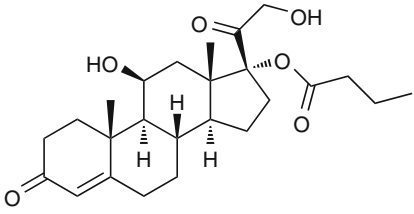
CAS Registry Number [13609–67–1]

Hydrocortisone 17-butyrate is a C_{17} ester of hydrocortisone. It represents the D2 group of corticosteroids: hydrocortisone 17-butyrate, hydrocortisone 17-valerate, hydrocortisone aceponate (17-propionate and 21-acetate), methylprednisolone aceponate, and prednicarbate. It is sometimes hydrolyzed in vivo into hydrocortisone, giving allergic reactions to group-A-sensitized individuals.

Suggested Reading

Lepoittevin JP et al. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. Arch Dermatol. 1995;131:31–7.

Fig. 25.34 Hydrocortisone 17-butyrate (NACS)



25.38 Hydroperoxide of Limonene (CBS) (Fig. 25.35)

Limonene: *d*-limonene + *l*-limonene

CAS Registry Number [138–86–3]

d-Limonene: (+)-limonene, *R*-limonene, α-limonene, *(R)-p*-mentha-1,8-diene, dipentene, carvene, citrene

CAS Registry Number [5989–27–5]

l-Limonene: (−)-limonene, *S*-limonene, β-limonene, (4*S*)-1-methyl-4-(1-methylethenyl)-cyclohexene

CAS Registry Number [5989–54–8]

Limonene is a racemic form of *d*- and *l*-limonene. *d*-Limonene is contained in *Citrus* species such as citrus, orange, mandarin, and bergamot. *l*-Limonene is contained in *Pinus pinea*. The racemic form is also named dipentene. Limonene, used as a solvent, may be found in cleansing or in degreasing agents. Its sensitizing potential increases with prolonged air contact, which induces oxidation and leads to oxidation products.

Suggested Reading

Karlberg AT, Dooms-Goossens A. Contact allergy to oxidized d-limonene among dermatitis patients. Contact Dermatitis. 1997;36:201–6.

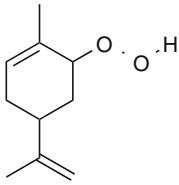


Fig. 25.35 Hydroperoxide of limonene (CBS)

25.39 2-Hydroxyethyl Methacrylate/2-HEMA (CBS) (Fig. 25.36)

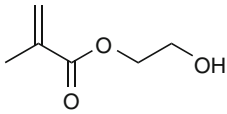
CAS Registry Number [868–77–9]

Sensitization to 2-HEMA concerns mainly dental technicians and dentists, but can also occur in other workers such as printers or beauticians. Consumers using photopolymerizable sculptured nails are also at risk.

Suggested Reading

Geukens S, Goossens A. Occupational contact allergy to (meth)acrylates. Contact Dermatitis. 2001;44:153–9.

Fig. 25.36 2-Hydroxyethyl methacrylate/2-HEMA (CBS)



25.40 Hydroxymethylpentacyclohexenecarboxaldehyde (EBS) (Fig. 25.37)

Lyral®, hydroxyisohexyl 3-cyclohexene carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl) cyclohex-3-ene-carbaldehyde

CAS Registry Number [31906–04–4]

Lyral® is a synthetic mixture of two isomers and one of the most frequently encountered allergens in perfumes. It has to be listed by name in the ingredients of cosmetics in the EU.

Suggested Reading

Johansen JD et al. Hydroxyisohexyl 3-cyclohexene carboxaldehyde – known as Lyral: quantitative aspects and risk assessment of an important fragrance allergen. Contact Dermatitis. 2003;48:310–6.

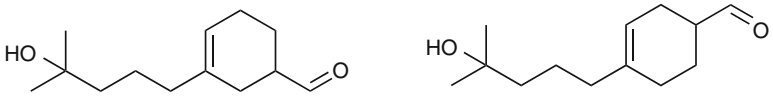


Fig. 25.37 Hydroxymethylpentacyclohexenecarboxaldehyde (EBS)

25.41 Imidazolidinyl Urea (NACS, EBS) (Fig. 25.38)

Germall® 115, Imidurea®

CAS Registry Number [39236–46–9]

Imidazolidinyl urea, a formaldehyde releaser related to diazolidinyl urea, is used as an antimicrobial agent often in combination with parabens. It is used as a preservative in aqueous products, mainly in cosmetics, toiletries, and liquid soaps.

Suggested Reading

Lachapelle JM et al. Proposal for a revised international standard series of patch tests. Contact Dermatitis. 1997;36:121–3.

