

European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice

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Summary

The present guideline summarizes all aspects of patch testing for the diagnosis of contact allergy in patients suspected of suffering, or having been suffering, from allergic contact dermatitis or other delayed-type hypersensitivity skin and mucosal conditions. Sections with brief descriptions and discussions of different pertinent topics are followed by a highlighted short practical recommendation. Topics comprise, after an introduction with important definitions, materials, technique, modifications of epicutaneous testing, individual factors influencing the patch test outcome or necessitating special considerations, children, patients with occupational contact dermatitis and drug eruptions as special groups, patch testing of materials brought in by the patient, adverse effects of patch testing, and the final evaluation and patient counselling based on this judgement. Finally, short reference is made to aspects of (continuing) medical education and to electronic collection of data for epidemiological surveillance.

Key words: contact allergy; guideline; patch testing; review.

Overall Objective and Methods

This guideline is intended for dermatologists involved in identifying the responsible contact allergen(s) in patients (including children) in whom allergic contact dermatitis or other types of delayed hypersensitivity reaction are suspected, or to exclude contact allergy. The guideline includes brief information on patch testing materials,

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techniques, test series, readings, final evaluation, individual factors that may influence the outcome of the tests, potential side-effects, and information for patients. Skin testing for immediate-type hypersensitivity, which is important for the diagnosis of other types of contact reaction, is not dealt with in detail in this guideline. For a more detailed presentation of the patch testing technique and related aspects, the reader is referred to current textbooks (e.g. 1–4) and, particularly for aspects of occupational contact dermatitis, to (5).

Process of developing the guideline

In October 2012, the European Society of Contact Dermatitis formed a working party to elaborate an up-to-date patch test guideline. An open call for contributors experienced in the field was made on the web-page of the society, and an international group (see author list) collaborated in the compilation of current information on best practice in diagnostic patch testing. During an initial meeting, topics were defined, and the resulting sections were associated with one to four authors. In a rotating review, the resulting first drafts of the sections were reassigned and reconsidered by a different team of authors. A pre-final agreement on the resulting preliminary draft was achieved during a meeting; this draft was then exposed to the comments of all members of the European Society of Contact Dermatitis (ESCD; www.escd.org). Amendments were accordingly made, provided that (i) the comment was substantiated – if possible, by scientific literature – and (ii) the guideline authors found it acceptable.

Search for evidence and methodology

Care was taken to identify scientific literature pertinent to those aspects, where it was available, by performing searches in MEDLINE™ (PubMed™), Web of Science™, and other bibliographic resources. Where applicable, the search strategy and search results are described in the sections. However, for several topics, no formal studies are available; hence, the statements are based on collective expert judgement and consensus. If, exceptionally, no consensus on a certain topic was achieved, phrasing such as ‘while most experts ... , some advocate ... ’ makes the different alternatives clear.

Definitions

Contact dermatitis is an inflammatory skin reaction caused by direct contact with noxious agents in the environment. The pathomechanism may involve immunological hypersensitivity (allergy) or not (irritant contact dermatitis), or may be mixed.

Contact allergy is an altered immune status of an individual induced by a particular sensitizing substance, a contact allergen. This involves a clinically unapparent sensitization phase, also called the *induction phase*, resulting in the expansion of a clone of allergen-specific T cells. At this point, an individual is immunologically sensitized. Upon re-exposure with the same, or a cross-reacting, allergen/antigen, the *elicitation phase* is triggered, leading to specific T cell activation with clinically visible disease. In this guideline, the term contact allergy is used synonymously with *contact sensitivity*. The substances inducing contact allergy are reactive chemicals, usually with a molecular weight of <500 Da, but exceptionally in the range of 500–1000 Da. These substances are generally not antigenic by themselves, but only after protein binding, and are also referred to as *haptens*. In this guideline, the term *allergen* will be used to include haptens.

An individual in whom contact allergy has been induced will develop a secondary immune response if there is skin exposure to the same (or cross-reacting) allergen. This process is called *elicitation*, and will manifest as *allergic contact dermatitis* (type IV hypersensitivity). The typical morphology of allergic contact dermatitis, also termed allergic contact eczema, is erythema, (papular) infiltration, oedema, and possibly vesicles. At a later stage, if exposure to the allergen continues, the dermatitis may become chronic and present with scaling, fissures, and lichenification.

A special case is allergic (‘immunological’) contact urticaria/protein contact dermatitis, where high molecular weight allergens such as peptides induce a specific IgE response (type I hypersensitivity), which may result in both urticarial and eczematous lesions.

Cross-sensitivity occurs when a person sensitized to a particular allergen also reacts to another, structurally related allergen to which he or she has not been previously sensitized (6). The allergens involved are usually chemically similar, sometimes after oxidation or metabolic transformation in the skin.

Indications

Patch testing is the standard procedure used to diagnose contact allergy resulting from type IV hypersensitivity. This *in vivo* test aims to reproduce the elicitation phase of the reaction to a contact allergen, that is, allergic contact dermatitis. The patch test is performed by applying allergens under occlusion on the skin under standardized conditions. Other types of epicutaneous test, including those used in the investigation of cutaneous type I hypersensitivity reactions, will be briefly mentioned.

Diagnostic patch testing is an investigation undertaken on patients with a history of dermatitis (eczema) in

order to determine whether they have a contact allergy and then evaluate the relation (if any) of the contact allergy to their dermatitis (see section 'Final evaluation: clinical relevance and diagnosis'). Patch testing should be performed in all patients in whom contact allergy is suspected or needs to be excluded, regardless of, for example, age (see section 'Children') or anatomical site of dermatitis. This also includes (i) other conditions that may represent a contact allergic reaction, such as erythema multiforme-like, lichen planus-like, psoriasis (of the hands), or granulomatous or lymphomatoid reactions (7), (ii) worsening of pre-existing dermatitis, such as stasis, atopic or seborrhoeic dermatitis, or discoid (nummular) eczema, (iii) certain drug eruptions (see section 'Patch testing in drug eruptions') (8), (iv) mucous membrane reactions [conjunctivitis, stomatitis (9), or vulvitis], or (v) implants (10, 11).

There are very rare reports that some biological materials, haptens such as ammonium persulfate (12) or drugs have been associated with anaphylactic reactions when patch tested in patients with strong immediate-type hypersensitivity. These patients should undergo investigations for type I hypersensitivity. It is at the discretion of the physician to include these substances in the patch tests of these individuals after considering the risks and benefit for the patient.

Immediate testing, namely prick testing or prick–prick testing, can be performed, in addition to patch testing, in immediate contact reactions, namely in protein contact dermatitis or contact urticaria and also in (hand) dermatitis, where immediate reactions can contribute to the lesions.

Recommendation:

Patch testing should be considered in patients with:

- Suspected contact dermatitis, acute or chronic, including dermatitis related to occupational exposures
- Other types of (chronic) dermatitis (eczema) not improving with treatment
- Skin and mucous membrane eruptions (including delayed-type drug eruptions) in which delayed-type hypersensitivity is suspected

Postponing a patch test

Postponing of patch test investigations should be considered in patients with the following conditions:

- Severe or generalized active dermatitis.

- Systemic immunosuppressive treatment in relevant doses where a pause is foreseen or possible.
- Dermatitis on the upper back or other sites chosen for the application of patch tests.
- Test sites recently treated with topical corticosteroids, because these suppress, at least to some extent, the elicitation reaction (13); according to current practice, 7 days are considered adequate (14), although there are no investigations concerning this.
- Recent ultraviolet (UV) exposure of the test area.

These and several other factors that may affect the outcome of patch testing are reviewed in section 'Influence of individual factors'.

Patch testing during pregnancy or lactation is not known to be harmful, but most dermatologists postpone testing during pregnancy and lactation as a general precaution.

Information for patients prior to patch testing

Patients should be informed about the purpose and benefits of patch testing, how patch testing is undertaken, and symptoms that may occur (see section 'Potential adverse effects of patch testing'). It is necessary to give information about avoidance of showers, wetting the test sites, UV irradiation and excessive exercise, and loosening of patches, and about symptoms such as itching and severe or late reactions. Patients should be given written information about the patch test procedure.

There are various national regulations concerning patch testing. Dermatologists should be aware of the national legal frameworks within their respective countries.

Materials

Search strategy

Contact dermatitis textbooks and a literature search in July 2014 using combinations of the search terms 'patch testing, contact dermatitis, contact allergy and technique' revealed numerous publications. A large number of those dealing with technical aspects (test systems, test materials, allergens, vehicles, concentration, and stability) were reviewed, and recent references were selected. The number of up-to-date controlled clinical experiments is limited, and many of the current standards in clinical use are based on old studies, which do not provide a high level of evidence.

Different systems are used to occlude and apply the allergens. In one commonly used system, the chambers

are supplied in strips of 5 or 10, and consist of small aluminium disks mounted on non-occlusive tape that has been chosen for its adhesive properties and hypoallergenic acrylic-based adhesive (15). Other systems consist of square plastic chambers on hypoallergenic tape. The small depressions that the chambers leave on the skin when the test is removed allow for the assessment of correct application and tight fit of patches.

Pre-packaged tests are also available, but only for a limited number of allergens, currently not fully covering the European baseline series. These pre-packaged tests contain homogeneously dispersed allergens in standardized concentrations in a hydrophilic gel base (hydroxypropylcellulose or povidone) mounted on an acrylic-based adhesive tape. There is no documentation proving that one test system is generally superior to the others. The choice of patch test system in a clinic is based on tradition and experience.

Information on patch test material producers can be found on the ESCD website (www.escd.org). Commercially available patch test allergens and systems should be of pharmaceutical quality. Some products are registered as drugs in some countries.

Selection of patch test materials

The history and examination of a patient offers clues regarding the possible sensitizers, and should guide the choice of patch test materials. Unfortunately, it is not sufficient to patch test with only suspected sensitizers, as unsuspected ones frequently turn out to be relevant. An experienced dermatologist will be able to correctly predict the clinically relevant contact allergens in some patients, on the basis of the history and the clinical appearance of the dermatitis. This prediction 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%) (16, 17).

