Chapter 29

Allergens from the Standard Series 29

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Contents

29.1 Introduction

The distinction between allergic and irritant contact dermatitis is based on a patient's history and clinical features, in combination with diagnostic patch testing. This test procedure is indicated in the investigation of long-standing cases of contact dermatitis and should also be used to exclude contact allergy as a complicating factor in stubborn cases of other eczematous diseases, such as atopic dermatitis, stasis eczema, seborrheic dermatitis, and vesicular hand eczema. A patch test is the cutaneous application of a small amount of the suspected allergen in a suitable concentration and vehicle. The test site, usually the back, is covered with an occlusive dressing for 2 days. The skin condition, vehicle and concentration, volume of the test substance, size of the test chamber, test site, application time, and the number of readings influence the result, and frequent errors are possible [1–4] (see Chap. 2). The proper performance and interpretation of this bioassay require considerable training and experience.

Patch testing is routinely performed by applying a standard series of the most frequently occurring contact allergens and those contact allergens that may be missed without routine screening. The choice of test concentration is based on patch test experience such that there is a minimum number of irritant reactions and a maximum of clinically explicable allergic positive reactions. Test concentrations are generally expressed in percentages. This can be misleading, since the molecular weight of allergens can be very different. A better way of expressing concentration would be both the percentage and molality (*m*=number of moles per 1,000 g of solvent or vehicle) [5].

An experienced contact dermatologist will be able to guess correctly the clinically relevant contact allergen in some patients, based on the history and the clinical appearance of the eczema. This guess is more likely to be correct for common allergens, such as nickel (50–80%), and less likely to be correct for less common allergens (<10%) [6, 7]. This failure to guess correctly explains the general acceptance of the use of a standard series in the evaluation of all patients suspected of having a contact dermatitis.

Supplementary tests with working materials properly diluted, and extra allergens selected on the basis of patient history and known exposures, are often required in order to determine the nature of the patient's suspected contact dermatitis. The standard series detects approximately 75–80% of all contact allergies [8].

The European standard series is dynamic and subject to continual modification depending on population exposures and prevalence of contact allergy [9, 10] (Table 1). Among the major patch test material companies, Hermal and Chemotechnique supply with

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Table 1. The current European standard patch test series from Trolab Hermal and Chemotechnique, and the contact allergens available from TRUE Test Panel 1 and Panel 2. The patch test concentrations are shown. (*aq.* water, *pet.* petrolatum)

	Trolab Hermal[a]	Chemotechnique[a]	TRUE Test[b]
Potassium dichromate	0.5% pet.	–	23 µg/cm^2
Neomycin sulfate	20% pet.	–	230 µg/cm^2
Thiuram mix	1% pet.	–	25 µg/cm^2
p-phenylenediamine free base	1% pet.	–	90 µg/cm^2
Cobalt chloride	1% pet.	–	20 µg/cm^2
Benzocaine	5% pet.	–	–
Formaldehyde	1% aq.	–	180 µg/cm^2
Colophony (colophonium)	20% pet.	–	850 µg/cm^2
Clioquinol	5% pet.	–	–
Balsam of Peru (*Myroxylon pereirae*)	25% pet.	–	800 µg/cm^2
N-Isopropyl-*N*′-phenyl-paraphenylenediamine (IPPD)	0.1% pet.	–	–
Wool alcohols (lanolin alcohol)	30% pet.	–	1,000 µg/cm^2
Mercapto mix	1% pet.	2% pet.	75 µg/cm^2
Epoxy resin	1% pet.	–	50 µg/cm^2
Paraben mix	16% pet.	–	1,000 µg/cm^2
para-Tertiary-butylphenol-formaldehyde resin (PTBP resin)	1% pet.	–	40 µg/cm^2
Fragrance mix	8% pet.	–	430 µg/cm^2
Quaternium-15	1% pet.	–	100 µg/cm^2
Nickel sulfate	5% pet.	–	200 µg/cm^2
Cl+Me-isothiazolinone[c]	0.01% aq.	–	4 µg/cm^2
Mercaptobenzothiazole	2% pet.	–	75 µg/cm^2
Primin	0.01% pet.	–	–
Sesquiterpene lactone mix	0.1% pet.	–	–
Budesonide	–	0.01% pet.	–
Tixocortol pivalate	–	0.1% pet.	–
Hydroxyisohexyl-3-cyclohexene carboxaldehyde (Lyral)	5% pet.	–	–
Caine mix	–	–	630 µg/cm^2
Quinoline mix	–	6% pet.	190 µg/cm^2
Black rubber mix	–	–	75 µg/cm^2
Carba mix	–	–	250 µg/cm^2
Thimerosal	–	–	8 µg/cm^2
Ethylenediamine	–	–	50 µg/cm^2

[a] Hermal and Chemotechnique offer more than these allergens
[b] TRUE allergens for a Panel 3 are under development
[c] Methylchloroisothiazolinone/methylisothiazolinone

some modifications the European standard series, as recommended by the European Environmental and Contact Dermatitis Research Group (EECDRG), and Mekos supplies TRUE Test Panel 1 and Panel 2, which, in the collection and preparation of the allergens, differ from the European standard series on several positions, as seen in Table 1. The standard series can be extended to include allergens of local importance to specific departments. The frequency of allergic contact sensitization to the allergens of the standard series varies from study to study, depending on the composition of the study population. Comparison of the frequencies in different populations is only valid when the results are standardized with respect to confounding factors, such as age, sex, presence of atopy, presence of diseased skin, and occupational exposure – the MOAHLFA index, indicating the frequency of occurrence of males, occupational dermatitis, atopy, hand dermatitis, leg ulcers or stasis dermatitis, facial dermatitis, and age above 40 years [11, 12]. Moreover, when evaluating multicenter patch test studies, the patch test application time, the amount of the allergens applied on the chambers, the reading time, and the reading scale should be taken into account as well [13].

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29.2 Nickel

Nickel is a metal which is used in a large number of alloys and chemical compounds. Only iron, chromium, and lead are produced in larger amounts. Nickel is ubiquitous in the environment and constitutes about 0.008% of the Earth's crust. Humans are constantly exposed, though in variable amounts [1]. Nickel is the most common contact allergen in children and adults [2, 3]. Metallic nickel (only after corrosion), as well as nickel salts, gives rise to contact allergy. The corrosiveness of sweat, saliva, and other body fluids to nickel and nickel alloys is of primary importance [4].

Nickel is the most common allergen in the standard series and the most common cause of allergic contact dermatitis, particularly in women. The frequency of nickel allergy in women is 3–10 times higher than in men [2, 5]. This gender difference is traditionally explained by increased exposure in women, due to direct skin contact with nickel-releasing metal, such as in jewelry, wristwatches, and clothing accessories. Wet work at home and exposure in certain occupational groups with a majority of women, such as hairdressers, cleaners, and food service workers, are also associated with the increased frequency of nickel allergy in women [6, 7]. The incidence of nickel allergy in women has increased until the most recent decade, and has reached a plateau of around 15–20%, depending on the source of reference [3, 5, 8]. The most common cause of sensitization is thought to be ear piercing [2, 9], even in men [10]. The clinical pattern of nickel dermatitis is described in the classic paper of Calnan and Wells [11]. The primary sites of dermatitis develop as a result of direct skin contact with nickel-releasing metal. The secondary sites are unrelated to direct skin contact. A systemic contact dermatitis may develop in particularly sensitive patients through oral intake through foods. The systemic contact dermatitis is symmetrical and often includes the neck and face, eyelids, elbow flexures and forearms, hands, inner thighs, anogenital region, and may be generalized [12]. Flare-up reactions of previous nickel patch test sites may oc-

cur. The systemic allergic nickel dermatitis is hapten-specific and with a clear dose–response relationship. Immunological investigations in nickel-sensitive individuals whose dermatitis flared after oral nickel provocation showed that CD8+ "memory" CLA+ T lymphocytes and T lymphocytes with a type 2 cytokine profile are involved in the development of systemic nickel dermatitis [13]. The doses used experimentally have been much larger than the normal daily dietary nickel intake, which varies between 0.1 mg to 0.5 mg nickel, and the induction of systemic nickel dermatitis from daily dietary nickel intake remains controversial [14–17]. However, nickel-sensitive patients with vesicular hand eczema worsened after an oral challenge with nickel in water and with a diet naturally high in nickel [18]. Nickel absorption and retention in the body is highly dependent on food intake and fasting, but nickel toxicokinetics is the same in nickel-allergic women and age-matched controls [19].

The relationship between nickel allergy and hand eczema is controversial as well. It is evident that allergic dermatitis of the hands occurs as a result of contact with solubilized nickel and takes place more rapidly if the patient has preexisting irritant hand eczema [20]. Hand eczema is more common in nickel-sensitized women than in the general population [21, 22]. However, a Swedish study in men [10] did not reveal a higher frequency of hand eczema among metal-sensitive subjects, nor in individuals with pierced ears, compared to a nonsensitized group, and recent Danish studies have shown contradictory results. Mortz et al. [2] found a significant association between hand eczema and nickel allergy in a population of unselected adolescents, and Bryld et al. found the same in a population-based twin sample [23, 24]. However, when the analysis was limited to twins with vesicular hand eczema, there was no association [23].

Other conundrums about nickel allergy remain unresolved; for instance, does nickel allergy render a person, even with normal skin, more vulnerable to irritant contact dermatitis? It would appear that it can [25], but atopic dermatitis is the major risk factor to the development of hand eczema [24, 26, 27]. A survey of 368 nickel-sensitive subjects attempted to determine the overall importance of nickel as an occupational allergen and it was found in about 23% of the cases to function as a secondary occupational allergen, in conjunction with other factors [6].

The incidence of allergy in men, even in those with earrings, is lower than in females; the cause not being clear. Some experimental studies claim that women are more easily sensitized than men [28]. A more likely explanation for the fewer nickel-allergic men may be less exposure from wet work and less skin contact with nickel-releasing jewelry.

Certainly, in nickel allergy, one can see patterns of dermatitis which are unusual for contact dermatitis; for instance, on the palmar aspects of the fingers and the adjacent palm. This can sometimes be explained by local contact. It is to be expected that a solid such as metal will produce a different distribution of dermatitis compared to liquids and detergents. However, intensive handling of nickel coins in a controlled experiment did not provoke allergic contact hand eczema in nickel-sensitive individuals [29].

There is no method of desensitization, but it is possible to produce immune tolerance in animals fed nickel prior to attempted sensitization, and this has been confirmed in humans. Adolescents who have dental braces (causing ingestion of nickel) prior to ear piercing develop much less nickel allergy [2, 30]. This is clearly not a practical method of solving the problem. Oral administration of nickel sulfate 5.0 mg once a week for 6 weeks in nickel-allergic patients lowered the degree of contact allergy significantly, as measured by the patch test reactions before and after nickel administration [31].

There is little doubt that metal plates on bones can initiate a dermatitis, which occurs particularly over the areas of the plate [32, 33], but it is now well accepted that nickel allergy is not a contraindication to a metal hip of stainless steel or vitallium type. There is no convincing evidence that these sensitize or exacerbate a preexisting dermatitis, or lead to rejection of the hip [34].

Nickel allergy was claimed not to increase the risk of developing other allergies [35, 36]. However, nickel allergy is often associated with reactivity to other metals. This seems, in most cases, to be caused by multiple exposure and sensitization and not to cross reactivity [37] and may simply be due to the fact that these metals are commonly associated. It is difficult to obtain pure compounds and most of these metals are contaminated with another. On the other hand, Moss et al. [38] suggested that the acquisition of sensitivity to one allergen might predispose to the acquisition of another unrelated sensitivity – based on a statistical analysis of patch test data from 2,200 consecutive patients and experimental sensitization using dinitrochlorobenzene (DNCB). Further, guinea pigs sensitized to nickel were found to be more easily sensitized to cobalt [39], and it has been shown that lymphocytes with monoclonal sensitivity to nickel will react to palladium and copper, but not with cobalt [40]. Nickel is an intriguing contact allergen, and some cases of nickel patch test reactivity may be unspecific, as nickel, in analogy to superantigens, may directly link to the T cell receptor (TCR)

and major histocompatibility complex (MHC) in a peptide-independent manner. However, nickel requires human histocompatibility leukocyte antigen (HLA) determined TCR amino acids [41].

The dimethylglyoxime (DMG) test, which is used to detect nickel release from metal surfaces, is accurate to about 10 ppm (0.001%=2.1 µg Ni/g) and is a good routine test to eliminate metals as a source of nickel which may be causing allergy. However, metals containing lower amounts can still produce an exacerbation of nickel dermatitis, and, therefore, the dimethylglyoxime test cannot be relied upon absolutely to rule out a piece of metal as the cause of a patient's dermatitis [42, 43]. The release of nickel from stainless steel is minimal and is directly correlated with its sulfur content, since sulfur affects corrosion resistance, and, hence, also the release of nickel [44]. Experimental studies have shown that nickel-sensitive patients rarely react following repeated exposures to levels below 10 ppm nickel [45].The EU nickel directive aimed at the prevention of nickel allergy covers metal items in direct contact with skin, piercing materials, and requirements on resistance to wear (Council Directive 94/27/EC, OJ No. L 188 of 22.7.94). The nickel release threshold is 0.5 µg/cm² per week, and a European standard for testing nickel release from articles intended to come in prolonged and direct skin contact has been adopted.

The nickel directive seems to be effective, as a significant decrease in the frequency of nickel allergy in Denmark is reported in the age group 0–18 years [46], and in Germany in patients below 31 years of age [47].