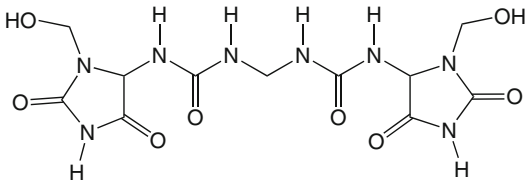


Fig. 25.38 Imidazolidinyl urea (NACS, EBS)

25.42 Iodopropynyl Butylcarbamate (NACS) (Fig. 25.39)

3-Iodo-2-propynyl-butylcarbamate

CAS Registry Number [55406–53–6]

Iodopropynyl butylcarbamate (IPBC) is a broad-spectrum preservative used for years because of its wide field of application, in polymer emulsions and pigment dispersions such as water-based paints and adhesives, cements, and inks, as a wood preservative, in metalworking fluids, in household products, and in cosmetics. Allergic contact dermatitis to IPBC was reported due to cosmetics, from sanitary wipes, and in metalworkers.

Suggested Reading

Badreshia S, Marks JG Jr. Iodopropynyl butylcarbamate. Am J Contact Dermatitis. 2002;13:77–9.

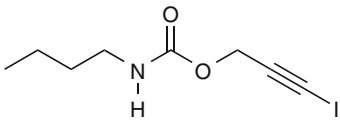


Fig. 25.39 Iodopropynyl butylcarbamate (NACS)

25.43 Isopropyl Myristate (CBS) (Fig. 25.40)

Tetradecanoic acid 1-methylethyl ester

CAS Registry Number [110–27–0]

Despite wide use in cosmetics, perfumes, and topical medicaments, isopropyl myristate is a very weak sensitizer and a mild irritant.

Suggested Reading

Uter W et al. Isopropyl myristate recommended for aimed rather than routine patch testing. Contact Dermatitis. 2004;50:242–4.

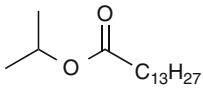


Fig. 25.40 Isopropyl myristate (CBS)

25.44 *N*-Isopropyl-*N*-phenyl-4-phenylenediamine (EBS, NACS, CBS) (Fig. 25.41)

IPPD, *N*-isopropyl-*N*-phenyl-*p*-phenylenediamine, *N*-(1-methylethyl)-*N*-phenyl-1, 4-benzenediamine

CAS Registry Number [101–72–4]

This rubber chemical is used as an antioxidant and antiozonant. The main occupational sources are tires.

Suggested Reading

Condé-Salazar L et al. Type IV allergy to rubber additives: a 10-year study of 686 cases. J Am Acad Dermatol. 1993;29:176–80.

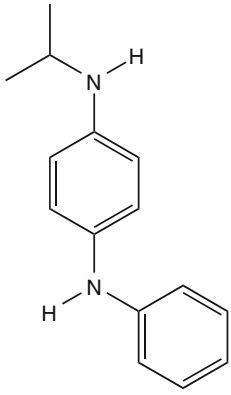


Fig. 25.41 *N-Isopropyl-N*-phenyl-4-phenylenediamine (EBS, NACS, CBS)

25.45 Lanolin Alcohol (EBS)

Wool wax alcohols

Lanolin CAS Registry Number [8006–54–0]

Lanolin also called wool wax is a yellow substance secreted by the sebaceous glands of wool-bearing animals. The products contain mainly long-chain wax esters and lanolin alcohols. Lanolin alcohols are mixture of aliphatic alcohols, steroid alcohols, and triterpenoid alcohols obtained by hydrolysis of lanolin. They can be found in cosmetics, pharmaceuticals, topical drugs, anticorrosives, printing inks, etc.

Suggested Reading

Lee B and Warshaw E. Lanolin allergy: history, epidemiology, responsible allergens and management. Dermatitis. 2008;19:63–72.

25.46 Linalool Hydroperoxide (CBS) (Fig. 25.42)

3,7-Dimethyl-1,6-octadien-3-ol, linalyl alcohol, 2,6-dimethyl-2,7-octadien-6-ol

CAS Registry Number [78–70–6]

Linalool is a terpene chief constituent of linaloe oil, also found in oils of Ceylon cinnamon, sassafras, orange flower, bergamot, *Artemisia balchanorum*, and ylang-ylang. This frequently used scented substance is a sensitizer by the way of primary or secondary oxidation products. As a fragrance allergen, linalool has to be mentioned by name in cosmetics within the EU.

Suggested Reading

Skold M et al. Contact allergens formed on air exposure of linalool. Identification and quantification of primary and secondary oxidation products and the effect on skin sensitization. Chem Res Toxicol. 2004;17:1697–705.

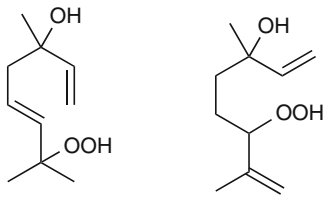


Fig. 25.42 Linalool hydroperoxide (CBS)

25.47 Mercaptobenzothiazole/MBT (EBS, NACS, CBS) (Fig. 25.43)

2-Mercaptobenzothiazole

CAS Registry Number [149–30–4]

MBT is a rubber chemical, an accelerant of vulcanization, and contained in the "mercapto mix." The most frequent occupational categories are the metal industry, homemakers, health services and laboratories, the building industry, and shoemakers. It is also used as a corrosion inhibitor in cutting fluids or in releasing fluids in the pottery industry.

Suggested Reading

Von Hintzenstern J et al. Frequency, spectrum and occupational relevance of type IV allergies to rubber chemicals. Contact Dermatitis. 1991;24:244–52.