This failure to predict correctly is the reason why a 'baseline series' of test allergens should be applied in the evaluation of all patients suspected of having contact dermatitis. An allergen is suggested for inclusion in the baseline series when routine ('consecutive') patch testing of patients with suspected contact dermatitis results in a proportion of contact allergy to the substance exceeding 0.5–1.0% (18, 19), and when this particular allergen is ubiquitous and/or clinically highly relevant. In particular cases (e.g. parabens and plants), a contact allergy rate much below 0.5–1% can also justify routine testing.

A number of allergens, mainly fragrances and rubber compounds, are compiled into mixes. The basic concept of using mixes of allergens instead of single allergens is

to save space. However, a positive reaction to some of the mixes, such as the fragrance mixes, should normally prompt a subsequent breakdown test of its single ingredients to provide specific information to the patient. In addition, when allergy is suspected, a mix should not be relied on to detect the allergy, and the individual components and additional allergens should also be tested. The mixes are frequently a compromise, in an attempt to balance sensitivity for detecting contact allergy to every single ingredient of the mix by including them in sufficient concentrations against the risk of irritation from the combination of several constituents in one test preparation. Consequently, false-negative reactions occur.

The European baseline series, as currently recommended by the European Environmental Contact Dermatitis Research Group (EECDRG), is shown Table 1 (20). New allergens emerge, and some are phased out. In most cases, application of just the baseline series is insufficient, and additional patch test substances or series, tailored to the history and exposures of the patient, must be considered.

The European baseline series is dynamic and subject to continual evaluation and occasional modification, depending on population exposures and the prevalence of contact allergy. It can be complemented to include allergens of local importance to specific dermatology departments.

Vehicles and concentrations

For the most part, allergens are dispersed in petrolatum (white soft paraffin), and are supplied in labelled syringes with the name and concentration of the substance on the label, together with an expiry date. Petrolatum (pet.) is inexpensive, practical, gives good occlusion, and can be mixed thoroughly with most substances. However, the choice of vehicle is important, and some substances are better tested in solution in, for example, water or ethanol. Test concentrations have been selected on the basis of experience to elicit an allergic response in those previously sensitized and to cause no positive reaction in those who are not allergic. For these allergens, patch test sensitization ('active sensitization') is considered to be extremely rare (22). For convenience in clinical practice and standardization, groups of test allergens are arranged into test series.

Several hundred test allergens are available from suppliers, and others can be prepared from the patient's own materials on the basis of exposure evaluation (23, 24) (see section 'Patch testing of patients' own materials').

It is sometimes necessary to obtain constituent ingredients directly from the product manufacturer in order

Table 1. The current European baseline patch test series. For mixes, the individual components of the mix and their concentration in the mix are given below each mix.

Allergen	Concentration (%)	mg/cm ²	Vehicle
Potassium dichromate	0.5	0.2	pet.
<i>p</i> -Phenylenediamine (free base)	1.0	0.4	pet.
Thiuram mix	1.0	0.4	pet.
Tetramethylthiuram monosulfide (TMTM)	0.25	0.1	–
Tetramethylthiuram disulfide (TMTD)	0.25	0.1	–
Tetraethylthiuram disulfide (TETD)	0.25	0.1	–
Dipentamethylenethiuram disulfide (PTD)	0.25	0.1	–
Neomycin sulfate	20	8.0	pet.
Cobalt chloride	1.0	0.4	pet.
Benzocaine	5.0	2.0	pet.
Nickel sulfate	5.0	2.0	pet.
Clioquinol	5.0	2.0	pet.
Colophony (colophonium)	20	8.0	pet.
Paraben mix	16	6.4	pet.
Methylparaben	4	1.6	–
Ethylparaben	4	1.6	–
Propylparaben	4	1.6	–
Butylparaben	4	1.6	–
<i>N</i> -isopropyl- <i>N'</i> -phenyl- <i>p</i> -phenylenediamine	0.1	0.04	pet.
Lanolin alcohols (wool alcohols)	30	12.0	pet.
Mercapto mix	2.0	0.8	pet.
<i>N</i> -cyclohexylbenzothiazyl sulfenamide	0.5	0.2	–
Mercaptobenzothiazole	0.5	0.2	–
Dibenzothiazyl disulfide	0.5	0.2	–
Morpholinyl mercaptobenzothiazole	0.5	0.2	–
Epoxy resin	1.0	0.4	pet.
<i>Myroxylon pereirae</i> (balsam of Peru)	25	10	pet.
<i>p</i> -tert-Butylphenol formaldehyde resin	1.0	0.4	pet.
Mercaptobenzothiazole	2.0	0.8	pet.
Formaldehyde	2.0	0.6	aq.
Fragrance mix I	8.0	3.2	pet.
Cinnamyl alcohol	1.0	0.4	–
Cinnamal	1.0	0.4	–
Hydroxycitronellal	1.0	0.4	–
Amyl cinnamal	1.0	0.4	–
Geraniol	1.0	0.4	–
Eugenol	1.0	0.4	–
Isoeugenol	1.0	0.4	–
<i>Evernia prunastri</i> extract (Oak moss absolute)	1.0	0.4	–
Sesquiterpene lactone mix	0.1	0.04	pet.
Alantolactone	0.033	0.013	–
Dehydrocostus lactone and costunolide	0.067	0.027	–
Quaternium-15	1.0	0.4	pet.
Primin	0.01	0.004	pet.
Methylchloroisothiazolinone/methylisothiazolinone, 3:1	0.02	0.006	aq.
Budesonide	0.01	0.004	pet.
Tixocortol pivalate	0.1	0.04	pet.
Methyldibromo glutaronitrile	0.5	0.2	pet.
Fragrance mix II	14	5.6	pet.
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	2.5	1.0	–
Citral	1.0	0.4	–
Farnesol	2.5	1.0	–
Coumarin	2.5	1.0	–
Citronellol	0.5	0.2	–
Hexyl cinnamal	5.0	2.0	–
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0	2.0	pet.

Table 1. Continued

Allergen	Concentration (%)	mg/cm ²	Vehicle
Methylisothiazolinone	0.2	0.06	Aq.
Textile dye mix *	6.6	–	Pet.
Disperse Blue 35	1.0	0.4	–
Disperse Yellow 3	1.0	0.4	–
Disperse Orange 1	1.0	0.4	–
Disperse Orange 3	1.0	0.4	–
Disperse Red 1	1.0	0.4	–
Disperse Red 17	1.0	0.4	–
Disperse Blue 106	0.3	0.12	–
Disperse Blue 124	0.3	0.12	–

The patch test concentrations are shown for a manually loaded chamber system. Note that the composition is periodically adapted; the present list is taken from (20). Single components of the mixes are also given.

*Recently added; see (21).

to identify the causative allergen, if it is not covered by the set of available commercial allergens. In this way, new allergens may be identified for further evaluation. Constituent ingredients can be made up for patch testing, but care should be taken to use the appropriate concentration and vehicle (25). Moreover, issues regarding purity, original concentration and reliability of materials and information obtained from the manufacturer should prompt extra caution.

Storage and stability

Patch test materials should be stored at 4°C and protected from light. Some contact allergens with high vapour pressure, such as some fragrance chemicals, acrylates, and isocyanates, are unstable and require more frequent renewal and strict storage conditions (26–28). For some of the products (or patch test substances), storage at –18°C is recommended, for example some diisothiocyanates. Glutaraldehyde in pet. and formaldehyde in aqueous solution are also subject to instability and deterioration. It is important to respect expiry dates (29, 30).

Recommendation:

Patch test materials should be stored at 4°C, protected from light. Special characteristics of the patch test allergens (volatility and stability) must be considered.

Technique

Dosing of chambers

The critical factor for sensitization and elicitation of contact allergy is the 'dose per unit area' (31). Therefore,

it is important for the dose of allergen to be standardized for each type of test chamber (32–34). For example, for 8 mm Finn Chambers®, 20 mg of each allergen in pet. (~40 mg/cm²) is pipetted from the syringe into the chamber such that it fills the well of the disk but does not extrude when the patch is applied to the back (35). For aqueous-based allergens, small filter papers are placed in the well, and these will hold ~15 µl of liquid. The dosing of liquids by use of a micropipette is strongly recommended (36). Besides the micropipette technique, there are two other major ways to apply a test solution onto a chamber. In the drop technique, a drop of solution is placed on the chamber by squeezing the plastic bottle containing the test solution. In the drop and wipe technique, a drop of test solution is placed on the filter paper of a test chamber by squeezing the container. Before testing, the excess solution is wiped off with a soft tissue. A study comparing the three techniques showed that the micropipette technique had the best accuracy and precision (36). If the same amount/volume of a test preparation is applied all the time with the same test technique (same area of skin) and occlusion time, it is appropriate to use concentration as a dose parameter. For most allergens, pet. is an appropriate vehicle, as it is stable and seems to prevent/diminish degradation, oxidization, and polymerization, but not evaporation, of the incorporated allergen (37–39). Dosing of pet.-based allergens needs training and experience to keep the variation within a limited range (40, 41). When other test chambers are used, the same dose/unit area skin can be used.

Generally, pet.-based patch test substances should be loaded into the chambers shortly before application of the patches (no longer than a few hours), liquids and some volatile pet.-based substances (e.g. acrylates) at the time of application.

Recommendation:

The optimal doses of pet. and liquid preparations, respectively, in different, commonly used chambers are as follows (42):

	Liquid		Preparation in pet.	
	μl	$\mu\text{l}/\text{cm}^2$	mg	mg/cm^2
Finn Chamber [®] (8 mm in diameter; area 0.5 cm ²)	15	30	20	40
Van der Bend [™] (area 0.64 cm ²)	20	30	25	40
IQ Ultra [™] (area 0.68 cm ²)	20	29	25	36

It is strongly recommended to dose liquids with a micropipette. Doses for all other chamber types can be calculated.

