# Immediate Skin Contact Reactions Induced by Chemicals

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**Abstract:**

An ever-expanding list of causes has been reported for immediate skin contact reactions, of which mostly proteins (molecular weight 10000 Da to several hundred thousands), but also chemical compounds of low molecular weight (lower than 1000 Da). Low molecular weight chemical agents can be indeed responsible for immediate contact skin symptoms in the different defined categories of contact urticaria. The most important chemicals responsible for non-immunological and immunological contact urticaria are described in this chapter. For simplification and comprehension purposes they have been classified into the major containing families of products that include fragrances and cosmetic ingredients, biocides and preservatives and drugs, together with other categories.

**Key words:** Immediate skin reactions, contact urticaria, non-immunological, immunological, occupational, low molecular weight compounds, fragrances, cosmetics, preservatives, drugs, chemicals.

## Introduction

## Non-Immunological and Immunological Contact Urticaria-Triggering Chemicals

Immediate skin contact reactions are characterized by the instantaneous skin development of itchy flares, wheals and/or dermatitis, following external contact with a substance. They usually manifest as Contact Urticaria (CoU), Contact Urticaria Syndrome (CUS) or Protein Contact Dermatitis (PCD).[1] CoU generally appears within approximately 30 minutes, and clears completely within hours without residual signs of irritation. An ever-expanding list of causes has been reported, of which mostly proteins (molecular weight 10000 Da to several hundred thousands), but also chemical compounds of low molecular weight (LMW) (< 1000 Da).

LMW chemical agents can be responsible for immediate contact skin symptoms in the different defined categories of CoU. According to the underlying mechanisms involved, CoU is classified as non-immunological or immunological. A third category exists for reactions with mixed features or undetermined pathomechanisms.[2] This third category is much less common and will not be treated herein.

Non-immunological CoU (NICoU) is the most common form of the disease. NICoU occurs without prior exposure to an eliciting substance and without previous sensitization. Chemicals inducing NICoU are frequently encountered in our environment as biocides or preservatives, fragrances and flavorings in cosmetic products, toiletries, drugs, topical medicaments and foodstuffs.[3,4] 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.[5] The pathogenesis is not clearly understood. It appears to involve the release of vasogenic mediators without involvement of immunological processes (Fig. 1a). Due to the lack of response to antihistamines and positive responses 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 mast cells.[6,7]

Conversely, immunologic CoU (ICoU) is an immediate type I hypersensitivity reaction, mediated by allergen-specific immunoglobulin E (IgE) in previously sensitized individuals.[2] Thus, ICoU needs sensitization, and will appear after repeated contacts with the trigger substance. It is more frequent in people with previous atopic symptoms. Histamine release is the major mechanism of action seen. This mechanism includes allergen penetration through the epidermis and binding to IgE at the surface of mast cells and basophiles, causing degranulation and release of histamine and other vasoactive substances such as prostaglandins, leukotrienes and kinins (Fig. 1b).[8] In rare cases, IgG or IgM have been also 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.

A large number of causes have been documented as producing ICoU. The commonest agents inducing ICoU are food proteins (animal or vegetal), animal proteins and natural rubber latex. These have been largely reviewed.[9,10] However, LMW chemicals including drugs, biocides and preservatives, metals or industrial compounds can also produce ICoU. They are very often present in drugs, cosmetics [11] and industrial preparations. There are extensive lists of proteins and chemicals reported as causing ICoU, only a part of them being reported as occupational.[2,10,12] Most publications about CoU concern case reports or little series and epidemiological studies are scarce. However, some data indicate that ICoU is not rare, although frequently underestimated. 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 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.[13] 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.

Table 1 resume the most reported LMW chemical agents producing immediate non-immunologic and immunologic skin reactions.[1,12]. **In this chapter, the most important LMW chemicals responsible for NICoU and ICoU are described**, and classified into the major containing families of products, fragrances and cosmetic ingredients, biocides and preservatives and drugs, together with other categories.

