Chemical Compounds as Trigger Factors of Immediate Contact Skin Reactions

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INTRODUCTION

Immediate contact skin reactions manifest as Contact Urticaria (CoU), Contact Urticaria Syndrome (CUS) and Protein Contact Dermatitis (PCD). These pathologies are characterized by the immediate skin development of itchy flares, wheals and/or dermatitis, following external contact with a substance (1).

CoU usually appears within 30 minutes, and clears completely within hours, without residual signs of irritation. Fisher defined it in 1973, even if this phenomenon had been recognized for many years (2). CoU is a very frequent pathology, and an ever-expanding list of causes, substances ranging from simple chemicals to macromolecules, has been reported. Mostly proteins (molecular weight 10000 Da to several hundred thousands), but also chemical compounds of low molecular weight (LMW) (< 1000 Da) are involved. The present chapter will focus mainly on these chemical compounds of LMW.

In order to review the LMW chemical agents responsible for immediate contact skin symptoms, it is first necessary to remind the defined categories of CoU according to the underlying mechanism(s) involved. Basically, CoU is classified as non-immunological or immunological. A third category exists for reactions with mixed features or undetermined pathomechanisms (3). Non-immunological CoU (NICoU) is the most common form of the disease, occurring without prior exposure to an eliciting substance, that means without previous sensitization. Substances inducing NICoU are frequently encountered in our environment as preservatives, fragrances and flavorings in cosmetics, toiletries, topical medicaments and foodstuffs (4, 5). The pathogenesis is not clearly understood but it appears to involve the release of vasogenic mediators without involvement of immunological processes. Due to the lack of response to antihistamines and the positive response to acetylsalicylic acid and non-steroidal anti-inflammatory drugs, it has been proposed that the physiopathology involves prostaglandin release from the epidermis rather than histamine release from the mast cells, as previously assumed (6, 7). On the other hand, immunologic CoU (ICoU) is a type I hypersensitivity reaction, mediated by allergen-specific immunoglobulin E (IgE) in previously sensitized individuals (3). In this case, the release of histamine is the major mechanism of action seen. The mechanism following skin challenge includes allergen penetration through the epidermis, binding to IgE on mast cells, causing degranulation and release of histamine and other vasoactive substances such as prostaglandins, leukotrienes and kinins (8). Again, a large number of causes have been documented as causing ICoU. Many are plant or animal proteins (9). However, many LMW chemicals including drugs, biocides and preservatives, metals or industrial compounds can also produce ICoU. Finally, a third category exists for substances that show mixed features of NICoU and ICoU, or where the mechanism remains unclear. The bleaching agent

ammonium persulfate is a classic example. Although the clinical picture looks like an IgE-mediated reaction, such antibodies against ammonium persulfate have not been identified (5, 10). However, this third category is much less common and will not be treated herein.

Tables 1 and 2 resume the most reported LMW chemical agents producing immediate non-immunologic and immunologic skin reactions (1, 11).

CHEMICALS AND NON-IMMUNOLOGICAL REACTIONS

Chemical compounds mainly described as triggering immediate contact reactions and NICoU are listed in Table 1. Many of these chemicals are used in fragrances, in cosmetic products, as biocides or preservatives, and as drugs or topical medications. Though, there are also other miscellaneous chemicals and metals responsible for these reactions. Most individuals react to these substances with local erythema and/or edema within 45 min after application, albeit with widely varying intensities of skin reaction (12).