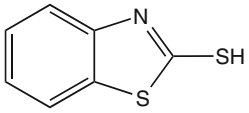


Fig. 25.43 Mercaptobenzothiazole/MBT (EBS, NACS, CBS)

25.48 Mercapto Mix (EBS, NACS, CBS) (Fig. 25.44)

This mix is based on three chemicals : dibenzothiazyl disulfide, morpholinyl mercaptobenzothiazole, and *N*-cyclohexyl-2-benzothiazyl sulfenamide all used as rubber vulcanization accelerators.

(a) Dibenzothiazyl Disulfide/CAS Registry Number [120–78–5]

The most frequent occupational categories are metal industry, homemakers, health services and laboratories, and the building industry.

(b) Morpholinyl Mercaptobenzothiazole/CAS Registry Number [102–77–2]

2-(4-Morpholinylthiobenzothiazole), 2-morpholin benzothiazyl sulfenamide, benzothiazole, 2-(4-morpholinylthio)

It is used as a chemical in the rubber industry, especially in the production of synthetic rubber articles. As a corrosion inhibitor, it can be found in cutting fluids or in releasing fluids in the pottery industry. It induces mainly delayed-type hypersensitivity, but a case of immediate-type hypersensitivity was reported in a dental assistant.

(c) *N*-Cyclohexyl-2-benzothiazyl Sulfenamide/CAS Registry Number [95–33–0]

The most frequent occupational categories are metal industry, homemakers, health services and laboratories, and the building industry.

Suggested Reading

Kiec-Swierczynska M. Occupational sensitivity to rubber. Contact Dermatitis. 1995;32:171–2.

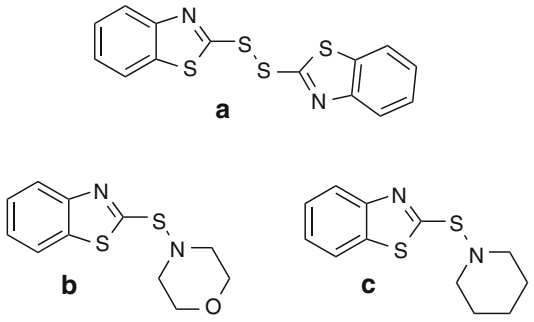


Fig. 25.44 Mercapto mix (EBS, NACS, CBS)

25.49 Methylchloroisothiazolinone + Methylisothiazolinone (MCI/MI) (EBS, NACS, CBS) (Fig. 25.45)

CAS Registry Numbers [55965–84–9], [96118–96–6]

KATHON® CG (CG = cosmetic grade) is a 3:1 mixture of MCI and MI, at a 1.5 % concentration. It is used for cosmetics and toiletries. KATHON® 886 MW (MW = metalworking fluids) is a MCI/MI mixture at a 13.9 % concentration, mainly contained in metalworking fluids. KATHON® FP 1.5 contains MCI/MI at 1.5 % concentration in propylene glycol. KATHON® LX (LX = LateX) contains MCI/MI at a tenfold concentration of KATHON® CG. KATHON® WT (WT = water treatment) is a MCI/MI mixture used in the paper industry.

Suggested Reading

Fernandez de Corres L et al. An unusual case of sensitization to methylchloro- and methyl-isothiazolinone (MCI/MI). Contact Dermatitis. 1995;33:215.

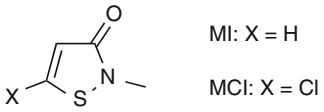


Fig. 25.45 Methylchloroisothiazolinone + methylisothiazolinone (MCI/MI) (EBS, NACS, CBS)

25.50 Methyldibromoglutaronitrile (EBS, NACS, CBS) (Fig. 25.46)

1,2-Dibromo-2,4-dicyanobutane

CAS Registry Number [35691–65–7]

Methyldibromoglutaronitrile is a biocide widely used as a preservative agent in cosmetics, toiletries, and metalworking fluids. It is a potent allergen, banned in all cosmetics in the EU since 2007. Euxyl® K 400 is a mixture of 1,2-dibromo-2,4-dicyanobutane 20 % and phenoxyethanol 80 %, widely utilized as a preservative in cosmetics, hand creams, and toiletries, but also in water-based paints, glues, metalworking fluids, and detergents.

Suggested Reading

Kynemund Pedersen L et al. Methyldibromoglutaronitrile in leave-on products elicits contact allergy at low concentration. Br J Dermatol. 2004;151:817–22.

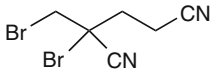


Fig. 25.46 Methyldibromoglutaronitrile (EBS, NACS, CBS)

25.51 Methylisothiazolinone (EBS, NACS, CBS) (Fig. 25.47)

2-Methyl-4-isothiazolin-3-one, MI

CAS Registry Number [2682–20–4]

MI is generally associated with MCI, in KATHON® CG, MCI/MI, and Euxyl® K 100 but has been more recently used as a single-component preservative. This preservative is currently used in water-based products such as cosmetics, paints, and glues. Airborne contact dermatitis has been reported after exposure to paints preserved with MI.

