

Clinical update on contact allergy

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Purpose of review

The aim of this article is to review recent findings in contact allergy, regarding clinical research.

Recent findings

The biocide methylidibromo glutaronitrile was identified to be an important sensitizer. Subsequently, it was banned from leave-on cosmetics in the European Union. Another group of important allergens that have been studied extensively included the fragrances oak moss absolute, isoeugenol, hydroxyisohexyl 3-cyclohexene carboxaldehyde and farnesol. A new fragrance mix II has been developed for standard testing, which includes the two latter compounds. Dose response studies have demonstrated broad individual variation of elicitation thresholds, dependent on the allergen concentration during induction, and other factors. Some unsuspected routes of exposure to allergens include oral, inhalational, connubial or airborne contact. Experimental studies provide a classification of newly introduced chemicals; increasingly, the local lymph node assay is supplementing and potentially replacing the guinea pig maximization test. Recent advances in occupational contact allergy include, for example, some attempts to improve diagnostics for epoxy resin and other plastic, glue, and cutting fluid components.

Summary

Constant awareness for new allergens, confirmed by critical evaluation, standardization of patch test materials, and the identification of temporal patterns and subgroups at risk will improve both the diagnosis and prevention of allergic contact dermatitis.

Keywords

clinical epidemiology, contact allergy, diagnosis

Abbreviations

ACD	allergic contact dermatitis
LLNA	local lymph node assay
MDBGN	methylidibromo glutaronitrile
PPD	p-phenylenediamine
SLS	sodium lauryl sulfate

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1528-4050

Introduction

Contact allergy to a wide spectrum of natural, or man-made substances of low molecular weight (haptens or allergens) causing allergic contact dermatitis (ACD) is not uncommon. Some 20 [1] to 30% [2**] of the general population has been diagnosed with contact allergy to at least one allergen in cross-sectional studies. For the diagnosis of contact allergy, the patch test introduced by Jadassohn more than 100 years ago is still the gold standard [3]. Regarding any specific allergen, the prevalence of clinical disease – ACD due to the allergen – is lower than contact allergy prevalence if sufficient allergen avoidance is attainable.

The induction, and subsequent elicitation of contact allergy depends on the mode of exposure to the allergen, such as concentration, duration, and other individual conditions such as integrity of the epidermal barrier or pre-existing dermatitis. The present paper will review recent findings regarding previously unidentified allergens, and well-known allergens identified in 'new' products. Moreover, new information regarding individual susceptibility, exposure conditions and the regulatory framework (e.g., current legislation) will be presented.

Emerging allergens and other trends

Virtually all biocides are potential allergens [4**], and are, at the same time, essential constituents of personal care and many other products as preservatives. With increasing use of a compound, an increasing number of cases of ACD will be identified. The incidence of contact allergy to this compound will decrease with reduction of its use, concentration, or even withdrawal, but alternative biocides will be substituted. These, in turn, will subsequently also evolve as frequent allergens: a cyclical phenomenon which has been already observed several times in the past. As a substitute for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), which was restricted in cosmetics several years ago, the biocide

Curr Opin Allergy Clin Immunol 5:429–436. © 2005 Lippincott Williams & Wilkins.

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methyldibromo glutaronitrile (MDBGN) has been increasingly used in the last decade. Unexpectedly, in view of initially negative experimental screening [5], the frequency of contact allergy to MDBGN increased quite dramatically [6,7]. Even at the lowest possible use concentrations in leave-on products, these were capable of eliciting ACD in many MDBGN sensitized patients [8[•],9[•]]. This prompted European Union regulatory institutions to ban its use in leave-on cosmetic products in March 2005 (Commission Directive 2003/83/EC). The use of liquid soaps, however, has also been identified as a relevant source of ACD in sensitized patients, refuting the perception that rinse-off products containing MDBGN in presently allowed concentrations are safe [10[•],11[•]]. This concern is supported by several observations: an increased prevalence of both MCI/MI and MDBGN contact allergy in hairdressers, presumably due to shampoo exposure [12]; an elevated proportion of MDBGN contact allergy in patients with ACD to their own bath and shower preparations [13[•]]; and clearance or improvement of ACD after avoidance of rinse-off or leave-on products in 19 sensitized patients [14]. As a consequence, the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers has recently recommended banning MDBGN from rinse-off products as well (website: http://europa.eu.int/comm/health/ph_risk/committees/04_sccp/docs/sccp_o_00f.pdf). MDBGN has now been added to the European standard series [15[•]]; the ideal patch test concentration still remains debatable: 0.2 or 0.3% in petrolatum, seeking a balance between sensitivity and positive predictive value [9[•]] versus 0.5% in petrolatum, with an emphasis on maximum sensitivity [16[•],17]. Iodopropynylbutyl carbamate (IPBC) is one of the potential successors of MDBGN as a biocide in cosmetics. It is a particularly difficult allergen to evaluate due to its marked irritant properties; 0.2% in petrolatum has been suggested for monitoring the future trend of contact allergy to IPBC [18[•]].