Fragrances and cosmetics ingredients

NICoU reactions to fragrances and to cosmetics ingredients are well known (13). NICoU has been reported for example to some of the constituents of the Fragrance Mix I (FMI), and to balsam of Peru (14). However, clinical relevance must be carefully examined because individuals may develop simple NICoU or contact urticaria associated with delayed hypersensitivity. Indeed, the components of the FMI (α-amyl cinnamic aldehyde, cinnamic aldehyde, cinnamic alcohol, eugenol, isoeugenol, geraniol, hydroxycitronellal, oak moss) are potent skin sensitizers responsible for delayed type allergic contact dermatitis. Actually, the FMI, developed in the late 1970s, and the Fragrance Mix II developed in 2005, are the most valuable screening tools for the detection of delayed hypersensitivity to fragrances (15, 16). Safford et al. conducted a study on 20 patients positive to the FMI in 48 hours and classified the FMI ingredients according to the decreasing ability to induce contact urticaria as follows: cinnamic aldehyde, cinnamic alcohol, isoeugenol, hydroxycitronellal and geraniol (17). Cinnamic aldehyde and cinnamic alcohol were the strongest urticaria inducers for non-allergic patients. Contact urticaria from cinnamic aldehyde has been reported by several authors (4), leading even to anaphylaxis (18). Among the many components of balsam of Peru, cinnamic aldehyde is described as well as the strongest agent inducing NICoU, followed by cinnamic acid, benzoic acid and benzaldehyde (19). Cinnamic aldehyde is the main component of cassia oil (ca. 90%) and cinnamon bark oil (ca. 75%). It is also the main component of artificial cinnamon oil. Smaller quantities are found in many other essential oils. In

nature, the *trans* isomer is predominant. It is a yellowish liquid with a characteristic spicy odor, strongly reminiscent of cinnamon. Being an α,β-unsaturated aldehyde, it undergoes many reactions of which hydrogenation to cinnamic alcohol. Its oxidation occurs readily on exposure to air yielding cinnamic acid. Cinnamic acid has been also used in perfumery, as a flavoring ingredient in pharmaceutical preparations and in food products. Forsbeck and Skog found contact urticaria from cinnamic acid 5% in petrolatum in three out of five patients with immediate skin reactions to balsam of Peru (19). The unsaturated terpene alcohol geraniol, a colorless liquid with a flowery-rose like odor, gave a patch test reaction after 20 min of application in a woman suffering from recurring oedema in the lips and neck. The test with a perfume containing geraniol gave generalized urticaria (20). CUS at stage IV has been reported in the case of people applying sunscreen and self-tanning products, being benzophenone-3 the major cause (21). Benzophenone-3, also named oxybenzone, is often incorporated into sunscreen formulations to offer enhanced UVA protection because its absorption spectrum extends to less than 350 nm. In toothpaste and in a make-up remover, menthol, belonging to the family of monoterpenols, was described as the reason for urticaria reactions, plus cephalgia, in a woman placed in a context of generalized urticaria (22). Symptoms disappeared with total eviction of menthol.

Biocides and preservatives

Many compounds used as preservatives, such as imidazolidinyl urea, bronopol and sorbic acid, have been shown to induce positive reactions at patch test after 45 min in a population of 50 patients (23). Contact urticaria from sorbic acid is however thought to be rare, and only few reports can be found in the literature. Some authors described that creams and shampoos containing sorbic acid caused erythema, slight itching and oedema sometimes (24, 25). Like sorbic acid, benzoic acid is a natural preservative, having antibacterial and antifungal properties. Present also in balsam of Peru, it induced contact urticaria at 5% in patients with immediate contact reactions to balsam of Peru (19). It has also been commonly used as a preservative in acidic food products. Thus, it was reported in a published study that benzoic and sorbic acid could elicit NICoU at concentrations in use in salad dressing in 18 of 20 school children (26). In the case of free formaldehyde, for which bactericidal and fungicidal properties confer it a place of choice for preservation of cosmetics, its use has been reduced because of the bad press it has received as an irritant, sensitizer and potential carcinogen (27). Formaldehyde is known to be a strong-ubiquitous skin sensitizer, including from non-cosmetic sources of contact. Because of this, exposure to formaldehyde in the EU is subject to restrictions. Free formaldehyde may be used as a preservative in all cosmetic products (maximum authorized concentration 0.2%, except