Suggested Reading

Schubert H. Airborne contact dermatitis due to methylchloro- and methylisothiazolinone (MCI/MI). Contact Dermatitis. 1997;36:274.

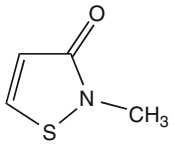


Fig. 25.47 Methylisothiazolinone (EBS, NACS, CBS)

25.52 Methyl Methacrylate (NACS, CBS) (Fig. 25.48)

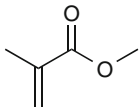
CAS Registry Number [80–62–6]

Methyl methacrylate is one of the most common methacrylates and causes allergic contact dermatitis mainly in dental technicians and dentists. Cases were also reported following the use of sculptured nails and in ceramic workers. The polymerization of the monomer results in polymethyl methacrylate which is used as sheets, molding, extrusion powders, surface coating resins, emulsion polymers, fibers, inks, and films. This material is also used in tooth implants and bone cements and to manufacture hard corneal contact lenses.

Suggested Reading

Kanerva L et al. Occupational allergic contact dermatitis caused by photobonded sculptured nails and a review of (meth) acrylates in nail cosmetics. Am J Contact Dermatitis. 1996;7:109–15.

Fig. 25.48 Methyl methacrylate (NACS, CBS)



25.53 Mixed Dialkylthiourea (CBS) (Fig. 25.49)

Mixture of dibutylthiourea and diethylthiourea. Both chemicals are used in the vulcanization of rubber in paints and glue removers as an anticorrosive. Cross-sensitivity to other thiourea derivatives is possible.

(a) Dibutylthiourea/CAS Registry Number [109–46–6]
1,3-Dibutyl-2-thiourea
(b) Diethylthiourea/CAS Registry Number [105–55–5]
Diethylthiocarbamide

Suggested Reading

Kanerva L et al. Occupational allergic contact dermatitis caused by thiourea compounds. Contact Dermatitis. 1994;31:242–8.

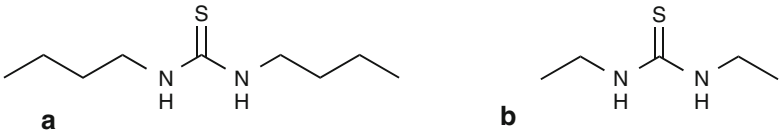


Fig. 25.49 Mixed dialkylthiourea (CBS)

25.54 *Myroxylon pereirae* Resin (Fig. 25.50)

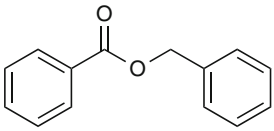
This natural resinous balsam is collected from the Central American tree *Myroxylon pereirae* Klotzsch after scarification of the bark. The composition varies, but the main chemicals are benzoate and cinnamate esters. Some chemicals of the FMI are also present in this resin (cinnamal, cinnamic alcohol, eugenol, etc.).

(a) Benzyl Benzoate/CAS Registry Number [120–51–4]
Benzoic acid phenylmethyl ester
Benzyl benzoate is the ester of benzyl alcohol and benzoic acid. It is contained in *Myroxylon pereirae* and tolu balsam. It is used in acaricide preparations against *Sarcoptes scabiei* or as a pediculicide. As a fragrance allergen, benzyl benzoate has to be mentioned by name in EU cosmetics.

Suggested Reading

Meneghini CL et al. Contact dermatitis to scabicides. Contact Dermatitis. 1982;8:285–6.

Fig. 25.50 Benzyl benzoate



25.55 Neomycin Sulfate (EBS, NACS) (Fig. 25.51)

Neomycin B hydrochloride, Neomycin B sulfate, framycetin, Soframycin®

CAS Registry Number [1404–04–2] (CAS Registry Number [25389–99–5], CAS Registry Number [1405–10–3])

Neomycin is an antibiotic complex of the aminoglycoside group, extracted from *Streptomyces fradiae*. It is composed of neomycin A (neamin) and an isomer neobiosamin, either neomycin B (framycetin or Soframycin®) or neomycin C. Its use has been progressively forbidden in cosmetics and as an additive for animal feed. Occupational contact dermatitis occurs in workers at animal feed mills, in veterinaries, or in health workers. Nonoccupational dermatitis mainly concerns patients with chronic dermatitis, leg ulcers, or chronic otitis. Cross-sensitivity is usual with other aminoglycosides (amikacin, arbekacin, butirosin, dibekacin, gentamicin, isepamicin, kanamycin, paromomycin, ribostamycin, sisomicin, tobramycin) and is rare with netilmicin and streptomycin, but nonexistent with spectinomycin.

Suggested Reading

Mancuso G et al. Occupational dermatitis in animal feed mill workers. Contact Dermatitis. 1990;22:37–41.