Anatomical site of patch test application

For practical reasons, the upper back is chosen. The back offers a flat surface for good occlusion, and usually a large enough surface for application of the necessary number of patch test substances. It is less often affected by skin diseases, is not regularly exposed to sun, and is less prone to scratching. Sometimes, the outer surface of the upper arms or thighs can also be used if the surface on the back of the patients is insufficient or cannot be used for other reasons, for example scars, acne, or large tattoos.

There are known variations in reactivity of the skin between different anatomical regions. For example, the forearm is less sensitive than the back to elicitation of contact allergy to nickel (43). When comparing the sensitivities of various skin sites in the repeated open application test (ROAT), Hannuksela (44) found that the lower arm was less sensitive than the upper arm, and that the skin of the back was most reactive (see section 'Other techniques'). Some studies showed higher reactivity of the upper back [especially when laser Doppler flowmetry was used for evaluation (45)] than of the lower back, but later studies (43, 46) have not confirmed such a difference. For comparability and standardization, it is important to always use (if possible) the same anatomical site.

Recommendation:

The upper back is the preferred site for patch testing. The outer surface of the upper arms or thighs can be

used if the back is not suitable for patch testing, or is fully used already.

Occlusion time

Occlusion time is the duration of application of the patch test allergen to the skin. Exposure of the outer surface of the horny layer to the haptens is obtained with an occlusive patch test chamber system. Penetration is forced by occlusion; the quantitative aspects of this process are not fully known. Penetration of substances and the process of enhanced penetration with the help of occlusion (which, among other factors, increases the hydration of the skin and most likely facilitates the penetration of less lipophilic or mainly hydrophilic substances) vary considerably between different chemical substances. The currently used occlusion time established for patch testing is a practical compromise, which makes it possible to patch test with many different substances at the same time.

It has been shown for nickel that 2 days of occlusion gives a higher frequency of positive reactions than 1 day of occlusion (47). However, it has been also been shown for nickel that shortening the occlusion time can be compensated for by a higher test dose (48). Isaksen et al. (49) compared 5, 24 and 48 hr of occlusion for several dilutions of budesonide in allergic subjects, and found that 48 hr of occlusion gave the most positive responses. In contact allergy studies on dinitrochlorobenzene (50), a longer duration of application at challenge evoked stronger responses because a larger effective dose had reached the skin immune system.

Neither the literature study of Manuskiatti and Maibach (51) nor the data of Brasch et al. (52) showed evidence for a general superiority of 1 day versus 2 days of occlusion. Hence, as no definite conclusion can be drawn from studies of the different methodologies, most handbooks and authors, including the latest recommendation by the ICDRG (53), recommend an occlusion time of 2 days. Longer application periods are not recommended.

In one study, a single case of putative, and no case of confirmed, active sensitization to *p*-phenylenediamine (PPD) was observed after 1 day of application, in contrast to 2 days (54). In studies on PPD-allergic subjects, it was shown that, with longer occlusion time, lower concentrations of PPD were necessary to elicit a positive response (55). In cases of strong contact allergy to PPD, 30 min of application of PPD 1% in pet. was sufficient to elicit positive responses. This was not the case for those patients who showed lower reactivity. Even for some contact allergens (in the particular case, a photocontact allergen), for example ketoprofen (56), a much shorter

occlusion time (1 hr) than 48 hr seems to be as effective as the traditional occlusion period.

Recommendation:

An occlusion time of 2 days is recommended.

Reading times

After test application (D0) and allergen exposure for 2 days, the patch test chambers are removed. The following reading times are often used in practice:

- D2 and D3 or D4 and around D7 (optimum): usually at D2, after 15–60 min, allowing for the resolution of pressure effects, the test reaction is read for the first time (1, 6, 57–61). A second reading at D3 or D4 is obligatory (57, 59). A reading between D5 and D10 is necessary for at least some allergens, for example corticosteroids and aminoglycoside antibiotics, for which 7–30% of contact sensitizations will be missed if a reading around D7 is not performed in addition to the reading on D3 or D4 (62–64).
- D3 or D4 and around D7 (fair alternative): in some countries, the first reading is on D3 or D4, in agreement with a previous recommendation from the ICDRG (53).
- D2 and D3 or, preferably, D4 (acceptable): if organizational circumstances dictate, two readings as above will allow for the diagnosis of the vast majority of contact allergies to most allergens, with, however, a risk of false-negative results, particularly for some allergens (see above).
- D4 only (not recommended as routine): in a study in which patch tested individuals were read several times in the range D2–D9, the single day that traced most contact allergy was D4, but to trace all contact allergy two readings on D4 and D7 were required (62). A D2 reading as the only reading is not appropriate (65).

Owing to geographical or organizational circumstances, the reading times may vary.

Recommendation:

At least two readings of the patch test reactions are required. Ideally, readings are performed at D2, D3 or D4, and around D7.

Table 2. Reading criteria of the ICDRG (53, 57)

Symbol	Morphology	Assessment
–	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

Morphology

The reading of patch test reactions is based on inspection and palpation of the morphology (erythema, infiltrate, papules, and vesicles). The globally acknowledged reading criteria of the ICDRG (53, 57) are shown in Table 2.

Morphologically positive patch test reactions (+, ++, or +++) at D3 – or at a later reading time – are usually assessed as allergic. Questionable reactions (?+) can sometimes be clinically relevant and important for the individual patient (19, 66), and may need further work-up (e.g. repetition of the patch test with several concentrations/serial dilutions, or use test).

Substances in a liquid vehicle may lead to a ring-shaped test reaction, as observed, for example, in serial dilution tests with corticosteroids, where clear allergic reactions were observed to other concentrations of the same allergen (49). Sharp-edged margins and fine wrinkling of the surface of the test area point towards irritant reactions.

Recently, inter-observer variability has been identified in the discrimination between doubtful and irritant reactions and in the distinction between doubtful and weak positive reactions (34, 66). Continuous standardization and reading training is advisable (34).

Different types of irritant reaction have been described. Well-demarcated erythematous reactions are often seen with fragrance mix and thiuram mix. Reactions appearing purpuric are commonly caused by metal salts, for example cobalt chloride. Pustular reactions are seen mainly with non-noble metals such as chromium, cobalt, and nickel. In special cases, pustular reactions may reflect contact sensitization (67). For the interpretation, it is necessary to keep in mind that, besides their properties as patch test allergens, many patch test chemicals also have some irritant potential (68), which is more predominant for some allergens (e.g. benzoyl peroxide, phenyl mercuric acetate, propylene glycol, benzalkonium chloride, octyl gallate, cocamidopropyl betaine, and 1,3-diphenyl guanidine), frequently resulting in weak erythematous

Table 3. Modified scale for reading repeated open application test results

Score points per criterion	0	1	2	3	4
1. Involved area of application	0	1–24%	25–49%	50–89%	90–100%
2a. Erythema (involvement)	None	Spotty	Homogeneous	–	–
2b. Erythema (strength)	None	Weak	Medium	Strong	–
3. Papules	None	<5	5–10	>10	Homogeneous infiltration
4. Vesicles	None	<5	5–10	>10	Confluent

The scale applies to a 3 × 3-cm² application area. The minimum requirement for a positive test is marked in bold, equivalent to that of 5 points (74, 75).

Each variable (1–4) must be given a score from 0 to 2–4. A positive reaction is characterized by erythema and infiltration as represented by papules, as a minimum, and the reaction should cover altogether at least 25% of the test area. The single scores are added, and a positive reaction will range from 5 points to a maximum of 17 points.

(questionable) test reactions (69–71). A relevant factor for the assessment of patch test results is the particular skin sensitivity and irritability of the individual tested at the time of patch testing. At times of individually increased skin irritability, more non-specific questionable test reactions may occur. An irritant control patch test is performed in some centres [e.g. sodium lauryl sulfate 0.25% aq., e.g. (72)] where it is considered to assist in the interpretation of weak reactions to allergens. The value of such a 'control' has not been unequivocally proven.

After the reading of patch test reactions, a conclusive interpretation is mandatory concerning the relevance of the test reactions in the respective case with regard to the patient's history, exposure, and clinical course (see section 'Final evaluation: clinical relevance and diagnosis').

Recommendation:

The patch test is scored according to morphology. A positive patch test reaction is defined as a reaction that fulfils the criteria of at least a 1+ reaction.

Other Techniques

Repeated open application test

The ROAT was developed by Hannuksela and Salo (73). It is a standardized exposure test mimicking a use situation. It aims at eliciting allergic contact dermatitis in the test area. With this method, it is possible to clarify the clinical importance of selected patch test reactions. In some cases, contact allergy to a product can only be proven with this technique. The ROAT may be useful both in experimental studies and in the routine clinic.

Methodology. Test solutions, either commercial products or special test substances, are applied twice daily for up to 2 weeks (but sometimes for up to 4 weeks) on the flexural

(volar) aspect of the forearm near the antecubital fossa. The size of the test area is usually 3 × 3 to 5 × 5 cm, and the amount of test substance should be sufficient to cover the test area. The applications continue until a reaction develops or until the end of the selected exposure period. It may be advisable in selected cases to include a control substance on the contralateral arm, and the ROAT may also be performed in a blinded fashion.

Reading and evaluation. A positive response in the form of 'eczematous' dermatitis may appear after a few days or later, depending on dose/area, matrix effects, and individual elicitation thresholds. However, a negative ROAT result after 1–2 weeks does not exclude a relevant contact allergy. Therefore, in cases with high suspicion, extended application periods of 3–4 weeks may be important, in order not to miss late-appearing reactions. Johansen et al. (74, 75) developed a scale for the evaluation of ROAT responses (Table 3). It is noteworthy that positive reactions often start with follicular papules in the application area.