The standard patch test concentration of nickel sulfate is in Europe 5% pet. or 200 µg/cm² in the TRUE test. In the USA, 2.5% pet. is recommended. Follicular and irritant reactions may occur and complicate clinical interpretation. A problem in patch testing is that, depending on the questioning procedure, 15–50% of those who give a clear history of reaction to metal jewelry, which strongly suggests nickel allergy, do not react [16, 48]. The reason for this is not clear. It does not appear to be due to a fault in the test reagent, or method of testing, as other salts, for instance, nickel chloride, or intradermal (ID) testing will increase the positive yield by a very small amount [49]. Nickel contact allergy seems not to be associated with atopic dermatitis [50, 51]. Positive nickel sulfate patch tests are, in general, very reproducible [52, 53]. However, the individual variation in nickel patch test threshold reactivity from test session to test session with a dilution series among nickel-sensitive patients may vary considerably [54].

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29.3 Chromium

It is probably more accurate to use the term "chromate," because chromium is unique in that the metal itself does not sensitize, but, rather, its salts. Both hexavalent ($Cr_2O_7^-$) and trivalent (Cr^{3+}) chromate may cause allergic contact dermatitis. Trivalent chromate is poorly soluble and penetrates the skin poorly, binding with proteins on the surface skin, whilst hexavalent chromate is easily soluble and penetrates skin easily but binds poorly with proteins. It is thought that hexavalent chromate penetrates the skin and is then reduced enzymatically to trivalent chromate, which combines with protein as the hapten. Using standard patch test techniques, Fregert and Rorsman [1] showed that, if the concentration of trivalent chromate is high enough, and the exposure time sufficiently prolonged, positive patch tests will also result. However, the evidence would suggest that, at a cellular level, the body develops an allergy to both hexavalent and trivalent chromate [2, 3]. Recent clinical dose–response patch test experiments using volunteer chromate allergic patients showed that the calculated minimal elicitation threshold (MET) giving a positive patch test reaction in 10% of the patients was 0.18 µg/cm² (6 ppm.) for Cr(III) and 0.03 µg/cm ² (1 ppm) for Cr(VI) [4].The frequency of patch test positives to chromate on routine patch testing varies considerably from region to region. In Denmark, about 2% of consecutively tested eczema patients have chromate allergy [5], much less than in neighboring countries such as Germany and England, where the frequency of chromate allergy ranges from 3.1% to 10.5% [6, 7]. Where higher rates are reported, some irritant reactions may be included. It is difficult to compare these results unless the patient materials are examined for confounding factors, such as age, sex, atopy, occupational dermatitis, site of dermatitis, etc. Cement has been considered as the main cause of chromate allergy. All authorities agree that cement dermatitis is decreasing in incidence and increasing evidence indicates that this may be partly due to the introduction of ferrous sulfate in cement in some countries in order to reduce the levels of hexavalent chromium [8–11]. However, the decline in cement dermatitis may also result from other factors, such as automation and prefabrication processes in the construction industry [12, 13]. A remarkable observation is the fact that chromate allergy was common among construction workers employed at the Channel Tunnel project, in which normal cement was used [14]. In contrast, only a few workers developed cement dermatitis during the construction of the Great Belt tunnel and bridge in Denmark, a project of a comparable size [5]. In Denmark, legislation has, since 1981, regulated the concentration of hexavalent chromate in ready-to-use cement, and, since 2003, a similar legislation has been adopted in the EU, making it illegal to sell cement and cement products containing more than 2 ppm hexavalent chromium. Recent epidemiological investigations support this legislation, since chromate sensitization among construction workers in Northern Bavaria, Germany was still common throughout the 1990s, without the declining frequency seen in Scandinavian countries, where the addition of ferrous sulfate to cement had been used since the 1980s [15]. Chromate allergy is more common in male than in female eczema patients, due to the occupational exposure in male-dominated occupations, such as building and machine industry [6].This has changed in Denmark since introduction of the legislation limiting the content of hexavalent chromate in cement. Now, chromate allergy is more common in female patients, probably caused by chromate tanned leather in gloves and shoes [16].

There are many causes of chromate allergy other than cement, including chrome tanned leather, anti-rust paint, timber preservatives, the wood pulp industry, ash either from burnt wood in general or matches with chromate in the match head, coolants and machine oils, galvanizing, defatting solvents, brine added to yeast residues, welding, the dye industry (due to either a dye, a reducing agent, or a mordant), printing, glues, foundry sand, boiler linings, television work (ammonium bichromate to produce cross-linking of light-sensitive polyvinyl alcohol), magnetic tapes (chromium dioxide), solutions used to facilitate tire fitting, chromium plating, hardeners and resins in the aircraft industry, preservatives used in milk testing, bleaches, and detergents. An extensive list of possible sources of contact allergy is in Table 2. Of these sources, many are rare and one-off contacts. The commonest sources of chromate aller-

Table 2. Industrial exposure to chromium is possible during contact with the following compounds or work procedures (from [17])

Analytic standards reagents
Anticorrosion agents
Batteries
Catalysts (for hydrogenation, oxidation, and polymerization)
Ceramics
Corrosion inhibitors
Chromate surface treatments
Drilling muds
Electroplating and anodizing agents
Engraving
Explosives
Fire retardants
Magnetic tapes
Milk preservatives
Paints and varnishes
Paper
Photography
Roofing
Surgical sutures
Tanning leather
Textile mordants and dyes
Television screens
Textile mordants and dyes
Wood preservatives

gy by far still remains cement, followed by welding, chrome tanning, leather, pigments, and chrome plating. The relevance of a positive chromate patch test may be difficult to ascertain. More detailed information can be obtained in references [3] and [17]. Allergic chromate dermatitis is often widespread and persistent, and may appear in a nummular eczema pattern [18]. However, if the patient carefully aims to avoid contact with chromate-containing products, the chromate dermatitis often clears [19]. A change of occupation may be beneficial in some cases, but it does not ensure the healing of the dermatitis. Substitution for the chromate-containing products is often possible for leather gloves, shoes, and printing material, among others. The occasionally seen persistent nature of chromate dermatitis is not clear. It may be due to chromate remaining in the skin for a long time, or it may require minute quantities of chromate to flare up a contact allergy, and minute quantities of an amount similar to that in cement are found in many everyday objects, such as paper, soil, ash, etc. Recent clinical experimental exposure studies in volunteer patients have revealed that the vast majority of sensitized individuals fail to react to levels of chromate below 10 ppm under realistic exposure conditions [20, 21]. It has been suggested that dermatitis can be aggravated in those allergic to chromate by oral ingestion, but this remains unproven and has not received the attention that the same theory has received in nickel allergy [22].

Chromium is an essential element in the body, especially for glucose metabolism.

Potassium dichromate 0.5% pet. is the standard dilution for testing. However, this percentage can produce an irritant reaction, which may explain the wide difference in dichromate allergy reported throughout the world. It has been suggested that 0.25% would be more accurate, but while this produces fewer reactions, it does miss some true dichromate allergies [23]; the same applies to a dilution of 0.375% [24]. The patch test concentration in the TRUE Test system is 23 µg/cm^2. The closeness of irritant concentration to that to detect contact allergy is a problem in assessing the true incidence of chromate allergy and in diagnosing individual patients.

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29.4 Cobalt

Today, more than 75% of the world's production of cobalt is used in the manufacture of alloys. It is also an integral and necessary component of vitamin B12. Meats, fruits, vegetables, and cereals are major sources of vitamin B12, and, thus, of cobalt [1].

A positive patch test to cobalt often occurs in association with a positive test to nickel or chromate, more particularly, nickel, although the pattern may be different in males and in females [2, 3]. However, cobalt allergy without nickel allergy may occur in about 30% of the cases [4]. The association between nickel and cobalt allergy is explained by the metals being commonly present in alloys and products so that considerable contact with nickel means a correspondingly high contact with cobalt, and, hence, a corresponding possibility of sensitization to both [5]. Experimental studies in guinea pigs have shown that concomitant nickel and cobalt patch test reactivity is due to multiple sensitizations rather than cross reactivity [6]. However, a positive test to cobalt occurs 20 times more frequently in those allergic to nickel than in those not allergic, and a person with a +++ nickel positive patch test is 50 times more likely to have +++ positive cobalt reaction [7]. Rystedt and Fischer [8] reported 7% positive patch tests in 4,034 eczema patients, and of these, 50 were isolated cobalt reactions.

Cases of allergy have been reported due to contact with nonmetal sources, such as cobalt naphthenate and oleate used as dryers for varnishes, paints, and printing inks, or as a contact catalyst in polyester resin systems, an oxidizing agent in automobile exhaust controls, in electroplating, and in the rubber tire industry. Exposure and allergy has also occurred to cobalt in wet alkaline clay in pottery and china plants; the latter may be due to porcelain dyes. Cobalt is often added to animal feeds and dermatitis has been described due to it. Cobalt and chromate are still prominent allergens in construction workers in Germany [9], though the cobalt content in cement is low. Cobalt chloride was the third most frequently occurring contact allergen among construction workers with occupational eczema, after chromate and epoxy resin [10]. It is often difficult to identify the source of a single positive cobalt patch test; that is, one with a negative nickel test. However, most of these patients are probably allergic to jewelry, as with nickel.

The importance of cobalt exposure for maintaining allergic hand dermatitis in sensitized individuals is questionable, as patients who immersed a finger in a cobalt salt solution containing 200 mg/l for 10 min daily for 2 weeks failed to develop a flare of hand eczema [11]. Cobalt chloride 1% pet. is the standard dilution for patch testing, and the concentration in the TRUE Test is 20 μg/cm². Cobalt reactions may appear late [12], and cobalt may also be an irritant, giving rise to false-positive reactions of a spotty nature ("poral") associated with a toxic effect on the eccrine acrosyringium [13].

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29.5 Fragrance Mix

Fragrance and flavor substances are organic compounds with characteristic, usually pleasant, odors [1]. They are ubiquitous and are used in perfumes and perfumed products and are found not only in cosmetics, but also in detergents, fabric softeners, and other household products where fragrance may be used to mask unpleasant odors from raw materials. Flavors are used in foods, beverages, and dental products. Common clinical features of fragrance contact dermatitis are (Fig. 1a, b):

- Axillary dermatitis
- Dermatitis of the face and neck
- Well-circumscribed patches in areas where perfumes are dabbed on (wrists, behind the ears) and (aggravation of) hand eczema

Depending on the degree of sensitivity, the severity of dermatitis may range from mild to severe with dissemination. Airborne and connubial contact dermatitis occurs. There is a possible association between fragrance allergy and hand eczema [2].

Other less frequent adverse reactions to fragrances are: photocontact dermatitis, contact urticaria, irritation, and pigmentary disorders [3, 4].

Evaluation of perfume allergy may be difficult. A complete perfume compound consists of from 10 to more than 300 basic components, selected from about 3,000 materials (http://pharmacos.eudra.org/F3/cosmetic/cosm_inci_index.htm), which can be divided into the following [1, 3, 4]:

- Natural products isolated from various parts of plants, e.g., blossoms, buds, fruit, peel, seeds, leaves, bark, wood, roots, or from resinous exudates
- Animal products and their extracts (ambergris from the sperm whale, tonkin musk from the testes of musk deer, castoreum from beaver glands, beeswax absolute from beeswax, and civet from glands of the civet cat)
- Numerous synthetic fragrance chemicals

Because of the difficulties in testing with individual fragrances, a perfume screening mixture for patch testing was developed to increase the ability to detect perfume allergy [5]. The current fragrance mix 8% in petrolatum consists of eight ingredients, each at a concentration of 1%:

- Amyl cinnamal
- Cinnamal
- Cinnamyl alcohol
- Eugenol
- *Evernia prunastri* (oak moss)
- Geraniol
- Hydroxycitronellal
- Isoeugenol

The fragrance mix from Hermal and Chemotechnique contains sorbitan sesquioleate as an emulsifier. This fragrance mix has been shown to be a valuable screening agent for perfume dermatitis: most reactions have been caused by oak moss (Fig. 2), isoeugenol, and cinnamal. The test concentration in the TRUE Test is 430 µg/cm².