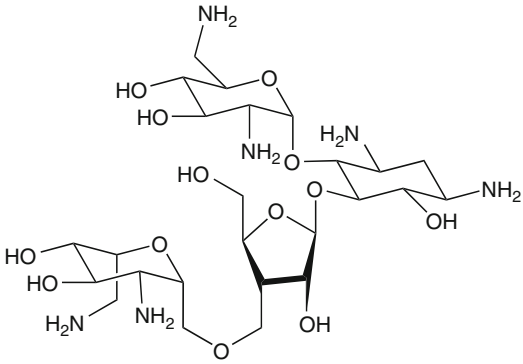


Fig. 25.51 Neomycin sulfate (EBS, NACS)

25.56 2-*n*-Octyl-4-isothiazolin-3-one (CBS) (Fig. 25.52)

KATHON® LM, KATHON® 4200, KATHON® 893, pancil, SKANE M-8

CAS Registry Number [26530–20–1]

This isothiazolinone, contained in relatively few products compared to other isothiazolinones, is used in cleaning and polishing agents, latex paints, stains, adhesives, wood and leather preservatives, metalworking fluids (cutting oils), and plastic manufacture.

Suggested Reading

Young HS et al. Contact dermatitis from 2-*n*-octyl-4-isothiazoline-3-one in a PhD student. Contact Dermatitis. 2004;50: 47–8.

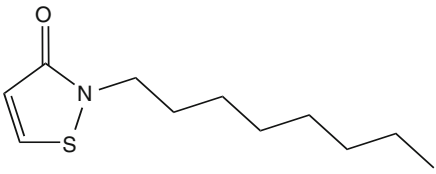


Fig. 25.52 2-*n*-Octyl-4-isothiazolin-3-one (CBS)

25.57 Paraben Mix (EBS, NACS, CBS) (Fig. 25.53)

The paraben mix is composed of five parabens: methyl-, ethyl-, propyl-, butyl-, and benzylparaben. They have been largely used as biocides in cosmetics and toiletries, medicaments, or food. They have a synergistic effect with other biocides. Parabens can induce allergic contact dermatitis, mainly in chronic dermatitis and wounded skin.

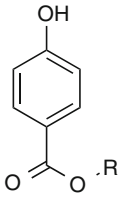
- Methylparaben, E218, E219 (Sodium Salt)
- CAS Registry Number [99–76–3], E219 (Sodium Salt), CAS Registry Number [5026–62–0]

- Ethylparaben, E214, E215 (Sodium Salt)
- CAS Registry Number [120–47–8], E215 (Sodium Salt), CAS Registry Number [35285–68–8]
- Propylparaben, E216, E217 (Sodium Salt)
- CAS Registry Number [94–13–3], E217 (Sodium Salt), CAS Registry Number [35285–69–9]
- Butylparaben
- CAS Registry Number [94–26–8]
- Benzylparaben
- CAS Registry Number [94–18–8]

Suggested Reading

Le Coz CJ. Fiche d'éviction en cas d'hypersensibilité aux esters de l'acide *para-hydroxybenzoïque* (parahydroxybenzoates ou parabens). Ann Dermatol Venereol. 2004;131:309–10.

Fig. 25.53 Paraben mix (EBS, NACS, CBS)



25.58 Paraphenylenediamine (EBS, NACS, CBS) (Fig. 25.54)

PPD, *p*-phenylenediamine, 4-phenylenediamine

CAS Registry Number [106–50–3]

PPD is a colorless compound oxidized by hydrogen peroxide in the presence of ammonia. It is then polymerized to a color by a coupling agent. Although a well-known allergen in hair dyes, PPD was more recently incriminated in severe contact dermatitis following pseudotattooing. It is also a marker of group sensitivity to *para*-amino compounds such as benzocaine, some azo dyes, and some previous antibacterial sulfonamides.

Suggested Reading

Frosch PJ et al. Allergic reactions to a hairdresser's series: results from 9 European centres. Contact Dermatitis. 1993;28:180–3.

Le Coz CJ et al. Allergic contact dermatitis caused by skin painting (pseudotattooing) with black henna, a mixture of henna and *p*-phenylenediamine and its derivatives. Arch Dermatol. 2000;136: 1515–7.

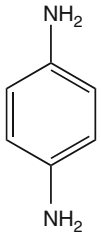


Fig. 25.54 Paraphenylenediamine (EBS, NACS, CBS)

25.59 Primin (EBS) (Fig. 25.55)

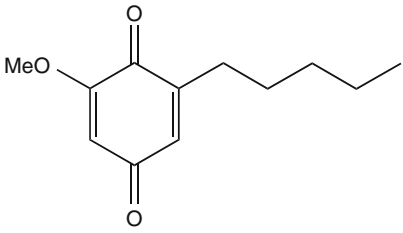
CAS Registry Number [15121–94–5]

Primin is the major allergen of *Primula obconica* Hance (Primulaceae family). Allergic contact dermatitis is mainly occupational, occurring in florists and horticulturists.

Suggested Reading

Christensen LP, Larsen E. Direct emission of the allergen primin from intact *Primula obconica* plants. Contact Dermatitis. 2000;42:149–53.

Fig. 25.55 Primin (EBS)



25.60 Propolis (CBS) (Fig. 25.56)

Propolis or bee glue is a resinous mixture that honey bees collect from tree buds. The composition of propolis varies from hive to hive and from season to season. Typical propolis (poplars and conifers) contains more than 50 constituents, primarily resins and balsams, waxes, and essential oils. Propolis is used in folk medicines due to its antimicrobial and antioxidant properties.