Recommendation:

The ROAT is used to clarify the relevance of selected positive and doubtful patch test reactions by testing (leave-on) cosmetics, topical drugs, and other suitable formulations

Semi-open test

Goossens (76) suggested the use of the semi-open test mainly for testing patient-supplied products with suspected irritant properties, for example shampoos, detergents, paints, varnishes, cooling fluids, pharmaceuticals, and some cosmetics. A small amount (~15 µl) of the product is applied with a cotton swab on an area (1 cm²) of the skin, allowed to dry completely, checked for signs of contact urticaria, and then covered with permeable tape.

Readings are performed in the same way as for patch testing. Immediate reactions may appear after 20–30 min as a sign of contact urticaria, and dermatitis reactions may develop at D2–D4. This is a diagnostic tool that requires some experience for interpretation.

Open test

In the open test, a product, 'as is' or dissolved in water or some organic solvent (e.g. ethanol or acetone), is dripped onto the skin and allowed to dry. No occlusion is used. The usual test site is the volar forearm, but it is less reactive than the upper back or the upper arm. An open test is recommended as the first step for testing poorly defined substances or products such as those brought by the patient (see section 'Patch testing of patients' own materials'). Readings are made at regular intervals during the first 30–60 min after application, in order to detect immediate reactions, including urticaria. A second reading should be performed at D3–D4. A negative open test result can be explained by insufficient penetration, but indicates that one may proceed with an occlusive patch test.

Recommendation:

These types of less standardized test should be undertaken only by clinicians experienced in patch testing who fully understand the hazards of the applied substances/products.

Photopatch testing

Photopatch testing is mainly indicated in the study of photoallergic contact dermatitis, where UV exposure is necessary to induce the hypersensitivity reaction. It can also be helpful in the study of any dermatitis on photo-exposed areas or photosensitivity resulting from the use of systemic drugs (77). For photopatch testing, a duplicate set of allergens is prepared and applied on two corresponding areas of the back. After 1 or 2 days of occlusion, one set of tests is irradiated with 5J/cm² of UVA while the other is completely shielded from light and kept protected until further reading. A retrospective study comparing 1–2 days of occlusion before irradiation showed the longer exposure time to be more sensitive; however, it was concluded that systematic studies were needed for definite conclusions to be drawn (78). The 1-day occlusion/reading is usually used in photobiology clinics for combination with the readings of photopatch tests, whereas, traditionally, contact dermatitis clinics use 2 days of occlusion before irradiation. Readings should be performed before and immediately after irradiation

Table 4. Diagnosis of contact allergy versus photo contact allergy based on the photopatch test

Non-irradiated	Irradiated	Final diagnosis
Negative	Positive	Photo contact allergy
Positive	Positive	Contact allergy

and at least 2 days thereafter, and if possible also later. Grading of the reactions should follow the general rules of patch test readings but, for result interpretation, it is necessary to compare reactions in the irradiated and non-irradiated sites. A positive photopatch test result occurs when there is no reaction at the non-irradiated site and a positive (+ to +++) reaction at the irradiated site. Positive reactions in both sets of tests represent contact allergy (Table 4).

At present, the recommended European photopatch baseline series includes mostly UV filters of the different chemical families, non-steroidal anti-inflammatory drugs (NSAIDs), and a few photosensitizers known for a long time (79). A more extended photopatch test series may be used, and any product suspected of being implicated in the reaction should also be photopatch tested. In cases with high suspicion, UVB can additionally be used to irradiate one set of allergens. In a photosensitive patient, it is recommended to first determine reactivity to UV light (phototests performed on the day of application of the patches), and the UV dose for irradiation of the test site should be only 75% of the patient's minimal erythema dose (80).

Patch Testing of Patients' Own Materials

The textbook chapters in the references provide more detailed information on this subject (23–25). The information in this section is based on practical observations and empirical evidence, as no experimental data exist in this area.

Patch testing with patients' own products is especially important in occupational dermatology, because standardized commercial patch test substances of many occupationally used chemical compounds are lacking. Approximately 4000 contact allergens are known, but only several hundred commercially available allergen preparations exist. The number of allergens in an ordinary test laboratory is usually much lower. Thus, all possible problems cannot be solved with commercial allergens, and testing with patients' own products is necessary. Moreover, our environment is constantly changing, and workers and consumers are exposed to new chemicals, some of which are allergens. Routine test substances will not identify new allergens. Testing with patients'

own products is the only way of finding new allergens in the clinic. Previously known allergens can be found in new types of product; that is, testing with patients' own materials may reveal previously unknown sources of sensitization. In addition, patch testing with patients' own materials often helps in the assessment of the clinical relevance of an allergic reaction to standard allergens: for example, when a cosmetic product induces an allergic reaction and the patient also reacts to some of the ingredients labelled on the product, the allergen is probably the cause of the patient's problems. It must be remembered that a negative result with a patient's own product does not exclude contact allergy to some of its components.

Wide-ranging, efficient testing of patients' own substances requires experience and well-trained staff. The concentration of an allergen in the product may be too low to provoke an allergic reaction, that is, yield a false-negative reaction. Many products need to be diluted because of their irritant components (e.g. shampoos and toothpaste), which may lead to a false-negative test result. If the product is not sufficiently diluted, the irritant components can induce false-positive reactions. Concentrations that are too high may lead to patch test sensitization. Testing individual allergenic components separately may be the only solution to these problems. Many cosmetic companies provide the separate ingredients of a cosmetic product at adequate concentrations for patch testing. However, some companies send the ingredients diluted to a concentration that is used in the product, which may be too low, and lead to a false-negative reaction. Dermatological clinics with experience in non-standard test materials prefer to decide on test concentrations themselves. Many European companies selling industrial products provide the components of their product for patch testing, but cooperation with non-European companies can be more difficult.

Centres that test patients' own materials on a regular basis ask patients to bring samples and all possible information on the products that they suspect: safety data sheets (SDSs), lists of ingredients on the packages [e.g. International Nomenclature of Cosmetic Ingredients (INCI) lists], or the products' information leaflets. Similar information may be found on the internet, and should be requested from manufacturers. SDSs provide only limited information, and all sensitizing components may not be listed. Totally unknown substances should never be tested, because necrosis, scarring, pigmentation/depigmentation and systemic effects caused by percutaneous absorption may appear. Extremely hazardous chemicals (strong acids, alkalis, and very poisonous chemicals) and products without sufficient information should not be tested.

Patch test concentrations

The choice of test concentration is based on the characteristics of the product (skin irritant components, sensitizing components, pH, etc.). Those ingredients of the product that are available as commercial test substances should also be tested at the initial patch test session. As far as the concentrations of ingredients in the product are known, the dilution of the product should be such that none of the ingredients is above the recommended test concentration for this allergen (25). As a drawback, this may lead to insufficient concentrations of other ingredients in the test preparation (false-negative results). Contact dermatitis or occupational dermatology textbooks contain recommendations on test concentrations (23–25).

When the number of suspected materials is low, and the level of suspicion is high, using a dilution series of the suspected material is recommended. When possible new allergens are investigated, retesting with a dilution series down to negative concentrations is of utmost importance. Allergic-appearing reactions that extend to very low concentrations strongly support the allergic nature of the reaction. The strength of allergic reactions gradually diminishes with decreasing concentration, whereas a false-positive irritant reaction vanishes abruptly when the concentration is lowered.

Identification of a new allergen often requires serial testing, because products are usually composed of many different chemical substances. The components of the product are tested in the second phase, preferably with a dilution series down to negative concentrations (often ppm level). Very low concentrations can usually be increased, and the concentration should not exceed the recommended test concentration for the type of product or chemical group (e.g. acrylates, 0.1%; methacrylates, 1–2%). A low threshold concentration itself strongly supports the allergic nature of the reactions, as irritant reactions to such low concentrations are rare. Detailed information regarding dilutions and vehicles, depending on the composition of the products, is available (23, 24).

In the following, aspects of testing with specific product categories are outlined:

- Leave-on cosmetic preparations, protective creams and topical medicaments can usually be tested 'as is', because they are intended to be applied to the skin. A negative test result does not exclude contact allergy to the product, for various reasons (the concentration in the products may be too low, corticosteroids may have an anti-inflammatory effect, etc.).
- Rinse-off cosmetic products such as liquid soap, shampoos and shower gels can be tested at concentrations of 1–10% in aq., depending on the formulation.

- Metal-working fluids are often diluted at the workplace before use. Used metal-working products can be dirty, and the concentration may not always be exactly in accordance with the use recommendations. The most significant allergens in metal-working fluids are biocides, rust preventives, emulsifiers, and tall oil derivatives. Although it is safer to use unused, undiluted products, and prepare the test dilutions at the clinic, some important impurities may be missed, especially preservatives and perfumes added as odour masks to the metal-working fluid in the circulatory system. Therefore, it may be advisable to test the metal-working fluid taken from the machine as well as a fresh dilution prepared from the concentrate.
- Water-based fresh metal-working fluids are tested at a 5% concentration in aq. The workplace concentration of water-based metal-working fluids is usually 4–8% in the circulatory system. After testing and, if necessary, adjusting the pH, the used water-based 4–8% metal-working fluids taken from the circulatory system can be tested as they are. If the use concentration is $\geq 8\%$, further dilution with water is necessary to obtain a 5% concentration. Further possible sources of impurities can be evaluated separately, for example the composition of tooled materials and the leakage of guide-way oil into the metal-working fluid system.
- Oil-based metal-working fluids (fresh and used) are tested at a concentration of 50% in olive oil.
- Solid materials (paper, textile, plastic, rubber, metal specimens of suitable shape, wood dust, etc.) can usually be tested as they are.
 - Powdery materials, ground dust, scrapings or small cut pieces can be tested in chambers (first moistened with water or organic solvents).
 - Larger pieces (glove material, textiles, etc.) can be tested semi-open, covered with surgical test tape without a chamber. Tests can be false negative if insufficient amounts of the allergen are released onto the skin. Pressure effects and mechanical traumas caused by sharp particles must be distinguished from allergic reactions.
- Plants. Certain plant allergens are commercially available (e.g. sesquiterpene lactones, primin, tulipaline A, and diallyl disulfide). Fresh or dried plant material may be tested 'as is', provided that the botanical identity is known. Some plants are irritants. It is advisable to test the plant material (flower,

leaf, or stem) with a drop of saline and ethanol (two patch tests for each part of the plant), because some allergenic components may be water-soluble and others ethanol-soluble. Tropical woods can also be strongly irritating and sensitize. Cooperation with a specialized botanist ('wood anatomist') and consultation of available references (e.g. 81, 82) is strongly recommended.