The frequency of contact allergy to the original fragrance mix, containing eight important fragrance allergens, has followed an unusual time course between 1996 and 2002. After an increase in the first few years, the prevalence of contact allergy to the fragrance mix dropped to 7.8% in 2002, suggestive of a lessening exposure to its constituents, such as regarding the concentration of these fragrances in perfumes and other scented products [19[•]]. Amongst these, oak moss absolute and isoeugenol were the most common allergens, while geraniol and α -amyl cinnamic aldehyde were comparatively rarer [19[•]]. Recently, 'new' fragrance allergens have been reported, probably due to their increased usage to replace those fragrances associated with high contact allergy risk. These include hydroxyisohexyl 3-cyclohexene carboxaldehyde (HMPCC) [20] and farnesol [21]. Five of these

allergens, including HMPCC and farnesol, have been combined into a new fragrance mix II (14% in petrolatum) [22^{••}] which is to be included in the (European) standard series [15[•]]. Exposure to fragrances is not always overt (e.g. perfumes, aftershaves, or eau de toilette [23]), but may also be present in less suspected sources. Recently, anecdotal reports identified relevant contact allergy to 'odor-neutralizing' cinnamon fragrances from shoe insoles [24], polyvinyl car seat covers [25] or in a mud bath [26].

Dose-response factors

Individual elicitation thresholds of contact allergy to nickel on patch testing vary by a factor of over 1000; approximately 5% of sensitized individuals react to 0.44 $\mu\text{g Ni/cm}^2$, and 10% to 1.04 $\mu\text{g Ni/cm}^2$ [27[•]].

Following oral exposure to graded concentrations of nickel and placebo in nickel-sensitive and control subjects, a definite dose-response reaction pattern was observed amongst the former. Those patients in whom nickel dermatitis flared showed a significant immunological response with decreases in fractions of CD3⁺CD45RO⁺CLA⁺ and CD8⁺CD45RO⁺CLA⁺ blood lymphocytes and elevated levels of IL-5 in serum [28[•]]. Such systemic elicitation probably only occurs, however, in a minority of nickel-sensitive individuals. Elicitation by oral route has also been observed in a nickel-containing orthodontic appliance [29], or after a generous helping of raw (and mercury contaminated) swordfish in a person with contact allergy to mercury [30].

Some allergens are sufficiently sensitizing to elicit ACD at very low concentrations. One example is chloroatranol, one of the main allergens in oak moss absolute. In a use test with graded concentrations, 50% of oak moss sensitive patients reacted to a concentration as low as 0.2 ppm [31]. Moreover, oak moss, and thus chloroatranol are found in many popular perfumes and eau de toilette, with median concentrations of 0.235 and 0.006 $\mu\text{g/ml}$, and a maximum concentration of 53 $\mu\text{g/ml}$ [32[•]]. These concentrations are well within an eliciting range. The advantages of lowering a concentration may, however, be adversely affected by the increased frequency of application of the allergen. In a comparative use test in 19 MDBGN sensitive patients and 12 controls a similar frequency of positive reactions was found with 0.04%, applied once daily, and 0.01% four times daily [33[•]].