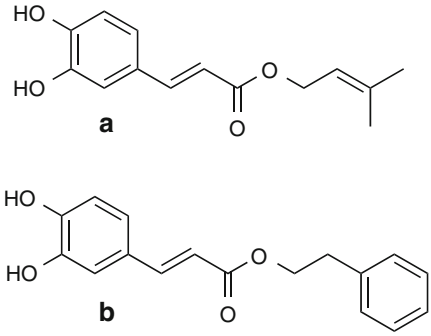
(a) Caffeic Acid Dimethyl Allylic Ester/CAS Registry Number [108084–13–7]
3-Methyl-2-butenyl caffeate
This is the major allergen of poplar bud resins and of propolis.

(b) Phenylethyl Caffeate Ester/CAS Registry Number [104594–70–9]
Caffeic acid phenethyl ester/CAPE
CAPE is one of the allergens of propolis. It is also contained in poplar bud secretions.

Suggested Reading

Oliwiecki S et al. Occupational contact dermatitis from caffeates in poplar bud resin in a tree surgeon. Contact Dermatitis. 1992;27:127–8.

Fig. 25.56 Propolis (CBS)



25.61 Propylene Glycol (NACS) (Fig. 25.57)

1,2-Propanediol

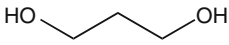
CAS Registry Number [57–55–6]

Propylene glycol is used as a solvent, as a vehicle for topical medicaments such as corticosteroids or acyclovir, as an emulsifier and humectant in food and cosmetics, and as antifreeze in breweries, in the manufactures of resins. Patch tests *in aqua* are sometimes irritant.

Suggested Reading

Connoly M, Buckley DA. Contact dermatitis from propylene glycol in ECG electrodes, complicated by medicament allergy. Contact Dermatitis. 2004;50:42.

Fig. 25.57 Propylene glycol (NACS)



25.62 Quaternium-15 (EBS, NACS, CBS) (Fig. 25.58)

N-(3-Chloroallyl)hexaminium chloride, hexamethylenetetramine chloroallyl chloride, Dowicil 200

CAS Registry Numbers [4080–31–3], [103638–29–5], [60789–82–4]

Quaternium-15 is a quaternary ammonium compound used as a broad-spectrum formaldehyde-releasing agent. It is contained as a preservative in cosmetics, toiletries, and aqueous products. Allergy is mainly due to formaldehyde and not to quaternium-15 itself.

Suggested Reading

Finch TM et al. Occupational allergic contact dermatitis from quaternium-15 in an electroencephalography skin preparation gel. Contact Dermatitis. 2001;44:44–5.

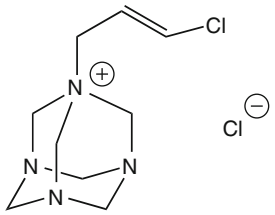


Fig. 25.58 Quaternium-15 (EBS, NACS, CBS)

25.63 Sesquiterpene Lactone Mix (EBS, NACS, CBS) (Fig. 25.59)

This mix is based on three individual chemicals (alantolactone, dehydrocostuslactone, and costunolide), each structure covering a different structural pattern. This mix is used to detect sensitization to Compositae/Asteraceae.

(a) Alantolactone/CAS Registry Number [546–43–0]
This eudesmanolide sesquiterpene lactone is isolated from elecampane (*Inula helenium* L.).
(b) Dehydrocostuslactone/CAS Registry Number [477–43–0]
This guaianolide sesquiterpene lactone is extracted from costus oil.
(c) Costunolide/CAS Registry Number [553–21–9]
This germacranolide sesquiterpene lactone is extracted from costus oil.

An erythema multiforme-like occupational contact dermatitis case occurred in a chemical student after an accidental exposure to costus oil.

Suggested Reading

Ducombs G et al. Patch testing with the "sesquiterpene lactone mix": a marker for contact allergy to Compositae and other sesquiterpene-lactone-containing plants. Contact Dermatitis. 1990;22:249–52.

Le Coz CJ and Lepoittevin JP. Occupational erythema-multiforme-like dermatitis from sensitization to costus resinoid, followed by flare-up and systemic contact dermatitis from beta-cyclocostunolide in a chemistry student. Contact Dermatitis. 2001;44:310–1.

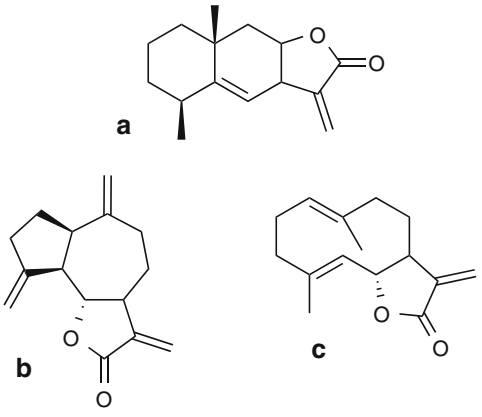


Fig. 25.59 Sesquiterpene lactone mix (EBS, NACS, CBS)

25.64 Tea Tree Oil Oxidized (CBS)

CAS Registry Number [68647–73–4]

This essential oil is extracted from *Melaleuca alternifolia* Raeush., a tree native of Australia. The essential oil is used in cosmetics but also for its antimicrobial properties to treat different dermatologic diseases. At air exposure, allergenic oxidation products are formed.