## Fragrances and Cosmetics Ingredients

NICoU reactions to fragrances and to cosmetics ingredients are well known.[14] They have been often reported to some of the constituents of the Fragrance Mix I (FMI) and to balsam of Peru.[15]

The FMI, developed in the late 1970s, and the Fragrance Mix II (FMII) developed in 2005, are the most valuable screening tools for the detection of delayed hypersensitivity to fragrances.[16,17] Indeed, the components of FMI (α-amyl cinnamaldehyde, cinnamaldehyde, cinnamic alcohol, eugenol, isoeugenol, geraniol, hydroxycitronellal and the natural extract oak moss) and FMII (hidroxyisohexyl 3-cyclohexene carboxaldehyde, citral, α-hexyl-cinnamadehyde, citronellol, farnesol and coumarin) are the most common skin sensitizers identified as responsible for delayed type allergic contact dermatitis to fragrances. Consequently, clinical relevance to these chemicals must be carefully examined because individuals may develop simple NICoU or CoU associated with delayed hypersensitivity. Chemical structures of FMI and FMII ingredients are shown in Fig. 2.

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 CoU as follows: cinnamaldehyde, cinnamic alcohol, isoeugenol, hydroxycitronellal and geraniol.[18] Cinnamaldehyde and cinnamic alcohol were the strongest urticaria inducers for non-allergic patients.

CoU from cinnamaldehyde has been reported by several authors [3], leading even to anaphylaxis.[19] Among the many components of balsam of Peru, cinnamaldehyde is described as well as the strongest agent inducing NICoU, followed by cinnamic acid, benzoic acid and benzaldehyde.[20]

***Balsam of Peru*** is derived from the sap of *Myroxylon pereirae* (MP) tree. It is composed of 250 constituents, of which 189 are of known chemical structure.[21] MP has been used in topical medicaments for its antibacterial properties, and in many countries it has been abandoned for that use due to its sensitizing potential. However, it may still occur in natural and herbal products, being used as a flavor or perfume ingredient. Extracts and distillates of MP are still used in perfumes.[22] It is thus possible that these can cause allergic reactions in MP sensitized individuals.

***Cinnamaldehyde*** 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 CoU from cinnamic acid 5% in petrolatum in three out of five patients with immediate skin reactions to balsam of Peru.[20]

***Geraniol*** is an olefinic terpene mainly present in palmarosa, geranium and rose oils. It is a colorless liquid, with a flowery-roselike odor. A case of a patient with CoU from geraniol has been reported to be caused by immunological mechanisms. The patient developed widespread urticaria and flare reactions on the face and neck at the 72 hours reading of the patch test.[23] Oxidation processes produce aldehydes geranial and neral, and in addition, hydroperoxides. Autoxidation greatly influences the sensitizing effect of geraniol, becoming a potent allergen.[24]

***Eugenol*** and ***isoeugenol*** are phenylpropene compounds. ***Eugenol*** is the main component of several essential oils; clove leaf oil and cinnamon leaf oil may contain > 90%. It occurs in small amounts in many other essential oils. It is a colorless to slightly yellow liquid with a spicy, clove odor. It is widely used in dental practice to relieve pain arising from various sources, such as pulpitis and dentinal hypersensitivity. It is also used in toothache drops, mouthwash, and antiseptics. Eugenol in dental preparations has been reported to cause CoU, gingivitis, stomatitis venenata and allergic hand eczema in dental personnel.[25,26] It is considered to be a less common sensitizer than isoeugenol, cinnamaldehyde or cinnamic alcohol. ***Isoeugenol*** occurs in many essential oils, mostly with eugenol, but not as the main component. Commercial isoeugenol is a mixture of *cis* and *trans* isomers, in which the thermodynamically more stable *trans* isomer dominates. It is a yellowish, viscous liquid with a fine clove odor. Isoeugenol is a strong allergen.[27] It caused contact allergy in 1.7% of 2261 consecutive tested eczema patients in an European multicenter study.[28] It is found in many cosmetic products and may be present in relative highly concentrations.

***Coumarin*** is an aromatic lactone naturally occurring in Tonka beans and other plants, determining for example the odor of woodruff. It is widely used in fine fragrances for spicy green notes. Considered for long time a sensitizer, impurities have been blamed for the sensitizing effect.[29]

Fragrances and cosmetic products contain also ingredients other than odorant compounds that have been described to produce NICoU and ICoU. Among them, benzophenone, polysorbates, sorbitan sesquiolate, propylene glycol and wool alcohols.