Results dating back to the 1980s, confirmed by new experimental results [34], noted that there is an inverse relationship between the induction dose, and the elicitation dose of an allergen [35^{••}]; that is, the higher the induction concentration, the lower the threshold for elicitation of subsequent ACD. This observation has

important practical consequences. Patients sensitized to p-phenylenediamine (PPD) by exceedingly high concentrations of PPD found in black henna tattoos (>15%) should be tested with lower than usual PPD patch test concentrations, such as 0.01–0.3%, to avoid extreme positive test reactions [36^{••}]. As an alternative, the same concentration could be used, but for a much shorter period of contact, possibly not exceeding 1–2 h [37]. Clinically, trace contacts, for example to cross-reacting textile dyes, may suffice to elicit ACD [38]. Extremely severe ACD, even necessitating intensive care treatment, may occur after application of hair dyes after induction by such high concentrations [39]. Thus, decreasing the maximum permitted use concentration of an allergen should reduce the risk of sensitization (induction), and of subsequent elicitation: when the induction concentration is lowered, the elicitation concentration threshold should increase. In this situation, the patch test may be the only exposure above the individual elicitation threshold for certain patients: a possible explanation for the lack of clinical relevance in these patients [35^{••}].

Contact with allergens via the patch test rarely induces contact allergy, the risk depending on the dose (test concentration) of the allergen. Active sensitization is defined as a negative patch test followed by a flare-up of this initial negative test reaction after 10–20 days, and then a positive patch test reaction when re-tested already observed after 2 or 3 days [3]. PPD has been of greatest interest as a putative cause of active sensitization. While some consider the risk to be extremely low [40[•]], others found a large proportion of unusually late positive patch test reactions [41] and, in the majority of these patients retested, subsequent early positive patch test reactions within 2 or 3 days to PPD [42], indicative of active sensitization as defined above.

Combined exposure to different allergens [43,44], and combined exposure to allergens along with irritants [45] significantly lowers the threshold for elicitation, and most probably also for the induction of contact allergy. This combination is very common in everyday exposures to consumer and occupational products, and perhaps the regulation of permitted concentrations for allergens should take this observation into account [46^{••}].

Individual susceptibility and irritability, 'polysensitization'

Children are usually tested with the same concentration of allergens as adults, albeit with a smaller scope of allergens appropriate for their potential exposures. When testing pediatric cases with suspected ACD, the majority of positive reactions, ranging from 56 to 93% in one study, [47[•]] are found relevant. Frequent allergens in children

and adolescents include nickel (and cobalt), fragrance mix, thiurams, PPD [47[•]], propolis [48], thiomersal [49] (e.g. due to thiomersal being present in hepatitis B vaccines), and a number of other allergens. Contact allergy to thiomersal is usually not relevant [49].

Increasingly, the relationship between an irritant reaction and contact allergy is being investigated both clinically and experimentally. In one approach, the routine patch test was supplemented with a sodium lauryl sulfate (SLS) patch test with the following rationale: in patients with an irritant SLS reaction, increased irritability is diagnosed. This, in turn, allows interpretation of doubtful (erythematous) or even positive (erythematous and infiltrated) patch test reactions to certain allergens, which are at the same time marginal irritants when patch tested, as irritant more confidently than without a concomitant 'irritant control' [50,51,52^{••}]. On the other hand, irritability might also imply increased susceptibility to contact allergy [53], and thus a true association between irritant reactions (to SLS) and patch test reactions to allergens may exist. At present, this conceptual conflict is unresolved [54].

According to clinical impressions multiple positive patch test reactions are more common than single patch test reactions, despite exclusion of cross-reacting allergens. Obviously, multiple exposures to the allergens is a prerequisite for 'polysensitization'. It has been postulated, however, that increased individual susceptibility is another prerequisite, especially regarding contact allergy to weak allergens, although such susceptibility is not fully understood. The concept of polysensitization as a clinical sign of increased susceptibility has been introduced by Moss and Friedman [55]. Recent studies identified polymorphisms of relevant enzymes [56] and cytokines [57] as possible reasons for such differences. Interestingly, independent of sex and age, polysensitization is a risk factor for contact allergy to neomycin sulphate [58], or combined contact allergy to metal ions (nickel, cobalt, dichromate) [59^{••}].

Experimental studies

In the last few years, the local lymph node assay (LLNA) has evolved as a graded method to estimate the potential sensitizing risk of a substance, supplementing and possibly replacing the guinea pig maximization test. Its measure of effect is the concentration of the chemical required to produce a threefold stimulation of proliferation in lymph nodes draining the site of application, compared to vehicle-treated controls ('EC3' value) [60[•]]. A database has been presented summarizing LLNA results along with other relevant information on a number of allergens [61]. In a comparison of LLNA and human data, a relatively good correlation was found among the limited set of 57 substances evaluated [62[•]].