Vehicle

The choice of vehicle depends on the characteristics of the product, solubility, and pH. When water-soluble chemicals are tested, it is important to check the pH before testing. Neutral products (pH 4–9) can be diluted with distilled water. For testing more alkaline or acidic substances, the use of buffer solutions is recommended, to reduce irritability and to allow higher concentrations to be used. Acid buffer is used for alkaline products (pH > 9) and alkaline buffer for acid products (pH < 4), with monitoring of the pH (83). Water-insoluble chemicals are usually diluted in pet., but acetone, ethanol, olive oil and methyl ethyl ketone are other alternatives (25).

Extracts and chromatograms

The use of ultrasonic bath extracts is an alternative to testing solid materials. Small pieces of the material are placed in water or organic solvent (ethanol, acetone, or ether), and extracted in an ultrasonic cleaner device, and finally filtered (84). Patch testing with thin-layer chromatograms can be valuable for products such as textiles, plastics, food, plants, perfumes, drugs, and grease (85).

Preparation of the test material

It is advisable to use disposable containers, syringes, stirrers and spatulas for preparing the test substances. Solid materials in crystal or powder form can be ground with a pestle and mortar. Liquids are diluted by using pipettes and syringes, and the percentage is given by volume (vol/vol). For solids distributed in a vehicle, the percentage is given by weight (wt/wt). Thorough mixing is important for a homogeneous distribution of the allergen in the vehicle. Serial dilutions can be prepared from these preparations. The test substances should be stored in a refrigerator in tightly closed containers or syringes.

Recommendation:

- Assess the products' composition by reading safety data sheets, ingredient lists, information from the manufacturer, and other data

- Test individual components of the patients' own products separately if possible
- If necessary, check the pH and adjust it with buffers before testing
- The test concentration of any individual ingredient in a product to be tested should not exceed the recommended test concentration for this substance
- Leave-on cosmetic preparations, protective creams and topical medicaments can usually be tested 'as is'
- Rinse-off cosmetic products such as liquid soap, shampoos and shower gels can be tested at concentrations of 1–10% in aq.
- Many solid materials can usually be tested 'as is'.

It is important to remember that a negative result with the product does not exclude contact allergy to some of the product's components.

Final Evaluation: Clinical Relevance and Diagnosis

Search strategy

The literature was searched by the use of PubMed with the search terms guideline, clinical relevance and patch test or contact dermatitis or clinical relevance and patch test criteria or allergy criteria, and relevant publications were retrieved in June 2014. Textbooks were checked manually.

Interpretation of positive patch test reactions and clinical relevance

A morphologically positive patch test reaction to a substance at a non-irritant patch test concentration is a sign of contact allergy, that is, that sensitization to the substance in question has occurred. The next step is to determine how the patient may have been exposed to the allergen and evaluate whether the patient currently has or in the past has had any pertinent clinical symptoms (e.g. allergic contact dermatitis) caused by exposure to the substance (86). Therefore, diagnosing allergic contact dermatitis involves a process with two major steps: (i) demonstration of contact allergy and (ii) assessment of clinical relevance. Clinical relevance is defined as (86):

1. Existing exposure to the sensitizer and
2. The presence of dermatitis, which is understandable and explainable with regard to the exposure

on the one hand, and the type, anatomical site and course of the dermatitis on the other.

A positive patch test reaction can be of current and/or past relevance, or unknown relevance. If a substance 'cross-reacts' with a diagnosed allergen, previous exposure and sensitization to this cross-reacting substance is not necessary (87). No commonly accepted relevance scoring system exists, but different systems have been suggested (88–90).

Recommendation:

The dermatologist must always assess whether an established contact allergy is of present, past or unknown relevance, or is attributable to cross-reactivity. Both personal and occupational exposures need to be addressed.

Elements in the assessment of current clinical relevance

The patient's history is crucial for understanding the causes of their dermatitis and the assessment of clinical relevance. It is important to go through the patient's history systematically, and it can be helpful to ask about rashes resulting from the use of specific product types, for example perfumes, creams, gloves, shoes, tools, and jewellery, depending on the anatomical site of dermatitis and the allergy under investigation. Such standardized questions have been used in various investigations of the clinical relevance of new allergens or screening markers of allergy, for example fragrance ingredients (91).

If a particular product is suspected on the basis of the history, it is important to qualify whether the sensitizer is present in the product. This can, in the case of cosmetic products, be performed (in Europe) by consulting the label of ingredients either on the product or on the container (where there is full ingredient labelling on cosmetics, apart from partial labelling of fragrance substances). The nomenclature is the standardized INCI system, which makes it easier to identify allergens; however, it should be remembered that the names on the patch test preparations are often chemical names or International Nonproprietary Name (INN) as used for medicinal products, and it can thus be necessary to look up synonyms for effective exposure assessment. Sometimes, the label is only printed on the box that comes with the product, and not on the cosmetic product itself. Labelling on medicinal products follows the INN system. In Europe, the labels of household detergents list preservatives and fragrances according to the requirements of cosmetic products.

For other product types such as shoes, gloves, textiles, and furniture, it is usually impossible to obtain information about composition, but a piece of the product can be tested (see section 'Patch testing of patients' own materials'), and textbooks can be consulted to give an indication of whether the type of substance that has caused a positive patch test reaction could be present in that particular type of product. For products intended for use in workplaces, for example cutting oils, paints, and other chemical products, see section 'Occupational contact dermatitis'.

For certain allergens, such as nickel, cobalt, chromium, and formaldehyde, spot tests exist, which are quick and easy ways to assess exposures. The nickel spot test is the best validated, and has high specificity (97.5%) and moderate sensitivity (59.3%) in detecting a level of nickel ion release that may cause dermatitis (92). In cases of suspected occupational exposure, the nickel spot test can be used directly on the hands (93). The cobalt test is based on similar principles, but is more difficult to read, and there is less experience with the test (94). Important new sources of exposure to cobalt have been identified by use of the cobalt spot test (95–97). The formaldehyde spot test requires laboratory facilities, but can detect small levels of formaldehyde, which have been shown to be of clinical relevance in those sensitized (98). The diphenylcarbazide test can detect chromium (VI) (99).

Recommendation:

INCI nomenclature must be used for identifying ingredients on the labels of cosmetic and household detergents. INN nomenclature is used for medicines. In the case of a positive patch test reaction to nickel, cobalt, or formaldehyde, it is recommended to use the spot tests to identify sources of exposure at the workplace and at home.

A special challenge occurs if the positive patch test reaction is to a mixture that is used for screening of contact allergy to a group of substances such as fragrance mix or mercapto mix, or even a natural mixture such as *Myroxylon pereirae* (balsam of Peru). In such a case, it may not be possible to pinpoint a particular sensitizer, and the decision may have to be made on the basis of the history of rashes resulting from the use of particular product types in such patient categories or general knowledge from textbooks.

The possibility of cross-reactivity should be kept in mind. This means that the sensitization has been caused by another substance that is, possibly after air oxidation or metabolic activation, chemically similar. If the clinician

looks for the substance that has caused the positive patch test reaction, and this is not present in the environment, the wrong conclusion may be drawn that the allergy is not relevant or, if the substance is present, the true culprit exposure will be overlooked.

Recommendation:

In the case of contact allergy to a chemically defined sensitizer, cross-reacting substances should also be looked for in the environment.

Facilitating the assessment of current clinical relevance. Means of facilitating the assessment of clinical relevance (86) include patch testing of products, patch testing with extracts, and use tests. The principles of patch testing of products are given in section 'Patch testing of patients' own materials'. A positive patch test reaction to a product in which the sensitizer is an ingredient and to which the patient is exposed usually means that the contact allergy is relevant (86). The dose required to elicit a positive patch test reaction is up to 28 times larger than the dose that is needed per open application to elicit a reaction in 14 days (100). This means that a negative patch test result with a product does not exclude current clinical relevance. If a specific product is suspected to have contributed to the dermatitis, but is negative on patch testing, a use test should be performed if possible. Extracts of solid products such as gloves may enhance the sensitivity of the patch test by concentrating the allergen in question (86), but this requires special equipment. A use test is often helpful in establishing clinical relevance, but is limited to products that are intended for repeated skin contact, such as creams and topical medicaments, or products for which skin contact similar to the ROAT or use test occurs regularly, for example cutting fluids at use concentration. Even a negative use test result does not exclude relevance. This means that, if relevance could not be established, it is recorded as a patch test reaction of 'unknown relevance' (101).

Past relevance. Past relevance reflects a past episode of contact dermatitis caused by exposure to the allergen, for example previous contact dermatitis caused by an earring in a person with a positive patch test reaction to nickel. Past relevance is usually based mainly on the patient's history.

Unknown relevance. The term 'unknown relevance' is preferred to 'no clinical relevance', as there are several reasons for not having detected the relevance, such as the following (53):

1. Lack of knowledge on the part of the clinician.
2. Some sources of the substance in question have not been traced.
3. The patient has not given sufficient information, partly, perhaps, because of the inability of the clinician to ask the proper questions.
4. The substance occurs widely in the general environment, so that the significance of the contact cannot be clarified from the history.
5. The patient has never developed dermatitis caused by the substances, as the patient has not been exposed to sufficient amounts after sensitization.
6. Contact has occurred only with cross-reacting substance, which may have a quite different usage.