***Benzophenones*** are photo-screen agents used in sunscreens and cosmetics, such as antiaging creams, hair sprays and shampoos, paints and plastics. Benzophenones have been documented to cause numerous adverse cutaneous reactions, including contact and photo-contact dermatitis, contact and photocontact urticaria, and anaphylaxis. In recent years they became particularly well known for their ability to provoke allergy and photoallergy.[30] They were named the American Contact Dermatitis Society's Allergen of the Year for 2014. CUS at stage IV has been reported in the case of people applying sunscreen and self-tanning products, being benzophenone-3 the major cause.[31] 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. Cases of anaphylaxis from topical application of benzophenone-3 have been published. The cases resulted in a generalized wheal and flare reactions and syncope after widespread application of a sunscreen or sunless tanning product with this filter. CoU developed after more limited exposure.[31,32]

***Polysorbates*** are a class of emulsifiers used in some pharmaceuticals and food preparations. But they are also often used in cosmetics to solubilize essential oils into water-based products. Oily liquids, they derive from esterification of ethoxylated sorbitan with fatty acids. The nomenclature used for polysorbates is characteristic. For example, polysorbate 80, also called polyoxyethylene 20 sorbitan monooleate. The number 20 following the 'polyoxyethylene' part refers to the total number of oxyethylene -($CH_2CH_2O$)- groups found in the molecule. The number following the 'polysorbate' part is related to the type of fatty acid associated with the polyoxyethylene sorbitan part of the molecule. Monolaurate is indicated by 20, monopalmitate by 40, monostearate by 60 and monooleate by 80. Already in the 70s, Maibach and Conant reported an urticaria case to polysorbate 60 in a male patient with redness on the forehead when applying hydrocortisone 1% cream.[33] The chemical responsible in the cream was determined to be polysorbate 60, an emulsifying agent mixture of estearate esters of sorbitol and sorbitol anhydrides, consisting mainly on the monoester. It is also known as Tween® 60 or polyoxoethylene 20 sorbitan monostearate. Since then, several cases have continued to be reported. More recently, a biologic-induced urticaria due to polysorbate 80 in a psoriasis treatment in Spain has been reported.[34] ***Sorbitan sesquiolate***, a sorbitol-based emulsifier, is actually added to the FMI ingredients to constitute the mixture. Sorbitol-based emulsifiers are commonly used in topical corticosteroids, topical antibiotics and antifungals, moisturizing creams and lotions. Contact dermatitis from sorbitol derivatives appears to be increasingly prevalent.[35] This trend goes hand-in-hand with the ICoU to sorbitan sesquiolate reported in a corticosteroid ointment.[36]

***Propylene glycol***, also called propane-1,2-diol, is a viscous colorless alcohol (chemically classed as a diol), nearly odorless but possessing a weak sweet taste. It is mainly used for the production of unsaturated polyester resins. It is also used as a humectant food additive (E1520), hygroscopic compound used to keep products moist, as a moisturizer in cosmetics, food, toothpaste, mouth wash and tobacco products, as the main ingredient in deodorant sticks, as an antifreeze liquid and as a solvent in many pharmaceuticals and topical formulations. Propylene glycol is one of the major ingredients of the cartridges used in electronic cigarettes where it is aerosolized in the atomizer. It has been associated with irritant and allergic contact dermatitis as well as CoU in humans. These sensitization effects can be manifested at propylene glycol concentrations as low as 2%.[37] Still, the Cosmetic Ingredient Review Panel found that propylene glycol is safe if used in cosmetic products at concentrations not exceeding 50%.[38] The above cited work of Maibach and Conant describing an urticaria case to polysorbate 60 concerned a hydrocortisone cream containing propylene glycol.[33] CoU could not be concluded in experiments with open propylene glycol application. Only one report describes NICoU after topical application.[39,40]

***Wool alcohols*** are the principle component of lanolin. Lanolin is a natural product obtained from the fleece of sheep. Sebum is extracted from the wool, cleaned and refined to produce anhydrous lanolin. This comprises wool alcohols, fatty alcohols and fatty acids. Currently wool alcohols are considered the main sensitizers in lanolin. Wool alcohols, wool fat, anhydrous lanolin, lanolin alcohol, wool wax and wool grease are just some of the terms used interchangeably with lanolin. Lanolin is a good emulsifier. This means it binds well with water thus it is particularly useful in the manufacture of pharmaceutical and cosmetic formulations. Wool alcohols are found in many pharmaceutical preparations, cosmetics and toiletries. They also have some industrial uses. The general incidence of lanolin allergy in consecutively tested eczema patients is around 2-3%.[41]

## Biocides and Preservatives

Preservatives are added to water-containing products (i.e. cosmetics) to inhibit the growth of non-pathogenic and pathogenic microorganisms, which may cause degradation of the product or be harmful to the consumer. After fragrances, they are the most important cause of allergic contact dermatitis, being this very well-documented.[42] CoU is less common. The literature consists essentially of case reports, and studies on actual incidence and prevalence are lacking.