0.1% in products for oral hygiene) except aerosol cosmetics. Annex VI of the Cosmetics Directive 76/768 EC further stipulates that all finished products containing formaldehyde or substances that release formaldehyde must be labelled with the warning "contains formaldehyde" where the concentration of free formaldehyde in the finished product exceeds 0.05% (28). As an alternative, chemical compounds that slowly release formaldehyde in the presence of water and under usage conditions, the so-called formaldehyde-releasers, are commonly employed as preservatives in cosmetics (water based preparations) instead of free formaldehyde. Examples are bronopol and imidazolidinyl urea. Unfortunately, many formaldehyde-releasers used in cosmetics are also skin sensitizers, due to released formaldehyde but also to reactive intermediates other than formaldehyde that could be involved in the formation of the hapten-protein antigenic complex, a key step of the sensitization process, and thus explaining their sensitizing potential *per se* (29). Even if it is a strong sensitizer, reported immediate reactions to formaldehyde are mainly classified as NICoU because they seem not to be mediated by IgE (30). However, there is still no consensus in the reports that have appeared as to whether the mechanism is immunological or non-immunological (31). Contact urticaria to other biocides such as *p*-chloro-*m*-cresol, benzyl alcohol, 2-phenoxyethanol and polyethylene glycols, used as preservatives in a wide number of cosmetics and topical preparations, has also been reported (32-35). Contact urticaria from alcohols was reviewed in the 90s, with cases classified as non-immunological and some as immunological based on open skin tests (36).

Drugs

Many drugs can also provoke immediate skin reactions. They include mainly antibiotics, because direct contact of nurses and health care personnel during their preparation, or employees during the production in the pharmaceutical industry. Penicillins and cephalosporins are the most incriminated. All of them seem to have an immunological physiopathology and will be discussed below. For most of the other drugs reported, observed immediate contact reactions cannot be definitely classified as non-immunological or immunological. Often, skin tests do not allow distinguishing between an IgE dependent reaction and a non-specific histamine release, and research of specific IgE by using the radioallergosorbent test (RAST) is only available for some drugs. One example is given by lidocaine. It is a common amino amide-type local anaesthetic applied topically, and the most important class 1B antiarrhythmic drug applied intravenously. An immediate positive patch test and prick test demonstrated its involvement in the simultaneous presence of contact urticaria and allergic contact dermatitis in the same patient (37, 38). Ketoprofen, an important cause of photocontact dermatitis, has

also been described as responsible for contact urticaria (39). Other immediate reactions have been observed in personnel of psychiatry services during the manipulation of phenothiazines, antipsychotic drug related to the thiazine class of heterocyclic compounds, such as chlorpromazine and promethazine (40).

To end with this section, among the many professional areas where case reports of contact urticaria have been reported, workers of pharmaceutical and chemical industries are of considerable concern. They are in contact with highly reactive substances (some listed in Table 1) used for synthesis for example that have been also described as inducers of immediate skin reactions.

The pathogenesis of NICoU to all these chemicals is not clearly defined. Different urticariogens may act by different mechanisms. For example, dimethyl sulfoxide can both damage blood vessels and cause mast cell degranulation. However, antihistamines do not inhibit reactions to dimethyl sulfoxide and other NICoU triggering agents, whilst acetylsalicylic acid and non-steroidal anti-inflammatory drugs do, both orally and topically, suggesting a role for prostaglandins (6, 7, 41). Release of prostaglandin D_2 without concomitant histamine release has been shown for instance following topical application of sorbic acid and benzoic acid (42, 43).

CHEMICALS AND IMMUNOLOGICAL REACTIONS

ICoU is an immediate type 1 hypersensitivity reaction, occurring in patients who have specific IgE against the agent(s) eliciting contact urticaria. ICoU needs sensitization, and will appear after repeated contacts. It is more frequent in people with previous atopic symptoms. The allergen reacts with the IgE at the surface of mast cells and basophiles and provokes the release of histamine and other vasoactive substances, except in rare cases where IgG or IgM have been incriminated. The consequences are potentially more serious than for NICoU, as reactions may not remain localized to the area of contact, and generalized urticaria, or even involvement of organs such as the respiratory and gastrointestinal tract may follow, and end with anaphylactic shock. The commonest agents inducing ICoU are food proteins (animal or vegetal), animal proteins, and natural rubber latex, and have been largely reviewed (9, 44). However, chemicals of LMW can also induce ICoU and are listed in Table 2. They are very often present in drugs, cosmetics (45) and industrial preparations. There are extensive lists of proteins and chemicals reported as causing ICoU, only a part of them being reported as occupational (3, 11, 44). Most publications about contact urticaria concern case reports or little series and epidemiological

studies are scarce. However, some data indicate that ICoU is not rare, although frequently underestimated.