In most centers, fragrance mix ranks second only to nickel as the most common contact allergen, with a response rate in dermatological patients of between 6% and 11% (Fig. 3). Fragrance allergy is more common among women than men due to greater exposure, though the differences are small [3, 6–8] and may increase with age [9]. Clinical studies have shown a highly significant association between re-

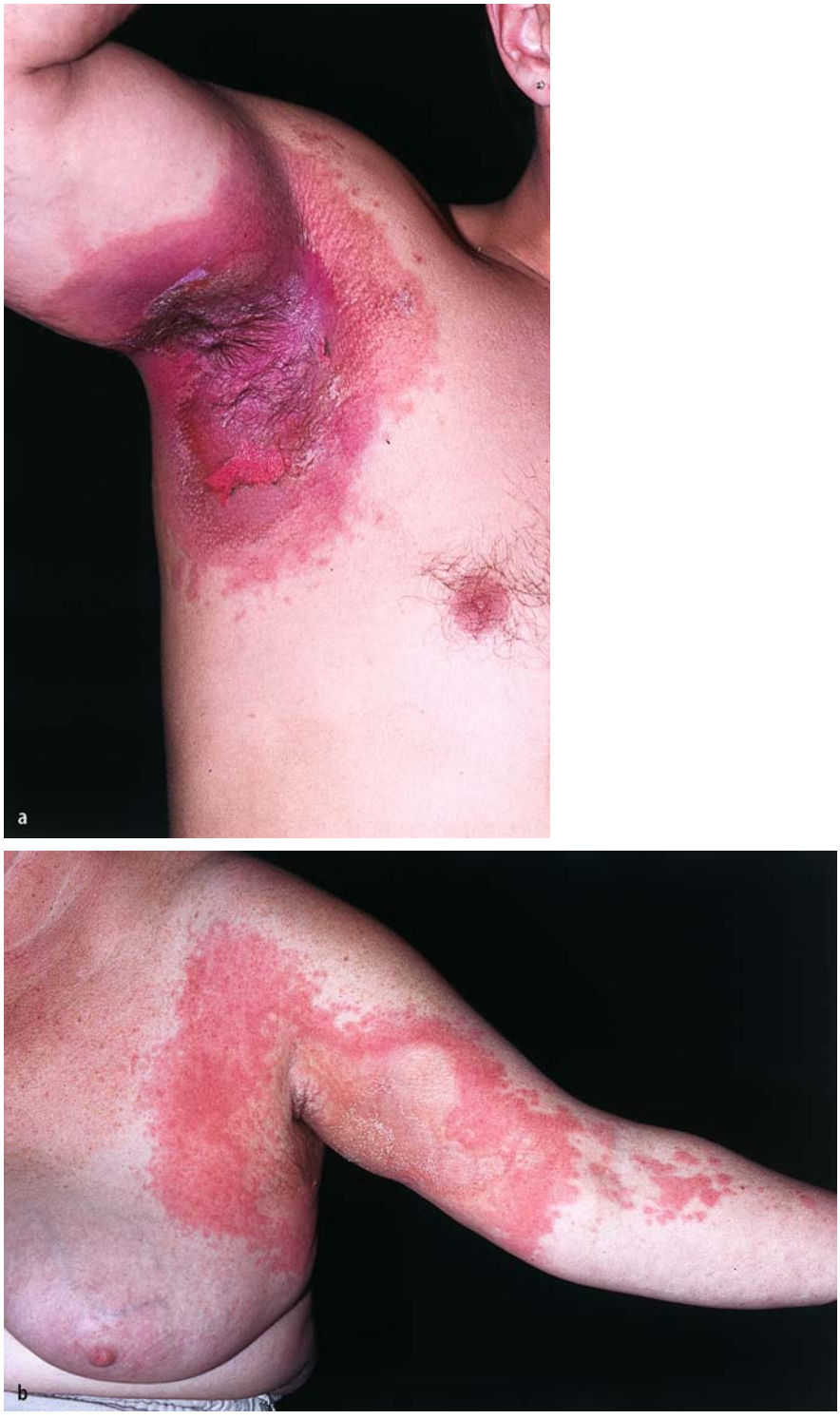


Fig. 1a, b.
Contact allergy to fragrances in deodorants can be very severe: formation of large blisters (**a**) and erythema-multiforme-like lesions with spreading (**b**). (Courtesy of P.J. Frosch)

porting a history of visible skin symptoms from using scented products and a positive patch test to the fragrance mix (Fig. 4) [10]. Provocation studies with perfumes and deodorants have also shown that fragrance-mix-positive eczema patients often react to use tests with the products, and subsequent chemical analysis of such products has detected significant amounts of one or more fragrance mix ingredients, confirming the relevance of positive patch tests to fragrance mix in these patients [11, 12].

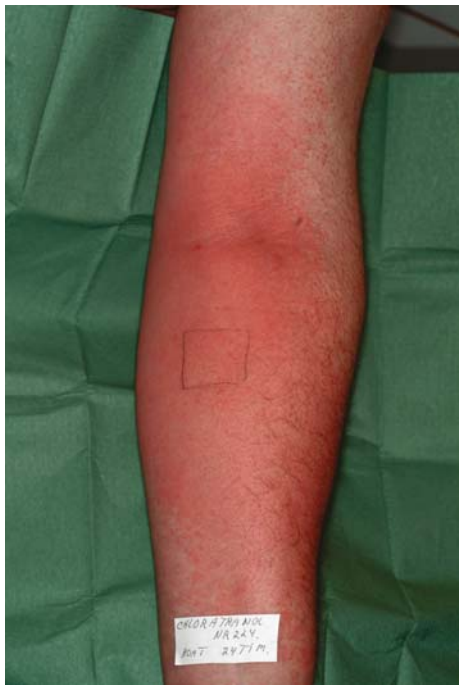


Fig. 2. Strongly positive ROAT to 5 ppm chloratranol solution in ethanol one day after one application of two drops in a male patient with oak moss allergy

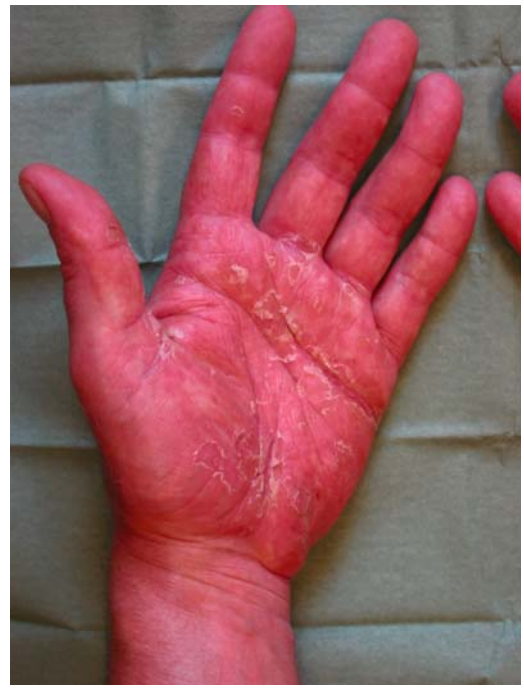
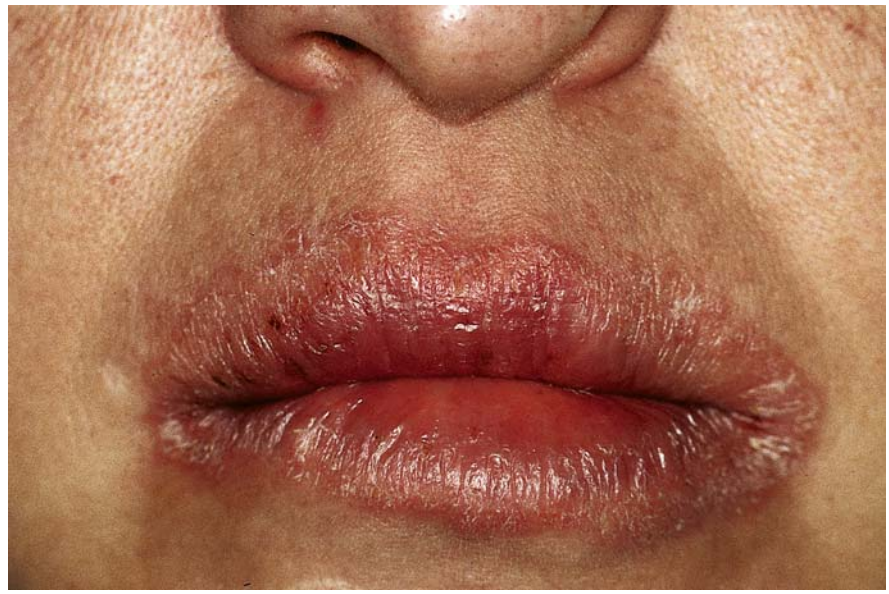


Fig. 3. Forty-year-old man with long-lasting hand eczema and strong allergic reactions to fragrance mix and balsam of Peru. Eczema cleared completely after elimination of skin contact with perfumed products

Fig. 4. Severe long-standing cheilitis in a patient allergic to iso-eugenol present in her lipstick. (Courtesy of P.J. Frosch)



It is estimated that the fragrance mix detects about 75% of all cases of fragrance sensitivity [13, 14]. A second mix has been developed to improve on this [15].

False-positive and false-negative reactions to the mix are common. Marginal reactions may, in some cases, be regarded as irritant, while in other cases, retesting with the ingredients of the mix may reveal positive patch tests to one or more of them. To avoid false-negative reactions, ingredient testing is necessary, but evaluation of the patch test results may be difficult because it appears that patch tests in perfume-sensitive patients with fragrance allergens in

combination give additive responses compared to patch tests with the allergens separately [16]. Thus, it is important to test patients with their own products.

Evaluation of perfume allergy within Europe is being eased by the mandatory listing on the ingredients label of the fragrance mix substances present in cosmetics and detergents (together with other household products) if present at 10 ppm or more in a finished leave-on cosmetic product, or 100 ppm or more in a rinse-off product.

- Alpha-isomethyl ionone
- Amyl cinnamal*
- Amylcinnamyl alcohol
- Anisyl alcohol
- Benzyl alcohol
- Benzyl benzoate
- Benzyl cinnamate
- Benzyl salicylate
- Butylphenyl methylpropional (lilial)
- Cinnamal*
- Citral
- Citronellol
- Coumarin
- D-Limonene
- Eugenol*
- Hydroxycitronellal*
- Iso-eugenol*
- Farnesol
- Geraniol*
- Hexyl cinnamal
- Hydroxyisohexyl-3-cyclohexene carboxaldehyde (Lyral)
- Linalool
- Methyl heptine carbonate
- 2-(4-*tert*-Butylbenzyl) propionaldehyde
- 3-Methyl-4-(2,6,6-tri-methyl-2-cyclohexen-1-yl)-3-buten-2-one
- Oak moss* [*Evernia prunastri*]

* Present in fragrance mixture

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29.6 Balsam of Peru

Balsam of Peru (INCI name: *Myroxylon pereirae*) is the natural resinous balsam which exudes from the trunk of the Central American tree *Myroxylon pereirae* after scarification of the bark. It consists of essential oil and resin and is, thus, of the oleoresin type. The composition varies and standardization is based on physical characteristics and the identification of some major chemical constituents. Balsam of Peru contains 30% to 40% resins of unknown composition, while the remaining 60% to 70% consist of well-known chemicals: benzyl benzoate, benzyl cinna-

mate, cinnamic acid, benzoic acid, vanillin, farnesol (which is also increasingly being used in deodorants) [1], and nerolidol. In a series of 93 patients with contact allergy to balsam of Peru, reactions were seen, in decreasing order, to the following components: cinnamic alcohol, cinnamic acid, coniferyl alcohol, benzoic acid, cinnamyl cinnamate, eugenol, resorcinol monobenzoate, coniferyl alcohol, and benzyl alcohol [2]. Many perfumes and flavorings contain components either identical to, or cross-reacting with, materials contained in balsam of Peru and other natural resins. Positive patch tests with one or more of these substances may be an indication of perfume allergy. In medicinal preparations, balsam of Peru is still used for its dermatological effects. Some chemicals present in balsam of Peru and similar resinous substances may also have antimicrobial effects and be used as preservatives.

The early epidemiology of perfume allergy is based on Hjorth's [3] classic monograph on balsam of Peru. It gave positive reactions in 4.0% of males and 4.0% of females in a Danish epidemiological study consisting of 2,166 eczema patients [4]. However, the importance of balsam of Peru as a marker for perfume allergy is now questionable, as the incidence of concomitant positive patch tests to balsam of Peru in fragrance-sensitive patients shows wide variation [5, 6]. Contact allergy to this compound is relevant to leg ulcer patients [7]. Immediate reactions to patch tests with balsam of Peru occur. Systemic contact-dermatitis-type reactions, like aggravation of vesicular hand dermatitis following ingestion of related compounds, has been reported in previously sensitized patients [8–11], but the benefits of a flavor-avoidance diet may not be obvious [9]. Because of its sensitizing properties, balsam of Peru is prohibited from use in Europe as a fragrance ingredient. Balsam of Peru 25% pet. is the standard dilution for patch testing, and 800 µg/cm² in the TRUE Test.

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29.7 Colophony

Colophony (rosin) (INCI name: colophonium) is a widespread, naturally occurring material that is the residue from the distillation of the volatile oil from the oleoresin obtained from trees of the *Pinaceae* family. Its chemical composition is complex and variable, depending on the manufacturing process, geographical area, and storage conditions. There are three kinds of colophony: gum rosin from the tops of living trees, the resin being distilled to yield turpentine oil and the gum resin residue; wood rosin, a distillate from pine tree stumps; and tall oil rosin, a by-product from pine wood pulp (see [1] for a review).

Colophony is composed of about 90% resin acids and 10% neutral substances. The principal allergens in colophony have not yet been determined. Oxidation products of abietic acid and dehydroabietic acid have been identified as allergens, but synthetically prepared derivatives and the neutral fraction also contain allergenic compounds [1]. In a 5-year retrospective study involving 16,210 consecutive eczema patients, 4.5% were colophony-sensitive [2]. In addition to contact eczema, it may also cause type I hypersensitivity [1] and photosensitivity [1, 3].

Concomitant and/or cross-reactions between colophony (rosin), balsam of Peru, oil of turpentine, wood tar, pine resin, spruce resin [4], sesquiterpene lactone mix [5], propolis, and fragrance mix may occur, often in the context of a fragrance allergy [6]. The presence of terpenes [5] in some of these materials, as well as contamination by resin acids in oak moss [7], a component of fragrance mix, only partly explain this phenomenon.

Table 3. Products commonly containing colophony

Adhesives	Paper
Chewing gums	Polishes
Cleansing agents	Printing inks
Cosmetics	Rosin (used by, e.g., violinists, sportspersons)
Cutting fluids	Soldering flux
Dentistry products	Surface coatings
Glues (shoes!)	Ulcer bandages
Insulating tapes	Varnishes
Ostomy appliances	Wood wool

Exposure to colophony and its derivatives [1] is likely during both work and leisure hours (Table 3; Fig. 5). In cosmetics, colophony occurs in depilatories, tonics, dressing and hair grooming aids, make-up, mascara, and hair products. In pharmaceutical products, it is used in topical medicaments, including surgical paints [8] and Chinese herbal medicine [9].