An interesting approach is the prediction of the allergenic potential based on quantitative structure–activity relationship models. Increasing recognition of molecular determinants of allergenicity has, at least for certain chemicals (aldehydes), greatly improved the validity of prediction, if assessed versus LLNA data [63[•]]. Moreover, quantitative structure–activity relationship analysis, together with information on exposure to various hair dye substances, has been employed to ascertain a more comprehensive test series of potential allergens for patients with suspected ACD to hair dye products [64^{••}]. As a novel screening method, the analysis of genes pertaining to dendritic cell maturation has been proposed [65[•]], but not yet evaluated on a larger scale. In spite of these advances, however, human data will remain the ‘gold standard’ for regulatory decisions [66].

Unusual or occult routes of exposure

The potential of isothiazolinone type biocides to elicit ACD via airborne contact is illustrated by the case of a PhD student with a history of contact allergy to 2-n-octyl-4-isothiazolin-3-one, experiencing a flare of ACD after entering a room in which a container of the neat chemical was being handled in the fume cupboard [67].

Percutaneous absorption of allergens may occur during patch testing. It has been observed that the median serum gold level rose from 0.03 to 0.34 $\mu\text{g/l}$ after the 48-h application of 0.5, 2.0 and 5.0% gold sodium thio-sulfate; presumably, other allergens are also systemically absorbed during patch testing [68^{••}].

Another unusual exposure is the subcutaneous exposure to heparin, heparinoids and (recombinant) hirudin. Contact allergy to these anticoagulants is of practical importance. The spectrum of derivatives causing allergic contact reactions, or being tolerated without dermatitis in the individual case is diverse and necessitates individual patch test, intradermal tests and subcutaneous provocation, as illustrated by different case series [69[•], 70–72].

Inhalation of an allergen may be sufficient to elicit systemic contact dermatitis, as illustrated by a case of contact allergy to *Parthenium hysterophorus*, in which ACD was provoked by inhalation of fresh plant material from a polythene bag [73[•]]. Moreover, according to a questionnaire-based study, inhalation of fragrances caused respiratory symptoms significantly more often in patients with contact allergy to fragrances than in those without [74[•]].

Table 1. A selection of new allergens according to authors or exposures reported in 2004/2005

Substance	Cases	Remarks	Reference
VP/eicosene copolymer	59-year-old man, after application of emollient	Tested 10% in petrolatum, 15 controls negative	[85]
1-Bromo-3-chloro-5, 5-dimethylhydantoin	41-year-old man, after spa disinfection	Negative to sodium hypochlorite	[86]
Pirfenoxone	77-year-old female, eye drops for treatment of cataract	1% and 50 ppm in water positive	[87]
Curcumin	2 cases to a yellow coloured disinfectant	0.05% in chlorhexidine solution	[88]
<i>Boswellia serrata</i> extract	28-year-old female, ‘natural’ cream applied after burn	Positive to cream and 0.1% extract in petrolatum, 12 controls negative	[89]
Diglycolamine	Several cases of cutting fluid dermatitis	2/108 positive	[83 ^{••}]
1,6-Bis(2,3-epoxypropoxy) naphthalene	2 workers in 1 plant, one-component epoxy coating	Tested 1% petrolatum; 10 controls negative	[90]
Tamanu oil (<i>Calophyllum inophyllum</i> ; INCI Europe)	53-year-old female, ACD after topical remedy against insect bites in Tahiti	Tested 1% in olive oil, 30 controls negative	[91]
Ethylbutylthiourea	59-year-old male, ACD from chloroprene rubber knee brace	Isolation with HPLC; strong positive reaction	[92]
<i>Astronium urundeuva</i> (Anacardiaceae) extract	3/134 patients positive to different extracts	Used as folk remedy in Brazil	[93]
Ethyl bromoacetate, bromoacetonitrile	28-year chemical engineer with hand eczema	Intermediates for ‘new pharmaceuticals’	[94]
Topiramate	55-year-old woman with rash after antiepileptic reaction	Also patch test positive to carbamazepine	[95]
Sodium lauroyl sarcosinate	41-year-old nurse with eczema after a liquid hand soap	Patch test positive to 30% water, 2 controls (only) negative	[96]
Tacrolimus	9-year-old boy, ROATs positive after 1 and 7 weeks, respectively.	5% in ethanol, 40 controls negative	[97]
5-Aminolaevulinic acid methyl ester	30-year-old female, after photodynamic treatment	Positive to 5–20%; 5-aminolaevulinic acid negative	[98]
Drometrisole trisiloxane	59-year-old female, ACD after sunscreen use	UV A and B filter, tested 2.5% ethanol, 15 controls negative	[99]