Diagnosis of occupational contact urticaria is based on the patient's previous medical history, chronology and description of skin symptoms. With exception to substances inducing NICoU, skin tests are generally necessary for diagnosis. An order of skin investigations for evaluation of immediate responses has been suggested (3, 46). Skin prick tests with fresh material or commercial reagents is the gold standard diagnostic test (8). But the ultimate evidence corroborating that a compound is responsible for ICoU is the measurement of specific IgE in the serum of the patient by the radioallergosorbent RAST test whenever possible. The RAST is a radioimmunoassay test to detect specific IgE antibodies to a suspected or known agent (protein, chemical compound) responsible of ICoU. The patient's serum is incubated with the agent bound to a solid phase, and the amount of specific IgE recognising and binding to the agent is quantified with radiolabelled anti-IgE (47). Determination of specific IgE by RAST will confirm type I hypersensitivity, but their ordinary detection is restricted to some compounds, particularly when they are non-proteinaceous. In this section, some examples reported in the literature are given.

Evidence on IgE-mediated urticaria to low molecular weight compounds: reported examples

Biocides and preservatives

Chloramine is commonly used as a sterilizer, disinfectant and chemical reagent. It has been described as an occupational hazard for pharmaceutical workers, nurses and cleaners. Goossens et al. reported the first case of immediate positive epicutaneous tests to chloramine powder solutions used by a nurse (48). All skin tests performed on the patient were suspicious of an immediate type reaction. The immunological nature of the clinical manifestations was investigated by RAST on serum of the patient. High levels of IgE antibodies to chloramine were found, those previously bound to human serum albumin (HSA). The clinical manifestation on the patient was confirmed by radioimmunoassay and classified as a stage 3 contact urticaria syndrome. Chloramine is often confused with chloramine-T as both are employed as sterilizer, antiseptic and disinfectant agents. However, they are two different chemicals. Chloramine-T is a *N*-chlorinated deprotonated sulfonamide, white powder, contrarily to chloramine, a simple monochlorinated amine (NH_2Cl) which is a colorless liquid usually handled as a diluted aqueous solution. Allergic asthma caused by chloramine-T is well known and the reactions are IgE mediated. Kramps et al. were able to demonstrate the presence of specific IgE antibodies in the serum of asthmatic-chloramine T allergic patients (49). However, skin symptoms of IgE dependent

contact urticaria have also been reported in the case of a hospital bath attendant in Finland. The performed RAST to chloramine-T showed specific IgE antibodies with values being defined as positive (50).

Chlorhexidine, a cationic chlorophenyl-biguanide, is also an effective antiseptic and disinfectant, that can trigger IgE-mediated type I hypersensitivity reactions in sensitized individuals (51). Many health care workers are exposed to hand washes containing chlorhexidine. In the United Kingdom, four cases of occupational IgE-mediated allergy to chlorhexidine were identified, the diagnosis being made on an appropriate clinical history with positive serum specific IgE to chlorhexidine and/or positive skin prick testing (52).

Interestingly, formaldehyde, described already in the previous NICoU section, is a primary skin sensitizer inducing allergic contact dermatitis also suspected to induce ICoU. There have been few reports on allergy to formaldehyde associated with IgE, and single cases of formaldehyde-specific IgE mediated urticaria exist in the literature (53). Thus, probably formaldehyde should be classified as a substance that shows mixed features of NICoU and ICoU, as the mechanism remains unclear.