Colophony allergy from adhesives has been known for nearly a century, but the use of adhesives based on acrylate polymers has reduced the incidence of contact dermatitis from this source. However, when strong adhesive effects are desired, such as in footwear, colophony or its derivatives may still be used [10–12]. Furthermore, their presence has also been detected in paper, including "no carbon required" (NCR) paper [13], as well as in diapers [14] and sanitary pads [15]. In the modern electronics industry, the use of colophony as a fluxing agent in assembly work produces a significant number of contact allergies appearing as allergic hand [16] and airborne facial [17] dermatitis. Airborne dermatitis may also result from exposure to sawdust – even associated with leukoderma [18] – cutting oils [19], and even jewelry [20].

The occurrence of contact allergy to colophony has been increasing over the past few decades (see [1]). The allergenicity of colophony can be reduced by chemical modification, i.e., by hydrogenation of the nonaromatic double bonds in the resin, which minimizes the content of easily oxidized acids of the abietic type [21]. A mixture of unmodified Chinese and Portuguese gum rosin is used in the standard series at a concentration of 20% pet. [22], and in the TRUE Test, the concentration is 850 µg/cm². Further studies are necessary to improve our understanding of colophony contact allergy and the optimal patch test material [23, 24]. Indeed, if the patient's history indicates heavy exposure to rosin, additional testing with other types of gum rosin and also tall oil rosin

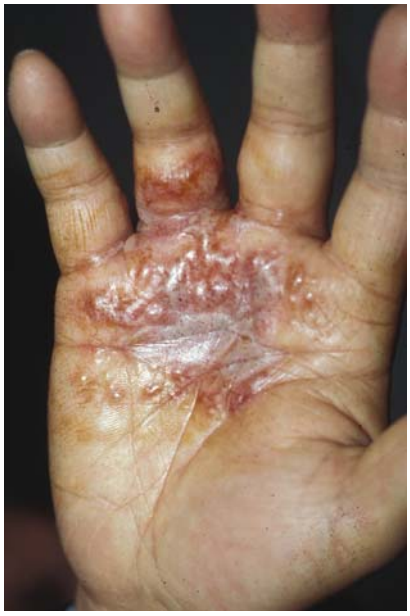

Fig. 5. Severe allergic contact dermatitis from colophonium in a Chinese balsam. (Courtesy of A. Goossens)

may be indicated. If negative responses are still obtained, the possibility of sensitivity to components of modified rosin must be considered [24], since tests with unmodified rosin (in the standard series) are most often negative in patients who react to modified-rosin derivatives, the latter probably being stronger sensitizers [25, 26].

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29.8 Neomycin

Neomycin is a widely used aminoglycoside antibiotic produced from *Streptomyces fradiae*. The frequency of neomycin sensitivity varies from clinic to clinic, depending to a large extent on local referral and prescription habits [1]. In a series of 40,000 consecutive eczema patients, the patch-test results of which were published in 1997, 1% to 6% had neomycin contact allergy. This is comparable to the results obtained in a recent study by the EECDRG concerning 26,210 consecutive eczema patients tested in 10 different centers [2], in which the frequency was 3%, with individual frequencies varying from 1.6% to 7.7%. Several patch test studies demonstrated that there is an upward trend in the occurrence of neomycin sensitivity over the years, probably due to increased use of topical drugs containing this antibiotic [3, 4]. The patients particularly at risk of neomycin sensitivity appear to be those with chronic and recurrent dermatitis in skin areas where occlusion or bandaging is prone to occur or is used, as in stasis dermatitis, but also those with otitis externa [5, 6] and perianal eczema. Occupational contact dermatitis, as well as systemic reactions, may occur.

The diagnosis of neomycin allergy may be difficult because the dermatitis is not vesicular or bullous, but often appears instead as aggravation or simply chronicity of a pre-existing dermatitis. It is instructive to note that the therapeutic concentration of neomycin is often 0.5%, while the patch test concentration is 20% in petrolatum. Even at this concentration (and in this vehicle) [7], some positives may be missed; the positive neomycin patch test appears late, after 3–4 days in many cases, and there are many inter-individual variations [7]. The neomycin concentration in the TRUE Test is 230 µg/cm².

The cross-sensitization pattern of neomycin is complex. Cross-sensitivity occurs, although not with the same frequency, between neomycin, amikacin, arbekacin, dibekacin, framycetin, gentamycin, isepamicin, kanamycin, paromomycin, ribostamycin, sisomycin, spectinomycin, and tobramycin [8].

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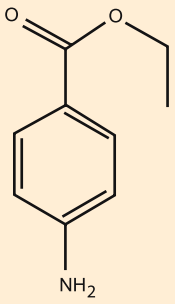
29.9 Benzocaine (Ethylaminobenzoate)

Benzocaine is a para-aminobenzoic acid (PABA) derivative and is used as a local anesthetic.



Scheme 1. 4-Aminobenzoic acid ethyl ester

The incidence of contact sensitivity reported varies widely from country to country, probably depending on the level of use of benzocaine in the community [1, 2]. The incidence of positive reactions to topical anesthetics in eczema patients ranges from 0.5% to 2% [2]. In some countries, such as the United States, it is widely used in over-the-counter preparations, whereas in others, such as the United Kingdom, its use is much less common [3].

According to Sidhu et al. [3], and in agreement with previous studies [4, 5], it would be good to include a "caine mix" in the standard series consisting of benzocaine, tetracaine HCl, and dibucaine HCl [each 5% pet.), since benzocaine [5% petrolatum) alone is inadequate. The TRUE test includes a caine mix containing benzocaine, dibucaine hydrochloride, and tetracaine hydrochloride (5:1:1) 630 µg/cm². In order to detect more patients sensitive to topical anesthetics, it is necessary to test with other "caine" anesthetics [5, 6]. Benzocaine-sensitive individuals can safely use amide derivatives, such as lidocaine (lignocaine).

Benzocaine can cross-react with compounds other than local anesthetics, such as para-phenylenediamine, sunscreens such as para-aminobenzoic acid esters used as sunscreens, sulfonamides, and certain dyes.

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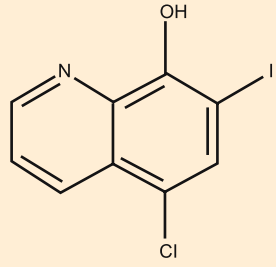
29.10 Clioquinol

Synonyms for clioquinol are: chinoform, chloroiodoquine, cliochinolum, iodochlorhydroxyquin, iodochlorhydroxyquinoline, and 5-chloro-7-iodoquinolin-8-ol.



Scheme 2. Clioquinol

Because of manufacturing problems, clioquinol 5% pet. replaced the quinoline mix in the standard series. The mix contained a mixture of clioquinol and chlorquinaldol [1]. These substances have both anti-

bacterial and antifungal activity, and are commonly used in creams and ointments to treat skin conditions in which an anti-infective agent is required. A concentration of 3% in such preparations is usual, and they are often combined with a topical corticosteroid. Clioquinol has been used in orally. Chlorquinaldol is 5,6-dichloro-2-methylquinolin-8-ol. These quinolines are not potent allergens. The acquisition of allergic sensitivity to them does not generally cause a marked worsening of eczema, and, when combined with a topical corticosteroid, the steroid will cause some suppression of the inflammatory response. Although Cronin [2] found that no particular pattern of eczema predisposed to clioquinol sensitivity, it may be more common in relation to stasis dermatitis and otitis externa [3, 4]. Geographical variation in the incidence depends on the types of products locally available and the type of patient being investigated. The prevalence of contact allergy to clioquinol is about 0.7% [5]. The oral administration of either clioquinol or chlorquinaldol has resulted in a generalized eruption in individuals allergic to these compounds [6–8]. A first drug eruption due to clioquinol has been reported [9]. An immediate-type reaction occurred in a woman intolerant of oral quinine when clioquinol was applied topically [10]; a quinoline ring is common to both. It may cause contact urticaria on patch testing [11]. Cross-reactions between clioquinol and chlorquinaldol are not common, and clioquinol is the more important of the two allergens. In patients tested consecutively to both quinoline mix and clioquinol, it was found that clioquinol alone missed 34% of the patients reacting to quinoline mix [1]. However, in three patients believed to have been sensitized previously to clioquinol, a spectrum of reactions was recorded to other halogenated hydroxyquinolines [12]. Irritant reactions to clioquinol-containing products have also been described, particularly when used in sensitive skin areas, such as the perineum [13, 14].

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29.11 Wool Wax Alcohols (Lanolin)

Lanolin is a natural product from sheep fleece and consists of a complex mixture of esters and polyesters of high-molecular-weight alcohols and fatty acids. The composition varies from time to time and from place to place. Wool wax alcohols (INCI name: lanolin alcohol) are a complex mixture of esters of alcohols and fatty acids derived from hydrolysis of the oily, waxy fraction of sheep fleece. The general incidence of lanolin allergy in consecutively tested eczema patients is around 2% to 3% [1, 2]. Lanolin and wool wax alcohols are weak allergens and experimental sensitization cannot be achieved in humans and animals [3].

The use of lanolin extends from topical preparations to industrial lubricants, polishes, anti-corrosives, printing inks, leather and textile finishes, and paper constituents. The literature on contact allergy to lanolin has been extensively reviewed [4–6].

Lanolin allergy is uncommon on normal skin and with cosmetic usage, but is common when applied to leg ulcers and other diseased skin, such as in the anogenital area [6]. Because of the rarity of lanolin sensitization when applied to normal skin, every positive patch test to wool wax alcohols and lanolin should be verified to determine whether it represents an allergy or nonspecific reactivity (e.g., the excited skin syndrome) [5, 7].

To detect contact allergy cases, wool wax alcohols at a concentration of 30% pet. are tested in the standard series, and the concentration in the TRUE Test is 1,000 µg/cm². Other derivatives have also been tested, among them include hydrogenated lanolin and Amerchol L-101 (mineral oil and lanolin alcohol), the latter having been found to be an additional marker for lanolin sensitivity [6, 8, 9]. However, irritant reactions with these compounds are not excluded [5].

The lanolin allergens are unknown, although they are probably present in the alcoholic fraction. Several modifications of lanolin have been tested to produce one with a less sensitizing capacity [10, 11].

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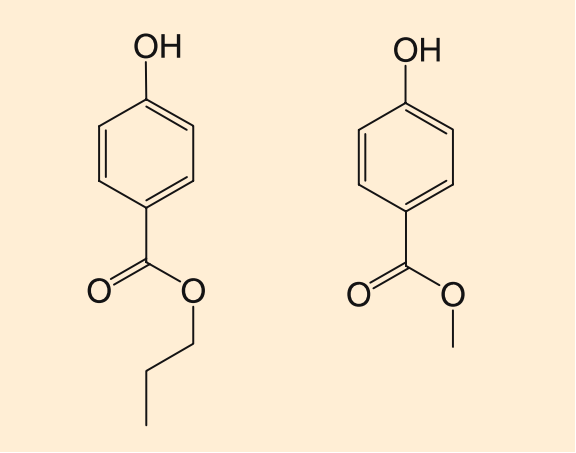
29.12 Paraben Mix

The most widely used preservatives in foods, drugs, and cosmetics are the parabens (alkyl esters of *p*-hydroxybenzoic acid) [1].



Scheme 3. Propylparaben and methylparaben

This group of preservatives has been used for more than 60 years and includes methyl-, ethyl-, propyl-, and butylparaben (INCI names). They are also marketed under a number of trade names for use in noncosmetic products, i.e., Solbrol, Tegosept, Betacide, Bonomold, Chemoside, Nipagin, and Propagin. 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 biocides. The vast majority of the cosmetics registered at the FDA contain parabens and the use concentration is usually in the range 0.1% and 0.8%. Cross-reactions between the four paraben esters methyl-, ethyl-, propyl- and butylparaben are common, but exceptions can occur. The paraben mix used to contain these four esters plus benzylparaben. Benzylparaben has been removed because it is no longer allowed for use in cosmetics and drugs as it is suspected to be a carcinogen. Further, butylparaben is now in discredit because of estrogenic effects in animal models; however, the clinical implications of this suspicion has not yet been determined [2].

In diagnostic patch testing, Menné and Hjorth [3] found that approximately 1.0% of more than 8,000 eczema patients tested were sensitized. Similar frequencies are reported in other large-scale patch test studies [4–6]. The frequency of positive reactions has been remarkably constant over a 15-year period [5]. 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. In animal experiments, they also seem to be

weak allergens; propylparaben was not able to show any sensitization in a guinea pig maximization test [7]. Clinical experience shows that the incidence of paraben sensitization in healthy persons is small, and agrees with the impression that occasional cases of paraben sensitivity occur and are important to the particular patient's welfare [8]. Cosmetics seems to be an uncommon source of sensitization. Clinical experience shows that patients with chronic dermatitis are at risk, particularly patients with stasis dermatitis and leg ulcers [9, 10]. 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 [11, 12]. In spite of the low frequency of paraben contact allergy, it is important to keep the allergen in the standard 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 battery series, the diagnosis will be missed.

Fisher et al. [8] and Schorr [13] assumed that repeated topical application of low concentrations of parabens in medicaments or cosmetics could cause sensitization, while Hjorth and Trolle-Lassen [14] stated that higher concentrations were necessary for the majority of cases. They reported a 1% incidence of paraben sensitivity, suggesting that this was due to the frequent use in Denmark of topical antifungal agents containing up to 5% paraben (Amycen). Cross-reactions have been described to other para compounds, such as benzocaine, para-phenylenediamine, and sulfonamides, but they are rare [15]. It has been reported that paraben-sensitive patients may experience flares of dermatitis from parabens in food and systemic medicaments [16, 17]. Placebo-controlled oral challenge with methyl-p-hydroxybenzoate in 14 paraben-sensitive patients was negative in 11, doubtful in one, and two had a flare of dermatitis. However, subsequent low-paraben diet had no effect on the dermatitis [18]. Immediate-type reactions (both systemic and contact urticaria) from parabens have been reported, but are very rare and not related to paraben-induced allergic dermatitis [19, 20].