The assessment of relevance is a complicated process with many pitfalls. The term 'unknown' relevance should be used with some caution, and only when the above points have been addressed to check that all potential sources of exposure have been identified.

Recommendation:

In the case of unknown relevance of a positive patch test reaction, it is recommended to repeat the clinical examination, re-evaluate the history and exposure, and to perform use tests, spot tests, chemical analysis and worksite visits, where indicated.

Interpretation of doubtful patch test reactions. A patch test reaction scored as doubtful means that the morphology is not clear-cut 'irritant' or 'allergic'. This implies that further investigations may have to be performed. The patch test concentration used may be too low, and, if it is increased, a positive patch test reaction may develop, which may even be of current clinical relevance. If, for instance, formaldehyde is tested only at 1% instead of 2% aq., positive reactions are missed, which have been shown to be clinically relevant by use tests with formaldehyde-containing creams (98). The weak patch test reaction may also be attributable to cross-reactivity to another substance, which is the primary sensitizer. Consideration should be given to the pattern of reactions. If reactions to some chemicals from the same 'family' are doubtful and others are (strongly) positive, such as reactions to formaldehyde releasers, rubber chemicals, or fragrance substances, this may be a sign of the same contact allergy. Evidently, 'doubtful' allergic reactions regularly occur to low concentrations of an allergen that is clearly positive at higher concentrations in serial dilution testing.

The patch test concentration may also be marginally irritant, and the doubtful reaction may be a sign of skin irritation. Repeat patch testing or serial dilution patch testing may be helpful in clarifying the nature of the reaction.

Interpretation of negative patch test results. As for doubtful patch test reactions, it should always be considered, particularly for non-standardized substances, that false-negative reactions are possible, for example because of inadequate patch test concentrations and/or vehicles. If this is strongly suspected, testing should be repeated. Standardized tape-stripping of the patch test area prior to allergen application has been suggested, and proven, to increase sensitivity, albeit at the expense of specificity, that is, with an increase in false-positive reactions (102). Moreover, the culprit substance may not have been included in the patch test programme at all. It is also advisable to check for some of the factors that may influence a patch test response (see section 'Influence of individual factors'), especially if the test unexpectedly gives a negative result.

Final diagnosis

If current clinical relevance is found in a person with established contact allergy, the diagnosis of allergic contact dermatitis can be made. In the case of unknown relevance, the person is sensitized, that is, has a contact allergy, but the criteria for the diagnosis of allergic contact dermatitis have not currently been met. However, the person is at risk of developing allergic contact dermatitis in the future if sufficiently exposed to the allergen. Hence, the contact allergy with unknown relevance must also be mentioned in the list of diagnoses, and counselling of the patient should include the respective substance(s).

In some cases, exposure to a contact allergen may explain the dermatitis entirely, but dermatitis with a multifactorial background frequently occurs. Besides the exposure to the contact allergen, constitutional factors may be of importance for the dermatitis, and there may be exposure to irritants and other allergens. It may be difficult to assess the relative significance of the various factors at a given time (86).

Influence of Individual Factors

Search strategy

Historical data were reviewed by reference to relevant chapters in Burns DA, Breathnach S, Cox N, Griffiths CEM, *Rook's Textbook of Dermatology*, 8th edition, Blackwell (Oxford), 2010, and Johansen JD, Frosch PJ, Lepoittevin JP, *Contact Dermatitis*, 5th edition, Springer (Berlin),

2011. This was supplemented by searching PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) with relevant search terms, and a hand search of the indexes of the journals *Contact Dermatitis* and *Dermatitis* from 2008.

When patch testing, it is important, among other factors, to consider the responsiveness of the patient. Many factors may theoretically weaken the patch test response, including medication, immunosuppression, UV light, and tanning, resulting in false-negative reactions, whereas other factors may increase the response, such as active dermatitis. Much evidence within this area is based on clinical experience, and limited controlled data are available.

Medication

There is little information in the literature about the effects of immunosuppressive agents on allergic patch test reactions. In practice, it may be difficult or impossible for patients to stop using their immunosuppressive drugs, for example corticosteroids, azathioprine, and cyclosporine. In such circumstances, patch testing may be undertaken, but the clinician must be aware that false-negative reactions may occur. However, positive reactions may still occur despite immunosuppressive therapy (103), although their number and intensity decrease, for example after 20 mg/day prednisolone administration (104). With respect to how many days in advance an oral treatment should be stopped to avoid a theoretical influence on patch testing, a period of five half-lives of the particular drug seems reasonable from a clinical point of view; however, this is only a rule of thumb, and pharmacodynamics need to be considered (e.g. receptor binding).

Antihistamines and disodium cromoglycate have not been reported to influence the allergic patch test reaction (105), and the same is true for NSAIDs. Concerning retinoids (alitretinoin), which are used in the treatment of hand dermatitis, there are no data in the literature. Ongoing topical treatment with corticosteroids is not believed to influence patch testing unless treatment is applied to the site of application of the tests. Typically, patients cannot themselves reach the upper back, and apply cream as demonstrated with a cream marked with a fluorescent dye (106); hence, accidental contamination of the back by topical corticosteroids applied to other anatomical sites is unlikely. If a potent corticosteroid is applied to the application site, vasoconstrictor effects and epidermal rebound phenomena might interfere negatively or positively with a patch test response, in addition to the immunosuppressive effect, which should be considered on a case-by-case basis.

Immunosuppressive diseases

Some patients with severe generalized inflammatory, infectious or neoplastic disease or certain cancers may have an impaired capacity for contact sensitization (107–109). Nevertheless, some still develop allergic contact dermatitis, and positive reactivity to a relevant allergen may therefore occur.

UV light/sun exposure

Exposure to UVB may reduce the risk of sensitization and temporarily diminish the ability to elicit allergic reactions in sensitized individuals. Although this seems not to be the case for UVA (110, 111), psoralen combined with UVA has been reported to cause a reduction in patch test reactions (112). UV irradiation results in a reduction in epidermal Langerhans cell numbers (113).

Recommendation:

If allergic contact dermatitis is suspected in patients under immunosuppression, it is recommended to proceed with patch testing, but to keep in mind that false-negative reactions may occur, and, if possible, to repeat patch testing at a later stage.

Atopic dermatitis and concomitant active eczematous disease

In most studies, the frequency of positive patch test reactions in atopic subjects is similar to that in other dermatitis patients. Therefore, patch testing is encouraged for the same reasons as in other patients (16), although the interpretation may be difficult, owing to their generally hyper-reactive skin with a risk of false-positive reactions. Filaggrin mutations, leading to impaired epidermal barrier function, seem to increase the risk of contact allergy slightly (114, 115).

Recommendation:

Patients with atopic dermatitis should be patch tested for the same reasons as other patients.

Special Groups

Children

Search strategy. The literature search was performed with PubMed; the keywords used in various combinations were 'allergic contact dermatitis', 'children', 'baseline series', 'active sensitization', and 'patch testing'. Recent articles

about epidemiological data and adverse effects associated with an allergen, as well as articles discussing concentrations of allergens or abbreviated baseline series were selected.

Introduction. Allergic contact dermatitis in children does occur, but has been under-recognized and only recently more extensively studied. Many physicians consider atopic dermatitis as the only diagnosis when children of all ages suffer from eczema. In reality, all children, whether atopic or not, may become sensitized to environmental chemicals such as topical pharmaceuticals and cosmetic products, to topical products used by their care-givers (dermatitis by proxy), or to any other material that comes into prolonged contact with the skin (116–118). The spectrum of contact allergens of adolescents is more similar to that of adults, including contact with occupational sensitizers. Patch testing in children is considered to be safe, and is recommended when allergic contact dermatitis is suspected or needs to be excluded, as in adults (119).

Technique and allergens. There may be practical problems involved with patch testing, particularly in very young children (120). The patch testing technique is exactly the same as in adults. However, certain factors need to be taken into consideration, such as the smaller test area on the back and the greater mobility of younger children, requiring the use of a stronger adhesive tape. Because of space limitations, it may sometimes be impossible to test the whole baseline series, and a selection of contact allergens is therefore required. Contact allergens found mainly in occupational settings, for example epoxy resin, can be omitted, whereas patch testing with the products that children actually are exposed to, such as topical products, antiseptics, and toys, along with their potential ingredients, is crucial (see section 'Patch testing of patients' own materials'). In young children, in particular, they may sometimes be the only allergens to be tested.

In cases of contact dermatitis after a so-called 'temporary black henna tattoo', concentrations of PPD much lower than 1% pet., shorter exposure times (55) or open testing may be advisable to avoid unnecessarily strong patch test reactions (121).

Recommendation:

Patch testing in children is safe, and the indications are the same as in adults.

Occupational contact dermatitis

Patients presenting with possibly work-related contact dermatitis require a number of special considerations, as outlined in the following section.

Patient history. In addition to a standard history, present and previous employments, occupational exposures, work tasks and other relevant aspects need to be documented in detail (and may be required later for medico-legal purposes). Some more common occupations may be familiar to physicians, depending on their experience. Nevertheless, checklists may help to cover all relevant aspects and, at the same time, assist documentation (e.g. 'EVA Hair' available at http://safehair.loungemedia.de/fileadmin/user_upload/documents/Documents/EVA_Hair_all_languages_all_languages/Final_Agreement_Evaluation_questionnaireEN.pdf, last accessed 4 May 2015). Other occupations may require consultation of textbooks (e.g. 3, 5) or information resources on the internet (see section 'Databases and surveillance') to appreciate the array of relevant exposures. It has recently been pointed out that sketches or photographs (enabled by mobile phones) provided by the patient can be very helpful in identifying an exposure-related problem. In particular cases, a visit to the patient's workplace may provide crucial information concerning the exposure.