Drugs

Antibiotics are very often associated to ICoU, such as penicillin (54). Allergic reactions are estimated to occur in approximately 2% of patients treated with penicillin. Most of these are maculopapular or urticarial rashes. Severe reactions to penicillin such as anaphylaxis can occur and are potentially life threatening. Penicillin belongs to the β-lactam group of antibiotics. All penicillin antibiotics contain a common nucleus (6-aminopenicillanic acid) composed of a β-lactam ring and a thiazolidine ring, this complex connected to a side chain. An intact β-lactam ring is necessary for bactericidal activity, and the side chain determines the spectrum of antibacterial activity, the susceptibility to destruction when exposed to acids and β-lactamases, and pharmacokinetics properties. Penicillin is a hapten and becomes immunogenic only when it binds to a protein. The β-lactam ring covalently binds to lysine residues of proteins and forms the penicilloyl group, known as the “major determinant” because it is the major penicillin metabolic product. Penicillin metabolites also form disulfide bonds with sulfhydryl groups of cysteine, producing the “minor determinants”, so called because they are formed in smaller quantities. Thus, immediate allergic reactions to penicillin are mediated through IgE antibodies against either the major or minor determinants or both.

Based on this, penicillin skin testing techniques have been developed demonstrating the presence or absence of specific IgE antibodies against major and minor penicillin determinants. The use of

benzylpenicilloyl-poly-L-lysine can test IgE antibodies against major determinants. Histamine is used as a positive control, and saline is used as a negative control. Skin detection of serum IgE specific for major penicillin determinants has a high positive predictive value but fails to identify patients with penicillin allergy. It has been suggested that, ideally, skin testing to major and minor penicillin determinants would improve diagnosis. Methods of preparation of reagents for minor determinants have been published, and penicillin G has been used as a partial source of minor determinants. Today, alternatives to benzylpenicilloyl-poly-L-lysine and minor determinant mixtures are commercially available for skin testing (55). Penicillin skin testing is believed to be safe if done properly, although severe reactions such as anaphylaxis have been reported, these produced because violation of the test protocols such as doing intracutaneous testing without first doing prick testing.

Concerning the RAST and the enzyme-linked immunosorbent assay (ELISA), they detect IgE antibodies to the major penicillin determinant only, with a sensitivity of approximately 80% (56).

The immunologic responses to different determinants of benzylpenicillin, amoxicillin and ampicillin have been also reported by using these methodologies (57). One study reported that the sensitization rate by skin prick and intradermal tests to benzylpenicilloyl-poly-L-lysine and a mixture of minor antigenic determinants was 12% in 83 asymptomatic Turkish nurses (58). Prick and intradermal penicillin sensitivity tests reported rates of 22% for benzylpenicilloyl-poly-L-lysine, 21% for minor determinant mixture, 43% for amoxicillin, and 33% for ampicillin in patients with a clinical history of urticaria and/or anaphylaxis (59).

After penicillins, cephalosporins are the most important β-lactams inducing IgE mediated reactions. Responses may be selective or cross-react with common β-lactam determinants. Unlike determinants derived from benzylpenicillin, cephalosporin allergenic determinants have not been well identified but it is possible to monitor serum specific IgEs. In a cross-reactivity study conducted with a group of Italian subjects who had immediate allergic reactions to one or more cephalosporins (ceftriaxone, cefotaxime, ceftazidime, cefuroxime), IgE evaluation was performed by skin tests and RASTs with the responsible drugs as well as to classic penicillin determinants (60). Prick and intradermal tests were performed with penicilloyl-polylysine, minor determinant mixture, penicillin G, ampicillin, amoxicillin, and with the cephalosporins. RAST used benzylpenicilloyl-polylysine, amoxicilloyl, ampicilloyl-polylysine and the cephalosporin conjugated to polylysine. The results suggested that a small percentage of cephalosporin allergic subjects reacted to penicillin determinants, and most had positive results to determinants generated only by cephalosporins. In a more recent study, the prevalence and risk factors of sensitization to cephalosporin was evaluated in a total of 161 health

care workers. The ELISA assay measured serum specific IgE antibodies to conjugates of three cephalosporins and HSA. Sensitization rates determined by this technique were 17.4% for any cephalosporin, 10.4% for cefotiam, 6.8% for ceftriaxone and 3.7% for ceftizoxime (61).