In the European standard series, the parabens are tested as a mix of 4% of methyl-, ethyl-, propyl-, and butylparaben, a total of 16% pet., and in the TRUE Test, the concentration is 1,000 µg/cm² (Table 1). In Menné and Hjorth's study [2], two-thirds of the patients reacting to the mix showed positive reactions to one or more of the individual esters. Multiple patch test reactivity is probably due to cross-sensitization, but concomitant sensitization to individual esters is a possibility because the esters are often used in combination. Patch testing with products preserved with parabens is often negative in paraben-sensitized 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 sensitizers. 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. It is too early to say if the estrogenic effect story changes this view. Technical and microbiological considerations sometimes make alternative preservatives necessary. However, the paraben mix is important in the standard series because paraben allergy is difficult to detect from the history or clinical appearance of dermatitis.

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29.13 Formaldehyde

Formaldehyde is a ubiquitous and potent sensitizer, industrially, domestically, and medically. Lowering its usage concentration to 30 ppm could decrease the cases of allergy observed [1]. 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, polymerized plastics, metalworking fluids, medicaments, fabrics, cosmetics, and detergents (Table 4) [2]. Therefore, the detection of the formaldehyde content by chemical analysis, such as e.g., the closed container diffusion method (CCD) as proposed by Karlberg et al., would be interesting for the prevention of recurrence of allergic contact dermatitis in formaldehyde-allergic patients [3]. 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 from them. However, hairdressers may get hand dermatitis from similar products due to their more intense exposure.

Table 4. 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 deodorizers
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 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 [4, 5]. Formaldehyde sensitivity is not necessarily accompanied by a simultaneous sensitivity to formaldehyde resins and formaldehyde releasers, and vice versa [6–9]. Forty five percent of the subjects tested in St John's were positive to formaldehyde alone, whereas 47% of the subjects reacted simultaneously to quaternium-15 [10]. Indeed, some of the formaldehyde releasers might act as prohaptens. 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% [11–13].

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. 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 [9, 14, 15]. 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 5,000 ppm, 3 reacted to 1,000 ppm, 2 reacted to 500 ppm, and 1 reacted to 250 ppm (Fig. 6). Positive reactions were not observed in nonoccluded patch test with a dilution series from 25 ppm 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) [16]. Thus, the threshold concentration for occluded patch test to formaldehyde in formaldehyde-sensitive patients seems to be around 250 ppm. The threshold level of formaldehyde required to elicit an eczematous reaction in the axilla of formaldehyde-sensitive volunteers was 30 ppm [17].

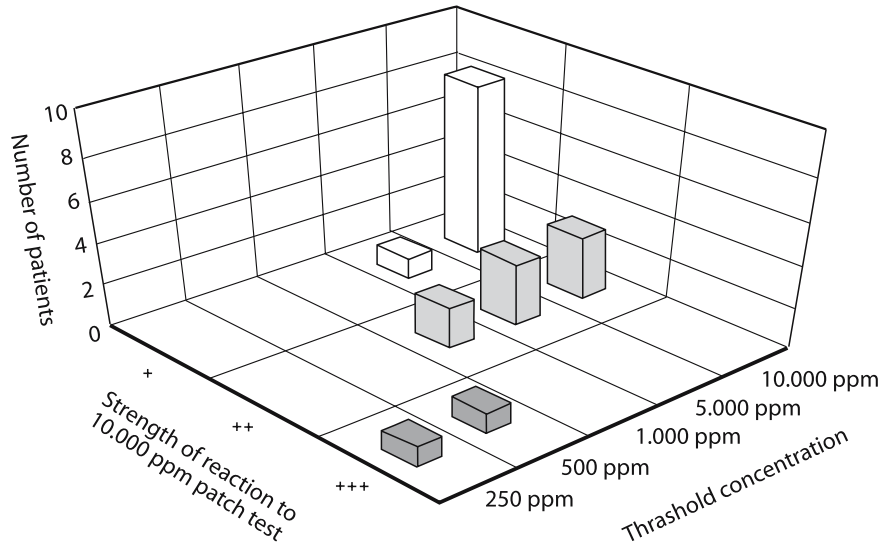

Fig. 6.
Lowest formaldehyde concentration giving positive reactions in occluded patch testing, compared to the strength of the reactions in diagnostic patch testing (10,000 ppm) among 19 formaldehyde-sensitive eczema patients. (From [16])

A follow-up study of 57 formaldehyde-sensitive eczema patients interviewed and examined 1–5 years after initial diagnosis showed that many of the patients were still exposed to formaldehyde-containing products. However, those who paid attention to their allergy had significantly fewer exacerbations of dermatitis than those who did not, and there was a trend that severe eczema was found more often in patients still exposed to formaldehyde. This study also showed that 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 [18].

Immediate reactions from formaldehyde may also occur, both of presumably allergic and nonallergic nature [19–21].

Formaldehyde releasers used as preservatives in cosmetics and technical products are often concealed by trade names or synonyms (Table 5) [22]. The epidemiology of formaldehyde sensitization requires re-evaluation. Most early studies utilized irritant patch test concentrations. The current recommended patch test concentration is 1% aq. [9, 23], and the TRUE Test contains 180 µg/cm².

Table 5. Formaldehyde releasers (from [22]

Bakzid P (mixture of cyclic aminoacetals and organic amine salts)
Biocide DS 5249 (1,2-benzisothiazolin-3-one and a formaldehyde releaser)
Bronopol (2-bromo-2-nitropropane-1.3-diol)
Dantoin MDMH (methylaldimethyoxymethan formal)
DMDM hydantoin (dimethyloldimethyl hydantoin)
Dowicil 200, Quaternium-15
Germall 115 (imidazolidinyl urea)
Germall II (diazolidinyl urea)
Grotan BK [1,3,5-tris(hydroxyethyl)hexahydrotriazine]
Hexamethylentetramine, methenamine [1,3,5,7-tetraazaadamantan –1,3,5,7-tetraazatricyclo(3,3,1,1^{3,7})decan]
KM 103 (substituted triazine)
Paraformaldehyde (polyoxymethylene)
Parmetol K50 (*N*-methylolchloracetamid, *O*-formal of benzyl alcohols)
Polynoxylin (polyoxymethylene urea)
Preventol D 1 [1-(3-chlorallyl)-3,5,7-triaza-1- azoniaadamantanchloride benzyl formal]
Preventol D 2 (benzylhemiformal)
Preventol D 3 (chlormethylacylamino methanol)

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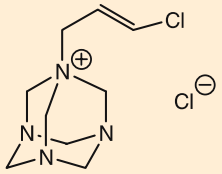
29.14 Quaternium-15

Quaternium-15 is a quaternary ammonium salt that conforms to the formula:



Scheme 4. Quaternium-15

It is a formaldehyde releaser used chiefly as a cosmetic preservative, and it is also an antistatic agent [1]. Formaldehyde releasers are in widespread usage in industry, household products, and cosmetics. They are marketed under a multitude of trade names. Chemically, they are linear or cyclic reversible polymers of formaldehyde, and formaldehyde is formed in different amounts, depending mainly on temperature and pH.

Quaternium-15 has several synonymous names: Dowicil 200, 100, and 75, CoSept 200, Preventol D1, 1-(3-chloroallyl)-3,5,7-triaza-1-azonia – adamantane chloride, chloroallyl methanamine chloride, *N*-(3-chlorallyl)-hexamine chloride, chlorallyl methenamine chloride. Formaldehyde is released in small amounts and formaldehyde-sensitive patients may react simultaneously to this preservative [2]. However, quaternium-15 sensitivity may also be directed towards the entire molecule. Allergic contact dermatitis from a formaldehyde-releasing agent may, thus, be due to the entire molecule, to formaldehyde, or to both [3–5]. Positive quaternium-15 patch tests are often of clinical relevance [6]. In about 50% of the cases, simultaneous reactivity is seen to formaldehyde [7]. The usual preservative concentration of 0.1% releases about 100 ppm free formaldehyde and this concentration can elicit dermatitis in formaldehyde-sensitive patients [8].

The repeated use of lotions and creams with this preservative may provoke dermatitis by mild irritation from the vehicles and subsequent sensitivity to the preservative. Sensitive patients should request cosmetics without formaldehyde releasers, even though some alternative formaldehyde releasers might be tolerated due to reduced formaldehyde production. Full cosmetic ingredients labeling, as that required today, makes it easy to avoid the use of specific ingredients in sensitized subjects (e.g., [9]). Occupational contact dermatitis due to quaternium-15 is extremely uncommon; two cases of hand dermatitis in hairdressers, one case of nail dystrophy in an

engineer, and a case of periorbital and hand dermatitis from an electrode gel in an electroencephalogram technician, and airborne dermatitis from a photocopier toner containing quaternium-15 have been reported [10–13]. The frequency of positive reactions varies from country to country, possibly due to variations in the frequency of use [14–17]. The patch test concentration is 1% pet. and 100 µg/cm² in the TRUE Test.

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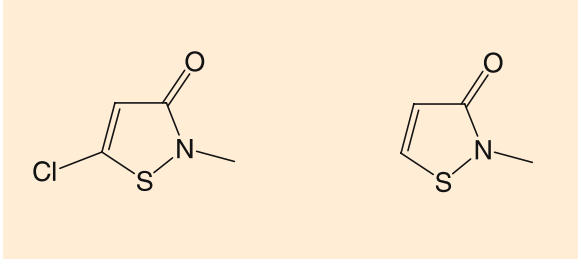
29.15 Chloromethyl- and Methylisothiazolinone (MCI/MI)

The isothiazolinones (5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one, 3:1 ratio by weight) are the active ingredients in Kathon CG (Rohm and Haas, Philadelphia), a cosmetic preservative. The INCI-adopted names for the active chemicals are methylchloroisothiazolinone and methylisothiazolinone (MCI/MI), and they appear in the preservative in the ratio of 3:1.



Scheme 5. Methylchloroisothiazolinone and methylisothiazolinone

Isothiazolinones are used extensively as effective biocides to preserve the water content of cosmetics, toiletries, household, and industrial products, such as metalworking fluids, water-based paints (Fig. 7), cooling tower water, latex emulsions, and for slime control in paper mills (Table 6) [1]. Also, other isothiazolinone derivatives, such as e.g., 2-methyl-4,5 trimethylene-4-isothiazolin-3-one (MTI) and 2-octyl-4-isothiazolin-3-one (Skane M8) are used as biocides for paints and latex emulsions [2, 3].

Isothiazolinones are marketed under many brand names [4], which make it easy to overlook the presence of these chemicals in the formulations. Approximately 25% of all cosmetic products and toiletries – in particular, rinse-off products – in the Netherlands in the late 1980s contained Kathon CG and synonymous preservatives [1]. A Danish study examined the content of Kathon CG in 156 of the most commonly used cosmetic products in 1990. Kathon CG was

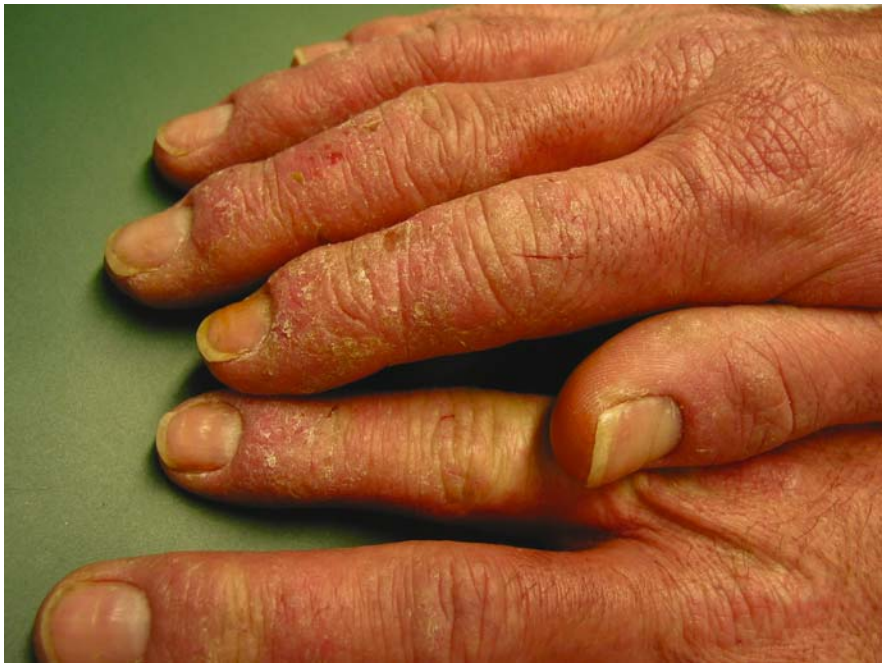


Fig. 7.
Painter with occupational hand eczema and contact allergy to Bronopol and Kathon CG used as preservatives in water-based paints

present in 48% of wash-off and 31% of leave-on cosmetic products [5]. A search of the chemical products database (PROBAS) in Denmark, containing information about approximately 30,000 products, showed that MCI/MI was registered in 550 products; 64% of them (paints, shampoos, skin care products, and cleaning agents) contained concentrations above or equal to 10 ppm. The authors also draw the attention to occupational exposure from isothiazolinones, as they may occur in many industrial categories, e.g., preservatives may contain up to 13.9% MCI/MI [6].