Suggested Reading

Hausen BM et al. Degradation products of monoterpenes are the sensitizing agents in tea tree oil. Am J Contact Dermatitis. 1999;10:68–77.

25.65 Textile Dye Mix (EBS, CBS) (Fig. 25.60)

This mix is based on eight disperse dyes (blue 106, blue 124, blue 35, yellow 3, orange 1, orange 3, red 1, and red 17) and is aimed at the detection of textile dye dermatitis. Disperse dyes are so called because they are partially soluble in water and have either an anthraquinone (disperse anthraquinone dyes) or an azoic (disperse azo dyes) structure. They are used chiefly in the textile industry to color synthetic fibers such as polyester, acrylic and acetate, and sometimes nylon, particularly in stockings, but they are not used for natural fibers.

(a) Disperse Blue 106/CAS Registry Number [74339–69–8]
This clothing dye used in synthetic fibers is one of the most potent sensitizers in clothes. Allergic contact dermatitis is relatively frequent in consumers.

(b) Disperse Blue 124/CAS Registry Number [15141–18–1]
This clothing dye used in synthetic fibers is one of the most potent sensitizers in clothes. It is a textile dye responsible for occupational contact dermatitis in the textile industry. Concomitant reactions with disperse blue 106 are due to their chemical similarities.

(c) Disperse Blue 35/CAS Registry Number [12222–75–2]
This textile dye of the anthraquinone type is used in nylon, acrylic, polyester, and acetate.

(d) Disperse Yellow 3/CAS Registry Number [2832–40–8]
This azoic dye is responsible for textile dermatitis from stockings and occupational contact dermatitis in workers in the textile industry. It can also be found in some semipermanent hair dyes.

(e) Disperse Orange 1/CAS Registry Number [2581–69–3]
Disperse orange 1 is an azo dye.

(f) Disperse Orange 3/CAS Registry Number [730–40–5]
Disperse orange 3 is an azo dye that can induce contact dermatitis in workers in the textile industry. It is positive in a great majority of PPD-positive people, because of metabolism in the skin into PPD. Disperse orange 3 can also be found in some semipermanent hair dyes.

(g) Disperse Red 1/CAS Registry Number [2872–52–8]
This azo dye is used in textiles for polyester fiber, yarn, nylon, and acrylic. It is also used in hair color formulation.

(h) Disperse Red 17/CAS Registry Number [3179–89–3]
This azo dye is used in textiles for polyester fiber, silk, wool, yarn, nylon, and acrylic. It is also used in hair color formulation.

Suggested Reading

Ryberg K et al. Patch testing with a textile dye mix in a baseline series in two countries. Acta Derm Venereol. 2011;91:422–7.

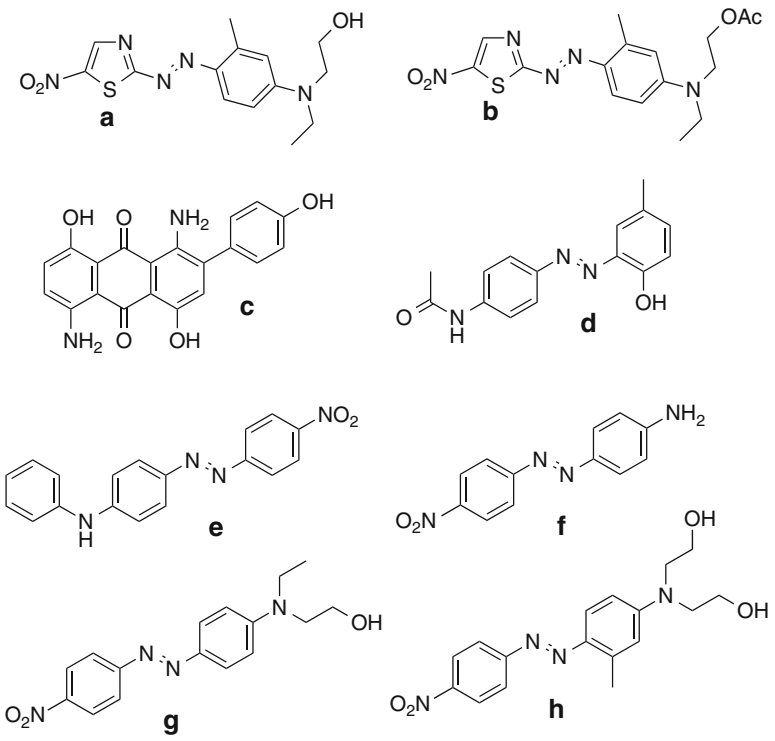


Fig. 25.60 Textile dye mix (EBS, CBS)

25.66 Thiuram Mix (EBS, NACS, CBS) (Fig. 25.61)

This mix has four accelerating agents used in the vulcanization of rubber. They increase the rate of cross-linking by sulfur, but in cured products unreacted accelerators remain.