To mention other drugs involved in immediate skin reactions, a case of contact urticaria and anaphylaxis reaction following administration of powder containing clioquinol and bacitracin was described (62) and also immediate hypersensitivity reactions presumably IgE mediated to pyrazolones (63).

Other chemicals

In plastic industry, workers are in contact with highly reacting chemicals. Cyclic acid anhydrides are synthetic highly reactive LMW compounds widely used as curing agents for epoxy resins and in the production of polyester resins. Commonly used anhydrides are phthalic anhydride, tetrahydrophthalic anhydride, methyl tetrahydrophthalic anhydride, hexahydrophthalic anhydride, methyl hexahydrophthalic anhydride, maleic anhydride and trimellitic anhydride. Cyclic acid anhydrides often cause allergic respiratory diseases, and in the literature only single case reports of contact urticaria of few patients were found. However, recently, occupational contact urticaria has been described by a Finnish study as workers may be exposed in powder or liquid form during manufacturing processes (64). Data are presented for 21 subjects who had been diagnosed with occupational contact urticaria because of exposure to organic acid anhydrides and examined during the period 1990-2006. Prick tests with HSA-acid anhydrides conjugates, RAST determination of specific IgE and open application tests were used for the diagnosis. The majority of the patients had been exposed to an epoxy resin containing methyl hexahydrophthalic anhydride. Specific IgE results were in line with the prick tests and the large reaction was seen for the acid anhydride the patient had been exposed to. Phthalic anhydride IgE was positive in 19 of 20 patients. Authors conclude that contact urticaria to these compounds may be more common than previously believed, as firstly shown by a previous Finnish study with two patients (65).

Another important constituent of epoxy resins that has been incriminated as producing immediate reactions is bisphenol A for which specific IgE were demonstrated to cause them (66). Similar studies have been reported for another known respiratory allergen, diphenylmethane-4,4'-diisocyanate (67, 68), and for acrylates such as 2-ethylhexyl acrylate, acrylic acid, cyanoacrylates and methyl methacrylate (69).

Contact urticaria to permanent hair dyes such as *para*-phenylenediamine, which is a very well known skin sensitizer, is almost exclusively reported in consumers, but has also been described in a

beautician (70, 71). Other chemical compounds of LMW reported as inducing ICoU are aliphatic polyamides (72), methyl ethyl ketone, widely used as solvent in plastic manufacture (73) and monoamylamine (74) a vehicle ingredient of topical medicaments.

Finally, metals and metallic salts can also cause occupational contact urticaria. Aluminum (75), chromium, cobalt (76), iridium salts (77), nickel (75, 78), platinum salts and rhodium have been reported. Among them, platinum salts are important allergens in the catalyst industry and clinical manifestations may involve both the respiratory system and the skin (79, 80). In some cases, an immunological mechanism with specific IgE is demonstrated (78, 81). A RAST was developed for example for the measurement of IgE antibodies specific to platinum chloride complexes in sensitized workers (82).

CONCLUSION

Numerous LMW chemical compounds may cause contact urticaria, and many of these are encountered in everyday life. Skin clinical manifestations of immediate contact reactions can be expressed as urticaria and/or dermatitis. Both manifestations can be developed by the same patient and can be induced by the same compound simultaneously. Establishing a diagnosis of ICoU is therefore important, in order to confirm the need for allergen avoidance and in view of the potentially life threatening nature of this pathology. Substances responsible for immediate contact skin reactions may be classified by molecular weight, mechanism of action and occupational relevance. Cosmetics, plants, vegetables and food are still the most common agents responsible for new cases of contact urticaria. However, detailed chemical and biological studies continue to be necessary to determine the how and why, and the behavior that provide immunological signs.