Methylchloroisothiazolinone and methylisothiazolinone are strong sensitizers in guinea pig allergy tests [7], and multiple reports have documented a varying and, in some countries in the late 1980s, an increasing incidence of allergic contact dermatitis from these chemicals, probably explained by increased exposure [8, 9]. Over the last 10 years, the incidence of MCI/MI contact allergy has remained stable around 2.0–2.5% of consecutively tested eczema patients in Europe [10]. MCI/MI is an important allergen for the hands and the face, and it may also cause urticaria [11, 12] and airborne contact dermatitis [13]. The airborne MCI/MI dermatitis may appear in the face of sensitized individuals who stay in newly painted rooms, and the diagnosis is easily missed unless specifically considered [14, 15]. 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 sensitized to MCI/MI tolerated the use of a shampoo preserved with MCI/MI for 2 weeks [16]. 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 is 100 ppm aq. This is the best compromise, as higher concentrations (200–300 ppm) may produce irritation and patch test sensitization [1, 17]. On the other hand, 100 ppm may, in some cases, perhaps give false-negative test results on normal back skin in patients with an isothiazolinone-induced aggravation of hand dermatitis. A use test is helpful in doubtful cases of allergy. Due to the activity of isothiazolinones on the skin, it is imperative that exact dosing be used when iso-

Table 6. Biocides containing methylchloroisothiazolinone/methylisothiazolinone. Some of these products may also contain other ingredients

Kathon CG	Metat GT
Kathon DP	Metatin GT
Kathon 886 MW	Mitco CC 31 L
Kathon LX	Mitco CC 32 L
Kathon WT	Special Mx 323
Acticide	Parmetol DF 35
Algucid CH 50	Parmetol DF 12
Amerstat 250	Parmetol A 23
Euxyl K 100	Parmetol K 50
Fennosan IT 21	Parmetol K 40
GR 856 Izolin	Parmetol DF 18
Grotan TK 2	P 3 Multan D
Grotan K	Piror P 109
Mergal K 7	

thiazolinones are used for patch testing. In the TRUE Test, the concentration is 4 µg/cm². Patch testing with products preserved with MCI/MI is often negative in sensitized patients, while a use test may be positive. With regard to the prevention of chemical burns and allergic contact dermatitis from higher concentrations, addition of sodium bisulfite seems to have the capacity to "deactivate" the MCI/MI mixture [18]. There is no cross-sensitization between MCI/MI and two other isothiazolinones, benzisothiazolinone (Proxel) and octylisothiazolinone (Kathon 893, Skane M8) [19].

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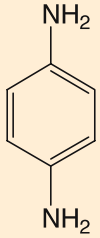
29

29.16 Paraphenylenediamine

Para-phenylenediamine (PPD) is a colorless compound that acts as a primary intermediate in hair dyes. It is oxidized by hydrogen peroxide and then polymerized to a color within the hair by a coupler (such as resorcinol). In Europe, it is permitted in amounts of up to 6% free base in hair dyes before the addition of peroxide. This equates to 3%, but, in practice, is not used at greater than 2%.



Scheme 6. *para*-Phenylenediamine

Most cases of contact allergy to PPD occur from contact with hair dyes, in either the consumer or the hairdresser [1]. In the United States, it is one of the three substances most useful in the initial patch test screening of hairdressers with dermatitis (besides glyceryl thioglycolate and formaldehyde) [2]. In a study performed in nine European centers, PPD was found to be the second most important allergen in hairdressers (after glyceryl thioglycolate), though marked regional variations were observed [3]. The information network of the Departments of Dermatology in Germany (IVDK) reported that PPD was the fifth most common allergen (4.8%) in 40,000 patients, again with considerable geographical variation in frequency, ranging from 2.8% to 7.1% [4]. The frequency of PPD allergy is high in India [5]. Many cases of PPD allergy are seen in men from the Indian subcontinent who are resident in the United Kingdom, due to the fact that they dye their hair and beard.

PPD is an important occupational allergen in hairdressers in relation to hand dermatitis. In this group, sensitization may be facilitated by irritation of the hands from wetness, shampoos, and perming lotions. The most important measures to reduce the risk of allergic reactions from hair dyes include, besides improved products, effective removal of excess hair dye formulation from newly dyed hair, the use of protective gloves, and adequate education and information. A multicenter German study of hairdressers with hand dermatitis showed that the prevalence of contact allergy to PPD dropped from 26.6% to 17.2% between 1995 and 2002 [6]. Amongst a series of 40 hairdressers with a known contact allergy to PPD, none reacted to a new generation of hair dyes containing FD&C and D&C colors, which suggests a possible safer alternative [7].

In consumers, allergic contact dermatitis caused by PPD can be severe [8], with edema of the face, scalp, and ears that may be clinically mistaken for angio-edema [9]. Although not legal in Europe, active sensitization to PPD has been increasingly observed from its use as a skin paint in so-called *temporary tattoos* when *black henna* is used [10, 11].

PPD often gives rise to strong patch test reactions in sensitive patients. The reactions may appear after a very short patch test application time. In six of 16 PPD-sensitive patients, 15 min exposure to 1% PPD was sufficient to elicit an eczematous reaction [12]. Patients with PPD allergy may show cross-reactions with benzocaine, procaine, sulfonamides and PABA sunscreens, azo and aniline dyes, anthraquinone, antihistamines, and the rubber antioxidant 4-isopropylaminodiphenylamine [13]. However, Cronin did not find that any of 47 hairdressers positive to PPD reacted to the PPD–rubber mix [14]. Cross-reactions occur to other related hair dyes, such as *p*-toluenediamine, *p*-aminodiphenylamine, 2,4-diaminoanisole, and *o*-aminophenol are seen. Also, cross-reactivity between azo dyes and *para*-amino compounds are common. Seidenari et al. [15] studied 236 consecutively tested dermatitis patients sensitized to at least one of six azo textile dyes. Co-sensitizations to *para*-phenylenediamine were present in most subjects sensitized to *p*-aminoazobenzene (75%) and Disperse Orange 3 (66%), while the following gave lower rates of co-sensitization; Disperse Yellow 3 (36%), Disperse Red 1 (27%), and Disperse Blue 124 (only 16%) [15]. Apart from the hands and face, the neck and axilla were the most frequently involved skin sites in these patients. Cross-sensitizations between azo dyes and *para*-amino compounds can partly be explained on the basis of structural affinities or metabolic conversion in the skin [16]. Further, clinical experiments in selected patients with contact allergy to *para*-group haptens have shown that patch test reactivity to oxidizable aromatic haptens depends on the amount of freshly reduced substance, the rate of oxidation on the skin, and, therefore, the quantity of reactive intermediates, such as quinones [17]. This cross-reactivity pattern may explain the difficulty in finding the relevance of some PPD positives. Immediate-type hypersensitivity to PPD, with urticarial reactions, have been reported [18, 19], including anaphylaxis. PPD base 1% pet. was replaced by PPD dihydrochloride 0.5% pet. in the standard series in 1984. There was a general impression that this led to fewer positives. A multicenter trial showed that the dihydrochloride missed some true positives, and so, it was replaced in 1988 by PPD free base 1% pet. [20]. The TRUE Test contains 90 µg/cm².

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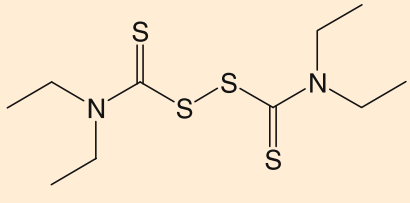
29.17 Thiuram Mix

The thiuram mix used in the standard series contains the following four compounds, each at a dilution of 0.25%. The concentration in the TRUE Test is 25 µg/cm²:

- Tetraethylthiuram disulfide (TETD, disulfiram)
- Tetramethylthiuram disulfide (TMTD)
- Tetramethylthiuram monosulfide (TMTM)
- Dipentamethylenethiuram disulfide (PTD)



Scheme 7. TETD

These chemicals are accelerating agents used in the vulcanization of rubber. They increase the rate of cross-linking by sulfur between the hydrocarbon chains of the uncured rubber and may also donate some sulfur to the reaction. In the fully cured product, unreacted accelerators remain. Over time, some of these may migrate onto the surface of the finished article, together with other rubber chemicals. By thorough washing with hot water of thin rubber items, such as latex-dipped gloves or condoms, it is possible to leach out most of these thiuram residues. Some hypoallergenic rubber articles are accelerated by thiurams, but have been treated by washing as described.

The use of thiurams is ubiquitous in the rubber industry. The compounds are encountered in rubbers for both industrial and domestic use. Different manufacturers have preferences for the particular thiurams that they use for particular applications. This fact may explain geographical variations in the incidence of sensitivity to components of the mix [1]. Gloves are the most common cause of rubber dermatitis, and the allergen is usually a thiuram [2, 3]. Rubber glove dermatitis is important in the healthcare setting [4], where an increase in thiuram allergy in healthcare workers with hand dermatitis has been reported [5]. Release of thiuram from rubber gloves into synthetic sweat may vary between brands [6]. Thiuram sensitivity is more common in women than in men. Foot dermatitis, particularly in children, may be caused by the rubber in shoes [7]. Construction workers also constitute a risk group regarding the development of rubber allergy due to frequent use of gloves and boots [8].

An allergic contact dermatitis from a thiuram in rubber often has no clear clinical pattern, and, in a glove dermatitis, the classical distribution of the eczematous reaction may not be present. This classical pattern consists of a diffuse eczema over the back of the hands and a band of eczema to the mid-forearm at the level of the cuff of the glove. Rubber sensitivity is often clinically significant for eczema.

In individuals who are sensitive to thiurams, the use of vinyl gloves, shoes with leather or polyurethane soles, and clothing elasticated with Lycra (a polyurethane elastomer) may be required where indicated to reduce personal exposure to the allergens.

Thiurams have found wide use as fungicides, particularly for agricultural purposes, but also for such applications in wallpaper adhesives and paints. They have also been used in animal repellents. TETD has been used in scabicidal soap. TETD, when administered systemically, causes inhibition of the enzyme aldehyde dehydrogenase. On taking an alcoholic drink, there is a build-up of acetaldehyde, which

causes skin irritation, erythema, and urticaria. In the form of Antabuse, TETD is used to treat alcohol dependence. Topical exposure to TETM and oral intake of alcohol has caused a similar toxic reaction, as has the taking of Antabuse and topical exposure to alcohol in toiletries [9–12]. TETD has been used to treat vesicular hand eczema in nickel-sensitive individuals [13]. A widespread eczematous reaction may develop after systemic administration of TETD to previously sensitized individuals [14, 15].

The carbamates are no longer included in the standard series of contact allergens [16, 17]. It has been shown that the majority of individuals who gave an allergic reaction to carbamix (diphenylguanidine, zinc dibutyl dithiocarbamate, zinc diethyl dithiocarbamate) also reacted to the thiuram mix. The thiuram mix is, therefore, a good detector of rubber sensitivity to this group of rubber chemicals, to which they are chemically similar – although a concomitant sensitization cannot always be excluded, since rubber gloves usually contain more than one accelerator [17]. However, a more extensive series of rubber components may be useful in selected risk groups of dermatitis patients with significant exposure to rubber in an industrial setting [18].

Both thiuram mix and the carbamates may cause false-positive patch test results [3, 19]. The carbamate mix produced false-positive irritant reactions, which were frequently misinterpreted.

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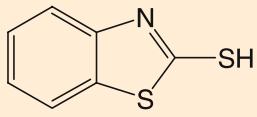
29.18 Mercapto Mix and Mercaptobenzothiazole

The mercapto mix contains the following four compounds, each at a concentration of 0.5% pet.:

- 2-mercaptobenzothiazole (MBT)
- *N*-cyclohexyl-2-benzothiazole sulfenamide (CBS)
- 2,2′-dibenzothiazyl disulfide (MBTS)
- Morpholinyl mercaptobenzothiazole [2-(morpholinothio) benzothiazole, *N*-oxydiethylene benzothiazole sulfenamide, MBS, MMBT]



Scheme 8. MBT

Mercaptobenzothiazole is tested alone at a concentration of 2% pet. The TRUE Test includes MBT 75 µg/cm² and MBS, MBTS, and CBS (1:1:1) 75 µg/cm² in two separate patches. These chemicals

are present in many rubbers, to which they are added as accelerators before vulcanization takes place (see Sect. 29.17 on Thiuram Mix), and, like thiurams, are ubiquitous in rubber products. The majority of individuals who react to the mix react to MBT if tested to the individual components of the mix, and it is, therefore, not possible to identify the primary allergen. Fregert [1] observed that benzene with a thiazole ring and a thiol group in the 2 position was required for cross-sensitization to occur.

According to Cronin [2], gloves or shoes have probably sensitized women who react to MBT, but, in men, the sensitization is mainly from footwear, in which MBT is one of the most important allergens [3]. Among the numerous other sources of contact with rubbers containing MBT are rubber handles, masks, elastic bands, tubing, elasticated garments, artificial limbs [4], and even cosmetic sponges [5]. MBT may be present in a variety of nonrubber products, including cutting oils, greases, coolants, antifreezes, fungicides, adhesives, and veterinary medicaments [6].

As well as the mercapto mix, MBT is included on the standard series at 2% pet. The mix failed to detect 30% of patients who were MBT-allergic when compared to simultaneous testing with 1% MBT, and 12 of 24 individuals who reacted to 2% MBT did not react to the mix [7].

The mercapto mix used in North America does not contain MBT, which is tested separately at 1% pet., the concentration of the remaining three allergens being 0.33%. On reviewing the sensitivity of patch test material, the German Contact Dermatitis Research Group (DKG) has recommended testing with the components of the mercapto mix when there is a reaction to either the mix or MBT itself [8]. Analysis of the stability of the mercaptobenzothiazole compounds has shown that the so-called cross-sensitivity reported for this group may be the result of chemical interaction resulting in one main hapten in the presence of reducing sulfhydryl compounds [9].