VP, vinylpyrrolidone; INCI, International Nomenclature of Cosmetic Ingredients; ACD, allergic contact dermatitis; HPLC, high-performance liquid chromatography; ROATs, Repeated Open Application Tests; UV, ultraviolet.

Repeatedly, ACD may not be caused by direct exposure of the patient, but by passive exposure via social contacts, termed 'consort' or 'connubial' dermatitis. Case reports add to our understanding of the multiple contacts, and the many allergens potentially involved. These include a case of sesquiterpene lactone contact allergy from exposure to a consort's 'natural' cosmetic [75], a case of ACD of the face due to budesonide contact allergy in a mother treating her asthmatic infant with an inhaler [76], and facial ACD to benzoyl peroxide of a mother following face-to-face contacts with her benzoyl peroxide-treated son [77].

Occupational contact allergy

Epoxy resins systems are gaining increasing importance in many technical applications, including not only the manufacture of plastic products, such as small craft, fishing rods or wind turbine rotor blades [78[•]], but also in the construction industry [79], and with painters [80[•]]. New compounds necessitate a constant updating of epoxy resins test series with regard to hardeners (e.g. *m*-xylene diamine or isophorone diamine) or reactive diluents (e.g. 1,6-hexanediol or 1,4-butanediol diglycidyl ethers and phenyl or butyl glycidyl ethers) [81[•]]. Epidemics of ACD suggest new allergens, or faulty workplace hygiene, as in the case of nine out of 81 workers manufacturing electric coils, who were sensitized to various acrylates, including triethyleneglycol diacrylate, diethyleneglycol diacrylate, 1,6-hexanediol diacrylate and others [82[•]].

Cutting fluids are a heterogeneous group of industrial lubricants containing a number of potential allergens. In view of the ever changing composition of cutting fluids, the accompanying diagnostic patch test series must be continually modified. According to patch test results in 251 German metal workers, monoethanolamine (11.6% positive reactions) ranked first among allergens currently on the market, followed by *p*-aminoazobenzene (6.0% positive reactions, often with uncertain relevance) [83^{••}]. Sensitization to fragrances may be due to agents added to cutting fluids as an odor mask. In another, previous study, colophony had been identified as an additional allergen, indicating contact allergy to oxidized resin acids introduced into cutting fluids by the addition of tall oil [84]. Further 'new' allergens reported during the period analyzed are presented in Table 1 [85–99].

Conclusion

Our knowledge of the spectrum of substances capable of inducing contact allergy and eliciting ACD is constantly expanding. Hence, for the optimal management of a patient with ACD on how to avoid future relapses, patch test allergens and series have to be continually adapted. Both national and international contact dermatitis

research groups can act as a forum for the exchange of scientific data to allow this to happen.

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- 42 Hillen U, Pirker C, Jappe U, *et al.* Detection of late patch test reactions to paraphenylene diamine 1% and epoxy resin 1% in the standard series: a prospective multicenter study of the German Contact Dermatitis Research Group (DKG) [abstract; in German]. *J Dtsch Dermatol Ges* 2005; 3 (Suppl 1):S11.
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- 46 Kynemund Pedersen L, Johansen JD, Held E, Agner T. Augmentation of skin • response by exposure to a combination of allergens and irritants: a review. *Contact Dermatitis* 2004; 50:265–273.
This is an important review on the effect of combined exposure to irritants and allergens. Implications for regulatory issues are discussed.
- 47 Lewis VJ, Statham BN, Chowdhury MM. Allergic contact dermatitis in 191 • consecutively patch tested children. *Contact Dermatitis* 2004; 51:155–156.
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