Chemicals with preservative properties that are worth to describe in the CoU context are described here. It is not always clear, depending on the underlying mechanisms involved, if the reactions are involving the immune system or not. Chemical structures are shown in Fig. 3.

***Sorbic acid***, or 2,4-hexadienoic acid, is a colorless solid slightly soluble in water. It is an antimicrobial agent often used as preservative in food and drinks (E200). In general the salts (sodium, potassium and calcium sorbates, E201-203) are preferred over the acid form because they are more

soluble in water, but the active form is the acid. CoU from sorbic acid is thought to be rare, but 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.[43-45] Like sorbic acid, ***benzoic acid*** is a natural preservative, having antibacterial and antifungal properties. It is well-recognized to cause NICoU with concentration-dependent reactions.[46] Present also in balsam of Peru, it induced CoU at 5% in patients with immediate contact reactions to balsam of Peru.[20] It is commonly used also as a preservative in acidic food products. Thus, cases have been reported in were food additives and benzoic and sorbic acids elicit NICoU at concentrations in use in salad dressings or other food products.[47,48]

***Formaldehyde*** (HCHO) and its releasers constitute an important class of preservatives in consumer goods. HCHO is the simplest of the aldehydes category of compounds. It is a frequent and potent sensitizer and a strong-ubiquitous allergen, including from non-cosmetics sources of contact. Its bactericidal and fungicidal properties confer it a place of choice for preservation of cosmetics, but its use has been reduced because of the bad press it has as an irritant, sensitizer and carcinogen.[49] Exposure to HCHO in the EU is thus subjected to restrictions. Free HCHO 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. EU regulation 1223/2009 permits the use in nail hardeners up to a maximum concentration of 5%. Annex VI of the Cosmetics Directive 76/768 EC further stipulates that all finished products containing HCHO or substances that release it must be labelled with the warning "contains formaldehyde" where the concentration of free HCHO in the finished product exceeds 0.05%.[50] On January 1st 2016, the EU officially adopted its reclassification under the CLP (Classification, Labelling and Packaging) Regulations EC 1272/2008, as a Class 1B carcinogen and Class 2 mutagen. In order to continue to be used in cosmetics the criteria specified for CMR 1A and 1B must be met, including the Scientific Committee on Consumer Safety (SCCS) to declare it safe for use in cosmetic products. The SCCS has published recently an opinion that states that nail hardeners with a maximum concentration of 2.2% free HCHO can be used. Even if it is a strong sensitizer, reported immediate reactions to HCHO are mainly classified as NICoU because they seem not to be mediated by IgE.[50] However, there is still no consensus in the reports that have appeared as to whether the mechanism is immunological or non-immunological.[51] Most literature on generalized urticaria, respiratory compromise, and anaphylaxis concerns exposure to HCHO-containing disinfectants used for root canals and other dental procedures.[52,53]. There have been few reports on allergy to HCHO associated with IgE, and single cases of HCHO-specific IgE mediated urticaria exist in the literature.[52-54] Thus, probably HCHO should be classified as a substance that shows mixed features of NICoU and ICoU, as the mechanism remains unclear.

As an alternative to the use of HCHO, chemical compounds that slowly release it 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 HCHO. Examples are ***bronopol***

and ***imidazolidinyl urea***. Unfortunately, many formaldehyde-releasers used in cosmetics are also skin sensitizers, due to released HCHO but also to reactive intermediates other than HCHO 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*.[55]

***Methylisothiazolinone*** (MI) and ***methylchloroisothiazolinone*** (MCI) are the active ingredients of the biocide ***Kathon® CG*** (MI/MCI 1:3 combination), used since the 1980s and one of the most common sources of allergic contact dermatitis caused by preservatives.[56,57] Following the introduction in the EU of a 15 ppm use limit in cosmetics, contact allergy to MI/MCI significantly decreased to a prevalence rate of about 2% after the 90s. The sensitizing potential of the mixture was mostly attributed to the chlorinated derivative MCI, shown to be the stronger sensitizer, while the non-chlorinated MI was reported to be a much weaker allergen. Thus, in the early 2000s, MI alone started to be used as preservative in industrial products and in 2005 in cosmetics, but at higher concentrations than in the MI/MCI mixture due to its lower biocide potential. As a consequence, over recent years there has been an alarming increase in the prevalence of allergic contact dermatitis to MI.[58,59] Occupational cases of contact dermatitis to MI started to be reported from paints [60], followed by non-occupational cases essentially seen from wet wipes for hygiene and cosmetics.[61] Severe cases of airborne and systemic dermatitis have appeared recently from exposure to MI present particularly in water based wall paints.[62] At the same time, MI/MCI contact allergy has increased significantly over the past few years.[63] It has been proposed that the rise in MI/MCI contact allergy was likely linked to the higher consumer exposure to MI, and was most probably due to a previous sensitization of individuals to MI. Because the occurrence of consumer products containing only MI since few years, questions were raised about the MI and MCI cross-reaction pattern. Studies of chemical reactivity *in situ* in a reconstructed human epidermis model showed that reaction mechanisms for MI and MCI were different, making it difficult to explain cross-reactivity.[64] CoU cases caused by isothiazolinones are rare and are generally classified as NICoU.[65]