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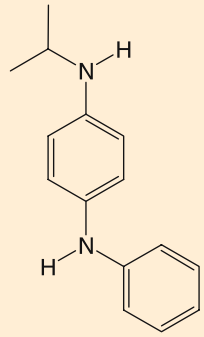
29.19 N-Isopropyl-N′-phenyl-p-phenylenediamine (IPPD)

N-Isopropyl-*N*′-phenyl-*p*-phenylenediamine (IPPD) 0.1% pet. replaced, in the standard series, the PPD–black-rubber mix, which contained the following three compounds in pet.:

- *N*-Isopropyl-*N*′-phenyl-*p*-phenylenediamine (IPPD), phenylisopropyl-p-phenylenediamine, 4-isopropylamino-diphenylamine: 0.1%
- *N*-phenyl-*N*′-cyclohexyl-*p*-phenylenediamine (CPPD): 0.25%
- *N*,*N*′-diphenyl-*p*-phenylenediamine (DPPD): 0.25%



Scheme 9. IPPD

Although IPPD is the most important allergen in the PPD–black-rubber mix, by testing only with IPPD in the standard series, approximately 10% of allergy to these industrial rubber chemicals may escape detection [1]. The TRUE Test includes IPPD, CPPD, and DPPD (2:5:5) 75 μg/cm². With time, vulcanized rubber gradually reacts with atmospheric oxygen and ozone to crack and crumble, a process known as perishing. To reduce this effect, antioxidants and antiozonants may be added before vulcanization, particularly to those rubbers intended for heavy and stressful uses, such as in tires and industri-

al applications. A number of antiozonant types are available, but those based on derivatives of *p*-phenylenediamine (PPD derivatives, staining antidegradants) are in common use [2]. The chemicals used as antiozonants are not related in use to *p*-phenylenediamine, which is a hair dye. IPPD was established as a contact allergen in heavy-duty rubber goods when Bieber and Foussereau [3] reported nine cases, including four men who had occupational contact with tires.

Manufacturers of rubber chemicals have attempted to produce an antiozonant with the desired technical properties of IPPD, but having a reduced potential for inducing sensitization. A substitute that has been proposed for IPPD is *N*-(1,3-dimethylbutyl)-*N′*-phenyl-*p*-phenylenediamine (DMPPD), which has been claimed to have a lower potential for inducing cutaneous sensitization and, as a result, it has replaced IPPD and some of its derivatives in many applications. However, in practice, it has been noted that individuals who are allergic to IPPD usually react to DMPPD on patch testing [4]. Herve-Bazin et al. [5] evaluated 42 tire handlers who were IPPD-sensitive and found that all 15 who were also tested to DMPPD reacted to it. Guinea-pig maximization performed independently by this group showed DMPPD to be a more potent allergen than IPPD in this animal model. DMPPD was not present in the standard series mix.

In factories where IPPD continues to be used as an antiozonant, no significant excess of allergic reactions to it was found [6]; this may be related to the considerably improved hygiene in rubber factories and automation in recent years. The hand dermatitis induced by hypersensitivity to PPD-derived antiozonants often has a palmar distribution, because this is the usual area of skin contact with rubbers most likely to contain these agents. Clinically, a PPD-derivative hand dermatitis can look endogenous. The prognosis of such a PPD-derivative hand dermatitis can be adversely affected by allowing chronic exposure to the offending allergen and may cause the dermatitis to persist after avoidance of further contact. IPPD has been shown to be an important occupational allergen for construction workers and farmers [7, 8]. Although PPD-derived antiozonants are commonly present in rubbers for heavy-duty applications, they may also be present in other rubbers. Examples of these include squash balls, scuba masks [9], motorcycle handles [10], boots [11, 12], watch straps [13], rubber bracelets [14], eyelash curlers [15], spectacle chains [16], and orthopedic bandages [17]. A purpuric contact dermatitis has been described in some individuals sensitive to IPPD. The dermatitis was summarized by Fisher [18] as being pruritic, petechial, and purpuric. The reaction is usually localized to the area of skin contact, but may also be widespread. Purpuric patch tests to IPPD have been reported. A lichenoid contact dermatitis from IPPD has been observed [19], although the histological features of the reaction were those of a lichenified dermatitis.

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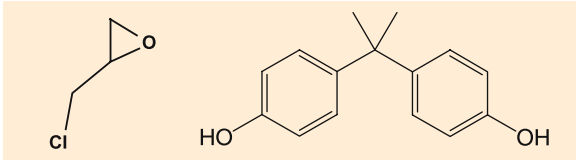
29.20 Epoxy Resin

Some 95% of all epoxy resins consist of a glycidyl ether group formed by reaction of bisphenol A with epichlorohydrin.



Scheme 10. Bisphenol A, epichlorohydrin polymer

Theoretically, there are many different chemical compositions that can be used to make an epoxy resin. Until recently, these have not been important, but they are rapidly becoming so as epoxy resins with different properties are being used. Epoxy resins are commonly used in everyday life as adhesives. Along with the resin itself in these compounds, there are fillers, pigments, plasticizers, reactive diluents, and solvents, and these compounds are then mixed with a hardening/curing agent that polymerizes the resin.

Epichlorohydrin/bisphenol A epoxy resin can vary in molecular weight from 340 to much larger polymers, the larger polymers having much less sensitizing capacity [1]. Epoxy resin compounds should, therefore, contain little or no low-molecular-weight epoxy resin.

Epoxy resins are used as adhesives (also in shoes!), in paints requiring hardness and durability, for instance in ships, in electrical insulation, as an additive to cement for quick bonding and strength, as well as in fiberglass (e.g., in boats), and for impregnating carbon fiber cloth [2, 3] used in situations of stress and heat, such as airplanes. They are all potential sources of contact allergy (Fig. 8). Epoxy resin has been reported to be the cause of occupational contact dermatitis in the production of skis [4] and in a windmill factory [5]. An unexpected source of epoxy allergy, epoxy compounds present in an immersion oil, caused a worldwide epidemic among laboratory technicians performing microscopy (see [6] for a review).

Epoxy resin systems are important sensitizers and are often responsible for occupational airborne dermatitis. Vitiligo, both to epoxy resin and reactive diluents, has been reported [7, 8].

In the standard series, it is the epoxy resin of the bisphenol A type that is tested (1% pet). The TRUE Test contains 50 µg/cm². In a recent retrospective study in 26,210 consecutively tested patients [9], the frequency was 1.3%. A negative patch test to epoxy resin does not mean that the patient is not allergic to the epoxy product that they have been using for the

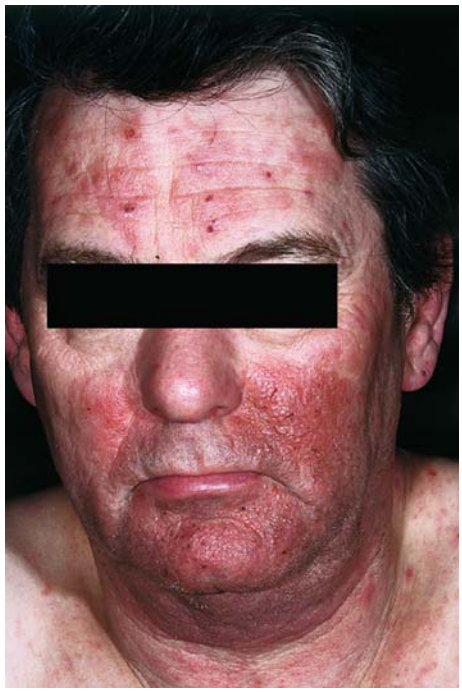


Fig. 8. Airborne contact dermatitis from epoxy resin in a patient who frequently repaired models (airplanes, ships) in his toy shop. He wore glasses due to presbyopia, explaining the sparing of the ocular region (Courtesy of P.J. Frosch)

following reasons: (1) there may be some other epoxy resin in the compound; (2) they may be allergic to some other compound in the resin, for instance, dyes, fillers, plasticizers, etc. (uncommon); or (3) they may be allergic to the hardener. If epoxy allergy is suspected, it is very important to test for other types of epoxy resins, such as bisphenol F-based resins [10, 11], dimethacrylated epoxy resins, which are used extensively in dental composite resins (e.g., [12]), UV-cured inks [13], which have become important allergens, as well as other epoxy systems [14]. Moreover, the specific compounds used by the patients [7] should also be tested, but extreme care must be taken to avoid primary sensitization [6].

Hardeners cannot be contained in the standard series because, although 95% of epoxy resins are one particular chemical, very many different hardeners are used. Both epoxy resins and hardeners can be irritant – also in patch testing – as well as sensitizing, although isolated contact allergy to hardeners without an allergy to epoxy resins is rare. Here too, patch testing with the hardeners to which the patients have been exposed may be advisable in order to detect the allergen [15, 16].

Many patients give a positive patch test to epoxy resin without any obvious contact with uncured epoxy resin. It may be that the source of sensitization is contact with the so-called cured epoxy, which may

contain pockets of uncured resin. Fregert and Trulsson [17, 18] have suggested that chemical tests may be of value in demonstrating uncured resin. There are two tests for epoxy resin, one a simple color reaction, which is not specific for uncured resin, the other thin-layer chromatography, which is specific.

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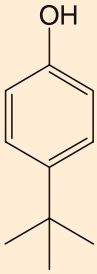
29.21 Para-Tertiary-Butylphenol-Formaldehyde Resin

Para-tertiary-butylphenol-formaldehyde resin (PTBP resin) is made by reacting the substituted phenol p-tert-butylphenol with formaldehyde.



Scheme 11. PTBP

It is a useful adhesive that sticks rapidly, is durable and pliable, and has high strength at raised temperatures. Because of its flexibility, it is used in shoe construction and in leather goods. It is also used in other contact adhesives, such as those used in laminating surfaces and in the rubber industry for bonding rubber to rubber and rubber to metal [1]. These contact adhesives based on PTBP resins are often formulated with neoprene (a synthetic rubber), which provides the initial bonding until the resin cures.

PTBP resins have commonly been reported as causes of both occupational and nonoccupational allergic contact dermatitis. The first occupational cases were described in individuals making or repairing shoes [2], who developed hand eczema, but PTBP resins are also among the most important allergens in those who wear shoes containing this adhesive [2–4].

There are, however, many other occupational sensitizing sources to PTBP resin, such as adhesives for fixing rubber weather-strip car-door seals in place in car assembly plants [5] and finishes for glass wool causing airborne dermatitis [6]. PTBP resin in athletic tape has been reported as an occupational sensitization source in female athletes in Japan [7]. Nonoccupational sources of hypersensitivity to PTBP resin include an adhesive of the pads of a derotation brace and a finishing agent in a raincoat fabric [8], leather watchstraps glued with the adhesive [9], some brands of plastic fingernail adhesive [10], and domestic

PTBP resin adhesives [11]. It may also be present on adhesive labels [12, and even in the adhesive dressing used to secure an intravenous canula [13]. More recent reports concern a wetsuit [14], a knee brace [15], a limb prosthesis [16, 17], and electrodes [18].

The frequency of PTBP-resin sensitivity reported by the Information Network of Departments of Dermatology (IDVK) in Germany was 0.9% in 40,000 patients [19] and 1.3% in a recent study by the EECDRG of 26,210 consecutively tested eczema patients [20].

There are many allergens in PTBP resin, including low-, medium-, and high-molecular-weight fractions, for which the pattern of reactivity differs among patients hypersensitive to the resin [21], but PTBP itself is a rare allergen (as is formaldehyde in the resin). Para-tertiary-butylcatechol (PTBC), a potent sensitizer used in paint manufacture and in the rubber and plastics industries [22], was found to be present in some PTBP-F resins and to cross-react with a strong allergenic monomer present in the resin [23]. This explains the statistically significant overrepresentation of simultaneous patch test reactions to PTBP resin and PTBC in contact dermatitis patients [22].

In a polychloroprene/PTBP resin adhesive that caused an allergic contact dermatitis, the allergens were found to be 2-hydroxy-5-tertiary-butyl benzylalcohol and a condensate of 4-*para*-tertiary-butylphenol molecules joined by methylene bridges [24]. In a case of contact allergy to a phenolic resin used as a tackifier in a marking pen, the patient reacted to PTBP resin in the standard series and to 2-hydroxy-5-tertiary-butyl benzylalcohol and 2,6-bis(hydroxymethyl)-4-tert-butylphenol identified in the phenolic resin [25]. Depigmentation of the skin caused by PTBP and other substituted phenols has been reported to occur in workers manufacturing the chemical when exposure has been excessive. Such depigmentation also occurred in those using PTBP resin adhesives in a car factory, where the problem was probably due to the excess PTBP in the adhesive. It has been pointed out that such depigmentation can occur without any accompanying skin irritation [26, 27]. Exceptionally, noneczematous pigmented [28] and lymphomatoid [29] contact dermatitis have also been described.

The patch test concentration of PTBP resin is 1% pet. It has been pointed out, however, that patch testing with PTBP resin is not sufficient to detect allergy to phenol-formaldehyde resins based on phenols other than para-tertiary butyl phenol [30]. The TRUE Test contains 45 µg/cm².

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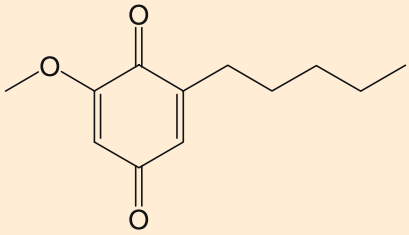
29.22 Primin

Primin or 2-methoxy-6-*n*-pentyl-*p*-benzoquinone is the major allergen in *Primula* dermatitis.