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Table 1. Chemical compounds reported as triggering immediate contact reactions and NICoU (1, 11)

Fragrances-Cosmetics	**Biocides-Preservatives**	**Drugs**	**Other**
α-Amyl cinnamic aldehyde[1]	Alcohols (amyl, ethyl,	Acetylsalicylic acid*	Acetic acid*
Anisyl alcohol	propyl, isopropyl,	Aminophenazone*	Butylhydroxytoluol*
Balsam of Peru	benzyl)*	Amoxicillin*	Chloroform
Benzaldehyde	Benzoic acid	Benzocain*	Diethylfumarate*
Benzophenone	Bronopol	Capsaicin	Dimethylammonium
Cassia oil	Camphor	Chlorpromazine*	chloride*
Cetyl alcohol (emulsifier)*	Chlorocresol	Dinitrochlorobenzene*	Dimethyl sulfoxide
Cinnamic acid	Formaldehyde	Ketoprofen*	Fumaric acid*
Cinnamic alcohol[1]	Imidazolidinyl urea	Lidocaine*	Panthenol* (hair product)
Cinnamic aldehyde[1]	Kathon CG	Nicotinic acid esters	Polypropylène*
Cinnamon oil*	2-Phenoxyethanol*	Pilocarpine*	Trichloroethanol*
Coumarin	Polyethyleneglycol*	Propyphenazone*	Turpentine (plant derivative)
Eugenol[1]	Sodium benzoate	Promethazine*	Vinyl pyridine*
Geraniol[1]	Sorbic acid	Steroids*	Xylene*
Hydroxycitronellal[1]			
Isoeugenol[1]			*Metals*
Menthol			Aluminum*
Propylene glycol			Copper*
Pyrrolidone carboxylate			Gold*
Resorcinol			Palladium*
Stearyl alcohol (emulsifier)*			Rhodium
Vanillin			Ruthenium
			Tin
			Zinc

* Immediate contact reaction, unclassified non-immunological/immunological

[1] Constituent of the Fragrance Mix I

Table 2. Chemical compounds reported as triggering immunological immediate contact reactions/ICoU (1, 11)

Fragrances-Cosmetics	**Biocides-Preservatives**	**Drugs**	**Other**
Allantoin[1]	Ammonia	Aescin[1]	Acetyl acetone
Polysorbates (emulsifier)[1]	Butylated-hydroxytoluene[1]	Albendazole	Acid anhydrides
Sorbitan monolaurate (emulsifier)[1]	Chloramine	Ampicillin	Acrylic acid[1]
Sorbitan monostearate (emulsifier)[1]	Chlorhexidine	Azithromycin	Acrylic monomers
Sorbitan sesquiolate (emulsifier)[1]	Chlorocresol	Bacitracin	Aliphatic polyamide
Wool alcohol	Formaldehyde	Benzoyl peroxide	*p*-Aminodiphenylamine (dye)
	Mercurochrome	Cephalosporins	Aminothiazole[1]
	Parabens[1]	Cisplatin	Aziridine
	Phenyl mercuric acetate	Chloramphenicol	Basic blue 99 (hair dye)
	Phenyl mercuric propionate	Diphenylcyclopropenone	Benzonitrile
	Sodium hypochlorite	Donezepil	Bisphenol A
		Gentamycin	Carbamates
		Iodochlorhydroxyquin	Chlorothalonil
		Levopromazine	Colophony (plant derivative)
		Lindane	Diethyltoluoamine
		Mechlorethamine	Dibutylphthalate
		Methamizole	Di-(2-ethylhexyl) phthalate
		Mezlocillin	Diphenylmethane-4,4'-diisocyanate
		Neomycin	Epoxy resins
		Penicillins	Formaldehyde resin
		Pentamidine isothionate	Methyl ethyl ketone
		Phenotiazides	Monoamylamine
		Pyrazolones	Nylon
		Rifamycin	*p*-Phenylenediamine (hair dye)
		Streptomycin	
		Sulbactam	
		Virginiamycin	*Metals*
			Chromium
			Cobalt
			Iridium
			Mercury[1]
			Nickel
			Platinum salts (Cisplatin)

[1] Described as (?)