(a) Dipentamethylenethiuram Disulfide/CAS Registry Number [94–37–1]
The most frequent occupational categories are the metal industry, homemakers, health services and laboratories, and the building industry.

(b) Tetraethylthiuram Disulfide/CAS Registry Number [97–77–8]
Disulfiram, TETD, Antabuse, Esperal®
TETD can cross-react with other thiurams, especially TMTD. TETD is used to aid those trying to break their dependence on alcohol. The disulfiram-alcohol reaction is not allergic but due to the accumulation of toxic levels of acetaldehyde. The implanted drug can, however, lead to local or generalized dermatitis, for example, ingested disulfiram, mainly in previously rubber-sensitized patients. As an adjunctive treatment of alcoholism, it caused occupational contact dermatitis in a nurse.

(c) Tetramethylthiuram Disulfide/CAS Registry Number [137–26–8]
Thiram, TMTD
This rubber chemical represents the most commonly positive allergen contained in "thiuram mix." The most frequent occupational categories are the metal industry, homemakers, health services and laboratories, the building industry, and shoemakers. It is also widely used as a fungicide, belonging to the dithiocarbamate group of carrots, bulbs, and woods, and as an insecticide. Thiram is the agricultural name for thiuram.

(d) Tetramethylthiuram Monosulfide/CAS Registry Number [97–74–5]
TMTM
This rubber accelerator is contained in "thiuram mix." The most frequent occupational categories are the metal industry, homemakers, health services and laboratories, and the building industry.

Suggested Reading

Kiec-Swierczynska M. Occupational sensitivity to rubber. Contact Dermatitis. 1995;32:171–2.

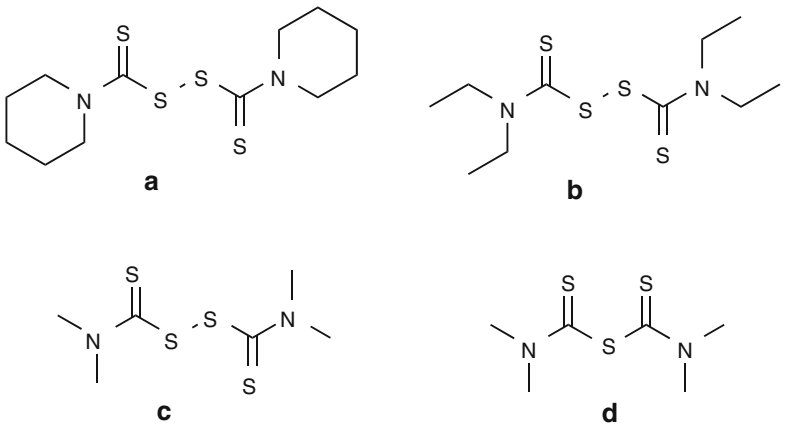


Fig. 25.61 Thiuram mix (EBS, NACS, CBS)

25.67 Tixocortol Pivalate (EBS, NACS) (Fig. 25.62)

Tixocortol 21-pivalate, tixocortol 21-trimethylacetate

CAS Registry Number [55560–96–8]

Tixocortol 21-pivalate is a 21-ester of tixocortol, widely used in topical treatments. It can induce severe allergic contact dermatitis. This corticosteroid is a marker of the allergenic A group: cloprednol, cortisone, fludrocortisone, fluorometholone, hydrocortisone, methylprednisolone, methylprednisone, prednisolone, prednisone, tixocortol, and their C_{21} esters (acetate, caproate or hexanoate, phosphate, pivalate or trimethylacetate, succinate or hemisuccinate, *m*-sulfobenzoate).

Suggested Reading

Lepoittevin JP et al. Studies in patients with corticosteroid contact allergy. Understanding cross-reactivity among different steroids. Arch Dermatol. 1995;131:31–7.

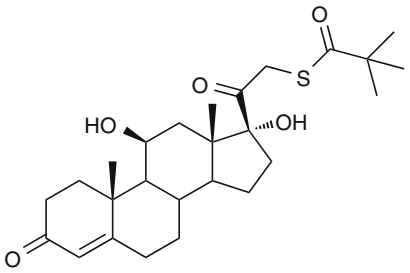


Fig. 25.62 Tixocortol pivalate (EBS, NACS)

25.68 Toluenesulfonamide-Formaldehyde Resin (NACS, CBS) (Fig. 25.63)

4-Toluenesulfonamide-formaldehyde resin

CAS Registry Number [25035–71–6]

Formed by condensation of formaldehyde and toluenesulfonamide, it is found in most nail lacquers, polishes, and hardeners. It may also be used in industrial applications as a modifier and adhesive primer for natural and synthetic resins.

Suggested Reading

Marks JG et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. J Am Acad Dermatol. 1998;38:911–8.

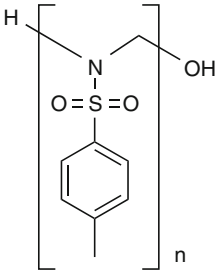


Fig. 25.63 Toluenesulfonamide-formaldehyde resin (NACS, CBS)