Exposure analysis. After the collection of basic information from the patient's history, it is often necessary to proceed to in-depth analyses of occupational exposures of the patient. Depending on the national and regulatory framework, these can be performed by, for example, the treating physician, the occupational healthcare or occupational hygiene specialist, or experts from the health insurance organization involved. Exposure analysis includes two levels:

1. Collection of products and materials handled by the patient, along with information on their ingredients, for example in terms of SDSs. However, even though a particular substance is not mentioned, it may be present, as only classified allergens have to be mentioned if they are present above a certain concentration limit (122, 123). Thus, clinically important and frequent allergens may not be listed on SDSs even with formally correct, but factually incomplete, declarations (99). It is therefore advisable to contact the manufacturer or supplier of the product(s) under suspicion to obtain a full list of ingredients.
2. Actual chemical analysis with suitable laboratory tests of working materials deemed to be possibly

relevant (99). Some spot tests are useful to screen the (working) environment for the presence of these allergens (see section 'Final evaluation: clinical relevance and diagnosis').

Ideally, exposure analysis should also include assessment of how much of the allergen is deposited onto the skin (93, 99). Such information may be used when the occupational relevance of patch test reactions is assessed and exposure reduction is planned. Only a few methods for the assessment of skin exposure to common allergens, such as some metals, hair dyes, epoxy, and acrylates, are currently available (99). The simplest detection method is that for nickel, where the dimethylglyoxime test on the skin, which is easily applied in the clinic or workplace, may be used for qualitative assessment of nickel exposure (93).

Regarding the application of special patch test series, such as hairdresser series and cutting fluid series, a case-by-case extension of these requires sufficient knowledge of the patient's exposure; referral to specialized institutions is advised. A missed allergen or allergens, besides other causes, must be suspected in cases of persisting skin problems.

Patch testing with work materials. The recommendations in section 'Patch testing of patients' own materials' should be followed. In practice, it may be difficult to obtain (i) a list of ingredients and (ii) the set of actual chemicals, to prepare allergens from these for patch testing. Difficulties may be attributable to company secrets, unwillingness of employers, retailers or manufacturers to respond, lack of information of downstream manufacturers or importers, lack of time, dedication or knowledge of the physician, and the patient's unwillingness to undergo further testing. If successful, however, such detailed work-up can profoundly assist patient management, and may prompt preventive measures in the workplace.

Relevance assessment and final diagnosis. Final evaluation with assessment of the clinical relevance of the patch test result is described in detail in section 'Final evaluation: clinical relevance and diagnosis'. Occupational exposures to chemicals with which the dermatologist has little experience makes this a particularly difficult task. The assessment may have a direct impact on the prognosis of the patient's dermatitis and future work career, on medico-legal decisions, including compensation or re-training, and on preventive measures in the workplace.

Regarding occupational relevance, the following two aspects need to be considered:

- The association between the onset and the course of dermatitis (improvement or healing when away from work; relapse after return to work) and the affected anatomical site (hand, face or other sites directly or indirectly exposed by airborne dust or liquid aerosol, gas, drips or spills, or other contamination).
- Exposure to work materials containing the allergen.

Occasionally, allergens may be relevant both occupationally and in a non-occupational context, and it may be difficult to estimate the relative contributions of the two exposure arenas. A statement on relevance should also include a reference to time, that is, whether relevance is current or previous.

Finally, one diagnosis or several diagnoses need to be made, each with a statement concerning the role of occupational exposure, which can be the sole, the predominant or a contributory cause, or not be a cause at all. Ideally, each diagnosis should give information on the affected anatomical site, the causative exposure/work material, and the actual allergen(s) (if allergic contact dermatitis or contact urticaria) or irritant(s) (if irritant contact dermatitis) involved, and, moreover, whether any pre-existing disease or disposition (mainly atopic dermatitis) or exogenous co-factors such as occlusion and friction are involved.

Recommendation:

Systematic evaluation of patients with occupational dermatitis needs to address diagnoses, the affected site, the offending work material and the causative allergen or irritant for optimal patient counselling and exposure reduction.

Patch testing in drug eruptions

Indications. Although less standardized in this context, patch testing with drugs may also be indicated in the investigation of delayed cutaneous adverse drug reactions (CADRs), namely in maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) (124, 125). Moreover, in cases of skin contact with drugs (e.g. during manufacture or handling) resulting in suspected allergic contact dermatitis, patch testing is also indicated, and the technical procedure is the same.

Method. Optimally, patch testing should be performed at least 4–6 weeks after complete resolution of the CADR, or possibly later in patients with DRESS (125). All possible culprit drugs should be tested, that is, all drugs taken within the relevant chronological period. The approach and technique for performing patch testing in CADR is the same as that for the investigation of allergic contact dermatitis, except for fixed drug eruption, where lesional patch testing is advised. In this case, apart from applying the allergen on the uninvolved skin of the back (control test), the allergen(s) is also applied in a residual pigmented lesion for 6–24 hr, usually under occlusion with a patch test chamber. The readings are performed at 1 and 2 days (possibly at 6 hrs), as the reaction is usually accelerated, owing to the retention of drug-specific T cells in the residual patch of a fixed drug eruption. Results are compared with the normal control skin, which is usually non-reactive (126).

For all other CADRs, patch test readings should be performed as for allergic contact dermatitis. Apart from erythema and papules, and possibly vesicles, different reaction patterns (pustular, lymphomatoid, or bullous) that simulate an acute CADR may occur (127).

Allergens for patch testing in patients with CADRs. There are only a few drug allergens commercially available for patch testing, such as some antibiotics, NSAIDs, and anticonvulsants, usually at 10% in pet. Therefore, in most cases, patch test material has to be prepared in-house from the drugs used by the patients. The powder from intravenous preparations or from capsules is preferred over tablets for preparing material for patch testing. After being ground to a fine powder, the material should be incorporated in pet., whenever possible to have the active principle in a final 10% (wt/wt) dilution. When the concentration of the active drug is too low in the patient's drug, the whole powder should be diluted in pet. at 30% (128, 129). Positive patch test results obtained with these in-house preparations should be validated with controls, as some drugs or their excipients may have irritant properties, as shown, for instance, for colchicine and desloratadine (130). For commercially available drug allergens, no further controls are needed (131).

Sensitivity and specificity of patch testing in patients with CADRs. Patch test specificity is usually high, with drug-specific T cells being isolated from positive patch test reactions. Patch test sensitivity in patients with CADRs is lower than in patients with allergic contact dermatitis (30–70%), and depends on the culprit drug and the clinical pattern of CADRs (125). Drugs such as carbamazepine, tetrazepam and pristinamycin elicit positive reactions in ~60% of

cases (124, 131, 132), whereas for other drugs, such as β -lactam antibiotics and clindamycin, a low percentage of reactivity is expected (20–30%) (133, 134), probably reflecting reduced absorption, the role of metabolites, or the need for concomitant factors for induction of the CADR; allopurinol patch tests usually give negative results (124, 125). Patch tests more frequently give positive results in patients with maculopapular exanthema, DRESS, and AGEP, and very rarely give positive results in patients with SJS/TEN.

Prick and intracutaneous tests, with immediate and late readings, can have additional value in patients with CADRs, but they are beyond the scope of these guidelines (130, 133). Patch testing is a safe procedure, even in patients with severe CADRs, apart from exceptional cases of reactivation of the CADR (125). Information on non-irritating concentrations of active ingredients in drug patch tests has recently been compiled (135).

Recommendation:

Although it has variable sensitivity, patch testing should be considered in patients with delayed CADRs. A positive patch test result can help to confirm a possible culprit drug, therefore avoiding oral provocation. A negative patch test result, on the other hand, cannot exclude the contribution of a possible culprit drug, determined on clinical grounds.

Potential Adverse Effects of Patch Testing

The following section on adverse reactions to the patch test refers to patch tests performed appropriately, following these guidelines.

Unexpected irritant reactions

Unexpected irritant reactions may be seen when non-standard allergens or products are tested, despite appropriate dilution based on the available product information.

Patch test sensitization

Although sensitization by patch testing is uncommon, it is an important potential complication of patch testing. It is defined as a positive patch test reaction generally beyond 2 weeks after an initially negative response at the same site. In practice, it may be difficult to differentiate between induction of sensitization from allergen exposure from the patch test and a delayed patch test elicitation reaction (136). To confirm the diagnosis of active sensitization,

repeat patch testing can be performed. A positive reaction, with 'normal' latency of elicitation (one to a few days), supports patch test sensitization, particularly if there is a positive reaction to the test preparation diluted 10–100 times (137), although boosting of a pre-existing, but weak, sensitization cannot be ruled out. Several allergens are known to carry some risk of patch test sensitization; examples include: PPD (54), *p*-tert-butylcatechol (136, 138), acrylates tested at concentrations historically higher than the present concentrations (139), chloroacetamide (140), Compositae mix (141), primula extracts, and isothiazolinones (after 6). The risk of sensitization by patch testing is very low, and the benefit far outweighs any risk.

Pigmentation changes

A patch test reaction may rarely result in localized transient hyperpigmentation or hypopigmentation

Flare-up of clinical dermatitis

Flare-up of an existing, or sometimes a previous, dermatitis may occur in the course of a (usually) strong positive reaction. Such flare-up reactions usually indicate that the responsible allergen is or has been, respectively, the cause of dermatitis (142).

Persisting reaction

A positive patch test reaction can sometimes persist for up to several weeks. Uchida et al. reported a case with a positive patch test reaction to PPD that persisted for >1 month (143). Gold chloride 0.5% aq. is notorious for causing persisting reactions (1, 144). Palladium tetrachloride has been reported to cause persisting granulomatous patch test reactions (145, 146).

Scarring and necrosis

Although most experts consider this to be extremely unlikely if the present guidelines are adhered to, some consider the exceptional possibility that secondary scarring may occur after strong (allergic and especially irritant) patch test reactions, in particular, if scratching or superinfection occurs.