Scheme 12. Primin

Primin is included in the European standard series because it is an important allergen in certain countries, e.g., in Northern Europe. The frequency of positive primin patch tests in European clinics varies from 0.1% to 1.2% of consecutively tested eczema patients. The vast majority of patch test positive patients are women. Florists, nursery workers, and housewives are particularly at risk when exposed to primula plants. Primin sensitization seems to be relatively more common in elderly patients [1], and primin allergy may be difficult to suspect because the patients may not be aware of contact with the plant. It is recommended to show color photos of the plant as a routine procedure in cases where there are positive patch test reactions to primin [2–4].

However, the sensitization rate is so low in some countries, for example, the USA, that it is not incorporated into the local standard series [5].

Primula obconica, which has round leaves covered with fine hairs, is the usual culprit, but other species of *Primula* may cause dermatitis. *Primula auricula*, *P. vulgaris*, and *P. forrestii* have been reported to cause dermatitis [6], and it may be more frequent than previously recorded. On the other hand, primin-free *P. obconica* have been introduced to the European market, and they mimic the allergenic variety in color and appearance [7].

Primin is a powerful sensitizer contained in the fine hairs, and the content varies with the season, hours of sunshine, and the care of the plant [4, 8]; the primin content is highest in warm summer and lowest during winter [9]. Besides primin, also, a potential other allergen is present in primula, i.e., miconidin, which is biogenetically related to primin [9, 10]. Primin may be emitted to the surrounding air from intact plants and plant parts, and may be a source of airborne contact dermatitis [11].

In *Primula* dermatitis, lesions are often arranged in linear streaks and most often appear on exposed skin. The parts most often affected are the eyelids, cheeks, chin, neck, fingers, hands, and arms. Sometimes, severe reactions, such as erythema-multiforme-like lesions [12] and photodermatitis have been observed [13]. Other plants and woods containing quinones may show cross-reactivity with primin [9].

The patch test concentration is 0.01% pet. Testing with synthetic primin is preferable to an extract of the plant for various reasons: standardization, decreased risk of active sensitization, avoidance of irritant or false-positive reactions, and of seasonal variation in the allergenicity of the plant [14, 15]. Testing may invoke flare reactions. However, we should take into account that testing with primin alone might miss allergy to the plant itself [4, 16].

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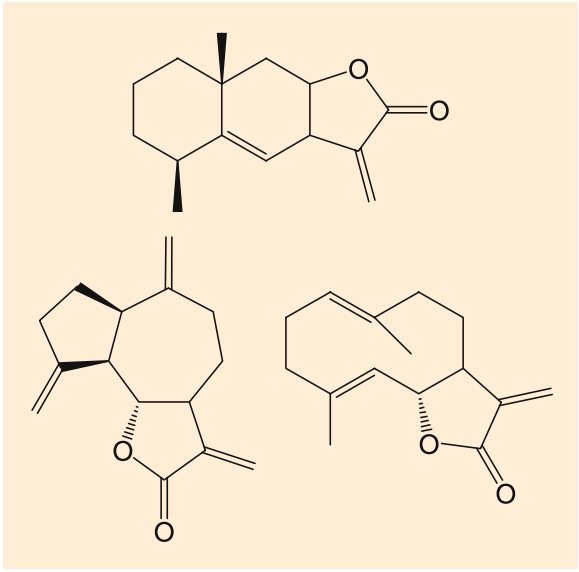
29.23 Sesquiterpene Lactone Mix (SL Mix)

The SL mix contains the following three sesquiterpene lactones in pet.:

- Alantolactone 0.033%
- Dehydrocostus lactone 0.033%
- Costunolide 0.033%



Scheme 13. Alantolactone. dehydrocostus lactone and costunolide

The SL mix was developed by Ducombs et al. [1]. These sesquiterpene lactones are contact allergens present in Compositae plants (syn. Asteraceae), which constitute one of the largest plant families in the world. More than 200 of the ~25,000 known Compositae species have caused allergic contact dermatitis. The Compositae family includes many of the common weeds, milfoil, yarrow (*Achillea millefolium* L.), tansy (*Tanacetum vulgare* L.), mugwort (*Artemisia vulgaris* L.), wild chamomile [*Chamomilla recutita* (L.) Rauschert], and feverfew [*Tanacetum parthenium* (L.) Schultz-Bip.] – and many cultivated garden flowers, such as chrysanthemum (*Chrysanthemum indicum* L.), marguerite, ox-eye daisy (*Leucanthemum vulgare* L.), marigold (*Calendula officinalis* L.), goldenrod (*Solidago virgaurea* L.), African marigolds (*Tagetes*), and sunflowers (*Helianthus annuus* L.). The edible types of Compositae include ordinary lettuce [2, 3], endive, and artichoke [4]. Cross-sensitivity between Compositae plants is common [4–6]. The SL mix detected about 65% of Compositae-allergic patients in a Danish investigation comprising of more than 4,000 consecutively tested eczema patients [7]. The remaining cases were diagnosed by testing with the Hausen Compositae mix and other Compositae extracts [8].

The Compositae are the most frequent cause of occupational allergic plant dermatitis in gardeners and greenhouse workers in Denmark, and important sensitizers are chrysanthemums, marguerite, daisies, and lettuce [9]. Besides localized eczema, most often hand eczema, caused by direct contact between the skin and the plants, the Compositae may give rise to

a more widespread dermatitis localized to light- and air-exposed skin areas causing suspicion towards an airborne contact dermatitis [10, 11]. However, that it is an airborne allergic contact dermatitis to sesquiterpene lactones remains to be proven [12]. So far, only emission of terpenes from feverfew plants have been documented, and these terpenes have only elicited few positive reactions in Compositae-sensitive patients [13]. Seasonal variation in the severity of the eczema with summer exacerbation is frequently seen [14, 15]. A number of patients have had localized eczema, particular hand eczema, for a number of years when it suddenly turns into a widespread dermatitis one summer [11]. The duration of exposure as well as a history of childhood eczema or hay fever, seem to be significant risk factors for the development of Compositae-related symptoms [9]. Compositae sensitivity may also predispose to photosensitivity [16]. Many Compositae-sensitive patients have multiple contact allergies. The high prevalence of other contact allergies in Compositae gardeners may reflect the impact of strongly allergenic sesquiterpene lactones [17]. They may also be responsible for severe systemically induced skin eruptions [18]. The allergens are present in all parts of the plant and also in dead plant material and dust. The SL mix reveals about 60% to 70% of all cases of Compositae contact allergy and it is important to supplement testing with the plants in suspicion and ether extracts of Compositae plants, such as the Hausen Compositae mix [8, 9, 19]. Paulsen et al. [9] found that, among gardeners, the Compositae extract mix detected twice as many of the sensitized as the SL mix. However, the Compositae mix seems to be more irritating and the overall detection rate with the two mixes was still not higher than 76% in the group of gardeners. The detection rate of both mixes was raised to 93% in the series of consecutive eczema patients [7]. It has been claimed that the Compositae mix 6% pet. may cause patch test sensitization [20, 21], and a reduced concentration of extracts in the mix has been proposed. However, this also reduced the sensitivity of the mix [22]. Late-appearing reactivation patch reaction to Compositae allergens is also documented in previously sensitized patients, and this phenomenon should be differentiated from patch test sensitization [7]. The mixes have their limitations and the importance of aimed patch testing in persons with specific exposures is emphasized. The addition of parthenolide, the main allergen in feverfew, to the existing SL mix did not turn out to be of great value, although it was a fairly good screen on its own, detecting 75% of the cases positive to the SL mix [23]. Therefore, the creation of another sesquiterpene lactone mix might be appropriate. Further, it is important to emphasize that the content of allergenic sesquiterpene lactones in plants may vary from season to season and from area to area. A European multicenter patch test study with the SL mix in 11 clinics showed 1% of patients as positive in more than 10,000 consecutively tested patients, three-quarters of which were of current or of old relevance. The prevalence varied between 0.1% and 2.7% in different centers; it was highest in areas with pot flower and cut plant industries. More than one-third were positive to perfume and/or colophony, possibly reflecting cross reactivity [24]. The SL mix is non-sensitizing and non-irritating.

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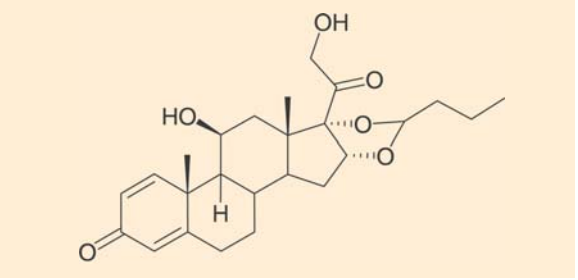
29.24 Budesonide

The corticoid budesonide is used topically (0.025% in a cream or ointment) in the treatment of various skin disorders, but is more often used by inhalation in the form of a metered aerosol, a dry powder inhaler, or a nebulized solution for the management of asthma, and as a nasal spray for the prophylaxis and treatment of allergic rhinitis [1]. It is also used in rectal preparations to treat inflammatory bowel diseases.



Scheme 14. Budesonide

Beginning in 1986, several publications appeared reporting budesonide-containing aerosols and sprays as the cause of eczematous eruptions, sometimes associated with endonasal complaints, with, in a few cases, indications of both type I and IV allergic mechanisms (for a review, see [2]). Although reactions to inhalation products do occur [3], sometimes, reactivating previous contact dermatitis lesions [4, 5], they seem to be infrequent relative to the large scale of their use [6], and, in most cases, they are secondary to sensitization via skin application of budesonide or a cross-reacting corticosteroid. Indeed, budesonide has been recognized as an important screening agent for the detection of contact allergy of corticosteroids of group B (acetonides) and of group D2 (the labile prodrug esters) [7]. Budesonide allergy has been detected in 1.0% to 1.5% of consecutively tested dermatitis patients [8].

As most contact allergies are missed if corticosteroids are not routinely tested, it has been recommended [9] that budesonide (0.01% pet.) be added to the standard series, although a uniform agreement on the patch test concentration has not been achieved with some authors favoring lower [10, 11] and others favoring higher [12, 13] patch test concentrations. With respect to the vehicle, several studies have shown equivalent patch test results when testing with budesonide in ethanol or petrolatum [13]. With respect to the reliability and adverse effects of the patch test, irritant reactions are not common. Reactions such as blanching, reactive vasodilation, and "edge" effects often occur and are the result of the pharmacological characteristics of the corticosteroid, which also make patch test readings necessary not only on D3 or D4 but also on D7 [9].

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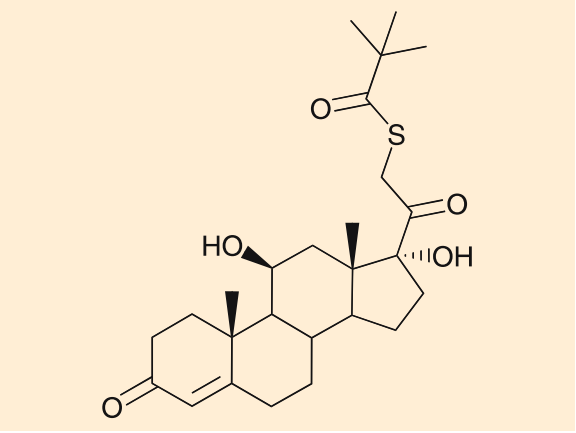
29.25 Tixocortol Pivalate

The corticoid tixocortol pivalate is used in buccal, nasal, throat, and rectal preparations [1], but not for the treatment of skin diseases.



Scheme 15. Tixocortol pivalate

It is, however, a good marker for detecting contact allergy to group A corticosteroids (e.g., hydrocortisone and derivatives) [2–4], which has been confirmed in guinea pig maximization tests [5]. Primary sensitization due to mucosal preparations, however, are clearly not excluded. Tixocortol pivalate allergy has been detected in 0.9% to 4.4% of consecutive dermatitis patients [6–8].

With respect to the vehicle, equivalent patch test results were found for both ethanol and petrolatum [9]. Based on a study performed by the EECDRG [8], testing with 0.1% pet. has been recommended. However, in selected cases in which tixocortol pivalate is strongly suspected and testing with the routine concentration is negative, additional testing with 1.0% pet. should be performed [10], which is the concentration is preferred by some other authors [11, 12]. Tixocortol pivalate does not produce irritant patch test reactions, and, the same as for budesonide, late readings should be performed.

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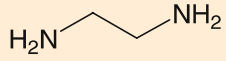
29.26 Ethylenediamine Dihydrochloride

(No longer included in standard series)



Scheme 16. Ethylenediamine

When patch testing, 1% pet. is the standard test concentration. The TRUE test contains 50 µg/cm². Allergy to this compound is commonest by far in the United States and Belgium where Mycolog cream, a preparation containing neomycin, nystatin, and triamcinolone, is widely used. A similar preparation is used in Britain – Tri-Adcortyl cream. In these preparations it is used as a stabilizer. The corresponding ointment does not contain it as a stabilizer.

Ethylenediamine has other uses, and dermatitis has been described due to its presence in the following sources – floor polish remover [1], epoxy hardener, and coolant oil [2–4]. Its use has also been described in a number of other industries, rubber, dyes, insecticides, and synthetic waxes. Occupational dermatitis has been reported in nurses and a laboratory technician working with theophylline and aminophylline [5, 6].

There is a potential problem with systemic administration in those sensitized, either with drugs that contain ethylenediamine, for instance aminophylline, or with drugs chemically related to it, including various antihistamines, among which are hydroxyzine hydrochloride and its active metabolite ceterizine, piperazine, and cyclizine [7–10]. Cases have been described with generalized erythroderma in patients who have become allergic to piperazine in local applications, who received piperazine phosphate to treat worms [11]. Patients seldom, if ever, become sensitized through systemic administration and problems only arise in those already sensitized who receive the drugs, and it is surprising how few reactions occur considering the number of patients sensitized. Immediate-type reactions have also been reported [12]. Few patients become sensitized through contact in industry, and ethylenediamine is a rare sensitizer outside the local application that contains it.

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