Subjective complaints

Itching at the site of application of the patches is commonly observed; it can either be attributable to a positive patch test reaction, or be a result of tape irritation. However, some patients experience more itching immediately

after removal of the tape (142, 147). Various subjective complaints of patch tested patients have occasionally been reported in the literature (2). There is no evidence of a cause–effect relationship.

Patient Education on Allergen Avoidance

The terms Allergic contact dermatitis, adherence, compliance, contact allergy, contact sensitization, education, information, memory, patch test, and patient had been searched in PubMed. Sixteen articles were identified as being more or less relevant for this topic.

Allergic contact dermatitis may completely resolve following successful education of the patient on allergen avoidance, with workplace conditions (employer and accident insurance) being addressed as required, provided that exposure can be sufficiently reduced.

Sufficient time should be allowed to discuss the allergies in detail with the patient, explaining potential sources of exposure (148), and to advise on how to avoid future skin contact with the allergen. For example, nickel-allergic patients should be informed about risk products such as jewellery, and be instructed on how to use the nickel spot test on metallic items that are likely to be in prolonged or repetitive contact with their skin (149, 150). Similarly, the cobalt spot test can be used for metallic items that could potentially release cobalt. Ingredient label reading of any personal products intended for use on their skin is recommended, so that the patients can identify whether the product is free of the allergen. However, this can be a challenge, because typical allergen names are complex, and often have numerous synonyms. Unfortunately, the names used to identify substances in the patch test syringes do not always correspond with the nomenclature used elsewhere, for example INCI.

The use of written, regularly updated information containing the INCI names (in the realm of cosmetics), and the different chemical names of the compound, together with the sources of exposure, is necessary. This is of particular importance for patients with positive patch test reactions to fragrance substances and preservatives (151). There is some evidence that written information can be superior to oral information in regard to a patient's perception (152). The dermatologist needs to consider that individuals from (educationally) disadvantaged backgrounds and with reduced personal resources may find it more difficult to read and understand ingredient labels on cosmetic products (153). Also, a socially driven need to continue using a certain product can affect adherence; for example, some patients with mild allergic reactions to PPD continue to dye their hair, whereas those with strong allergic reactions will tend to follow the recommendations

(154). Patients need to be aware that ingredient labels can sometimes be misleading and may not show all contact allergens in the product (155). Reasonable advice for fragrance-allergic patients can be to simply smell the product prior to use, and only apply it if they do not sense any fragrances. Marketing terms such as 'fragrance-free', 'dermatology recommended', 'organic' or 'does not contain synthetic fragrances' are often misleading, and cannot be used for guidance. Many clinics provide a card with the allergen names printed, which patients can carry with them and easily access when shopping.

To help the patient identify safe personal care products, databases have been developed. Examples include, in the United States, the Mayo Contact Allergen Replacement Database (156). In Europe, the Leuven department provides similar advice (157). There is a wealth of internet sites with information on allergens in different products. Obviously, the quality varies, and interested readers are referred to a recent review (158). Regarding occupational products, see section 'Occupational contact dermatitis'.

To underscore the fact that patient education can be a challenge, a UK study showed that, among 135 patch tested patients, ~25% could not even recall having received any information about their test results 2–3 months later (159). Also, a US survey, including 757 patch tested patients who were given a questionnaire on average 13 months after patch testing (the mean age of the patients was 59 years), showed that only 50% of 238 patients with positive patch test reactions to one or two allergens remembered their allergies (160). Moreover, among 342 patients with three or more positive patch test reactions, only 24% remembered their allergies. There was a tendency for there to be better recall of allergens among those aged 50–59 years of age and among women, similarly to the results of a recent Swedish study (161). Although the correlation was weak, recall decreased, as expected, with the time since patch testing. Importantly, all patients were given oral and written information about their allergies after patch testing. Also, information about how to use a contact allergen avoidance database that provides a list of safe cosmetic products was given. If possible, it might be useful to repeat the information at a new appointment, for example months later.

Advice that the dermatologist can consider in a given patient:

- Marketing terms such as 'free of synthetic fragrances' or 'hypoallergenic' can be misleading.
- Reading the ingredient labels of cosmetic products and detergents routinely to avoid allergen exposure is recommended.

- Not every glove is suitable to prevent exposure from each allergen.
- Regular use by nickel-allergic patients of a nickel spot test on metallic items to avoid products that release nickel.

Recommendation:

Patients should be given written information, which should be specific for their situation, including the name(s) of allergens. In case of cosmetics allergens, INCI names must be provided; in other cases, INN are helpful. Chemical Abstract Service (CAS) numbers and common names are helpful in other fields. Information should be repeated during follow-up visits.

Professional Training in Cutaneous Allergy

In this section, the term 'cutaneous allergy' is used to comprise contact allergy (delayed-type hypersensitivity) and contact urticaria/protein contact dermatitis (immediate-type hypersensitivity). Investigation of cutaneous allergy is time-intensive, usually requiring a minimum of three visits over 5–7 days, and, for effective use of resources, it is important for the patient to be seen at an appropriate centre from the outset. Speciality training in dermatology provides core skills to develop the specific competencies required to practise independently as a dermatologist. We consider this background of training to be the minimum to enable an individual to fully consider the differential diagnosis and management of a patient with a potential cutaneous allergic reaction. Aspects of immediate-type hypersensitivity skin testing (prick test) are not considered here.

Dermatologist with an interest in cutaneous allergy

For dermatologists who spend a major part of their working career in the field of cutaneous allergy, a higher level of training should be expected (162). Specialist dermatology centres may provide diagnostic services for complex cases, for example those involving outbreaks of allergic dermatitis in the workplace (163) or wider community, multiple allergens, and photo-allergy. Factory or workplace visits, specialist patch and photo testing and specialist pharmacy services are sometimes needed. An individual would be expected to gain the knowledge and skills in cutaneous allergy set out below (beyond the dermatological core skills) during an indicative duration of training of 12 months, with 250–300 patients being seen during this period to achieve competence. The skills related to this field of work are described in detail in Appendix S1.

Maintenance of expertise

Minimum standards for provision (http://www.cutaneousallergy.org/BAD_BSCA_Working_Party_Report_on_Cutaneous_Allergy_Services_2012_FinalMW.pdf, last accessed 4 May 2015) of a cutaneous allergy service have been defined in the United Kingdom. To maintain competence, it was recommended that clinicians should investigate at least 200 cases a year. Investigation of cutaneous allergy is delivered by a multiprofessional team. The team should have regular meetings (at least four times a year). The broad aim of these regular clinical governance meetings is to ensure that the service is focused on the need to provide timely, safe and effective services to patients. Their agenda should include the following elements:

1. Review of activity since the previous meeting.
2. Review of waiting list data to assess demands on the service and issues regarding service delivery.
3. Review of adverse events.
4. Discussion of difficult or instructive cases.
5. Equipment issues.

It is recommended that results from investigations should be recorded in a database. The results should be benchmarked annually against national pooled data, and the outcome be presented to the local dermatology team to encourage best use of the service; see also section 'Databases and surveillance'.

There is a need for ongoing training of team members. To ensure a uniform inter-individual patch test reading technique, continuous training is necessary, for example in the context of 'patch test courses' at scientific meetings. As another possibility, an online patch test reading course is provided by the German contact dermatitis research group (<http://dkg.ivdk.org/training.html>, last accessed 4 May 2015). New evidence-based practice, research, national standards, guidance and audit results all need to be disseminated to staff, to ensure the implementation of procedures that achieve quality outcomes. Training and Clinical Professional Development should be discussed and planned to ensure that all team members fulfil professional requirements to be fully up to date. It is recommended that the lead attend update meetings on contact allergy at least once every year. The unit should have up-to-date reference books on contact allergy, including occupational skin disease and access to relevant journals.

Databases and Surveillance

In the practice of patch testing, the term 'databases' refers to two aspects: (i) retrieval of information for patient management or scientific publication, and (ii) collection

of departmental patch test results, usually with a view to later analysis and publication. Sufficiently standardized patch test data collected in the course of several years and/or by different centres can serve the important purpose of contact allergy surveillance, that is, the observation of time trends or geographical differences in sensitization prevalences. In this section, key issues of both aspects are briefly outlined; for further details, see (164).

Information sources

Currently, the internet offers a wealth of accessible information. Regarding product information, the full INCI labelling information of cosmetics can often be found on the manufacturer's website if the patient is unable to produce the package. In other cases, it is helpful to download SDSs for review of the limited information provided by them. However, the amount and accessibility of information offered by different companies vary greatly. Chemical and toxicological information on allergens is available from services that either need subscription (such as the CAS) or are freely available. The following list includes just some selected examples in the English language:

- CosIng database (<http://ec.europa.eu/consumers/cosmetics/cosing/>, last accessed 4 May 2015).
- Expert opinions of the Scientific Committee on Consumer Safety and its predecessors (http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm, last accessed last accessed 4 May 2015).
- Toxicological monographs, including on contact sensitization, by the German MAK Commission (<http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>, last accessed 4 May 2015).

Software for documentation of patch test results

There are several options regarding software suitable for the documentation of patch test results, along with relevant demographic and clinical data. These have been briefly reviewed in (164).

Contact allergy networks and surveillance

A collection of results of all patients patch tested, that is, also including completely negative cases for representativeness, by one department offers interesting possibilities for data analysis. However, these possibilities are vastly increased by joining a (national) data network, including, but not limited to, benchmarking and quality control of one department's results against the average of the peer group, with the possibility of enhancing standardization and quality (59).

Cosmetovigilance/pharmacovigilance

In the context presented here, cosmetovigilance (or, similarly, pharmacovigilance) describes different concepts of a special type of contact allergy surveillance implemented by dermatologists. Existing examples include the REVIDAL/GERDA in France (165) and the IDOC in Germany (166).

Recommendation:

Structured electronic documentation of patch test results, together with basic demographic and clinical information, is required for (i) auditing of departmental results and benchmarking in a national network, and (ii) scientific analyses addressing public health issues.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Professional training in cutaneous allergy.

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