CoU to other biocides such as ***benzyl alcohol***, ***2-phenoxyethanol*** and ***polyethylene glycols***, used as preservatives in a wide number of cosmetics and topical preparations, has also been reported.[66-69] CoU from alcohols was reviewed in the 90s, with cases classified as non-immunological and some as immunological based on open skin tests.[70]

Other important biocides have been correlated to ICoU such as parabens, and many antiseptics such as mercurochrome, chloramine, chlorhexidine and chlorocresol.

***Parabens*** (methyl, ethyl, propyl, butyl) are a series of parahydroxybenzoates or esters of parahydroxybenzoic acid (also known as 4-hydroxybenzoic acid). Parabens are effective preservatives in many types of formulas, especially in cosmetic products. They are also used as food additives. In individuals with normal skin, parabens are, for the most part, non-irritating and non-sensitizing. Routine testing in the European standard series yields low prevalence rates of sensitization. [71,72] At the usual concentration of 0.1-0.3% in cosmetics, parabens rarely cause adverse reactions. They have

been reported to cause localized CoU when applied to the skin and an IgE immune-mediated mechanism is suspected.

***Mercurochrome*** is the trade name of merbromin, an organomercuric disodium salt and a fluorescein, used as topical antiseptic. Due to the high toxicity of mercury, it is no longer sold in the US from 1998 and in France from 2006. Mercurial compounds are known as causing allergic contact dermatitis and immediate hypersensitivity is rarely induced. Few cases have been reported were immediate hypersensitivity to mercuric fluorescein compounds has been proved by skin test and histamine liberation.[73,74]

***Chloramines*** are derivatives of ammonia by substitution of one, two or three hydrogen atoms with chlorine atoms. Monochloroamine (commonly called ***chloramine***) is an inorganic compound with the formula $NH_2Cl$. 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.[75] 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 CUS. 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 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.[76] However, skin symptoms of IgE dependent CoU 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.[77]

***Chlorhexidine*** is a synthetic chlorophenyl-bis-biguanide compound, containing two chloroguanide chains linked by a hexamethylene chain. It is a strong base and a dication at physiological pH. Usually insoluble in water, it needs to be formulated with gluconic or acetic acid to form water-soluble digluconate or diacetate esters. Chlorhexidine, especially as digluconate ester, is widely used in many dental topical applications (toothpaste, dental gel, mouthwash solutions) as it binds oral mucosa inhibiting dental plaque formation. It is also used as disinfectant and antiseptic of minor cuts and wounds. It can cause both type I immediate allergy and type IV delayed allergy. In spite its common usage the sensitization rate seems low, but this is certainly underestimated. It may induce immediate-type sensitivity reactions either by topical application or by insertion of coated catheters in surgical fields. The mechanism suspected is an IgE-mediated pathomechanism in sensitized individuals.[78] 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.[79] The main aspects of chlorhexidine toxicity have been reviewed.[80]

***Chlorocresol*** (*p*-chlorocresol) is a chlorinated phenol used as an antiseptic and preservative. It forms colorless crystals at room temperature and is slightly soluble in water. For medical use it is dissolved in alcohol combined with other phenols. Several case reports involve chlorocresol as a cause of CoU but whether this occurs through an immunological mechanism is not clear.[81,82]

## Drugs

Drugs, small reactive chemicals, can induce both NICoU and ICoU within minutes to one hour after exposure. 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 (Fig. 4.). 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.

***Lidocaine*** is a common amino amide-type local anaesthetic applied topically. It is also an antiarrhythmic drug applied intravenously. An immediate positive patch test and prick test demonstrated its involvement in the simultaneous presence of CoU and allergic contact dermatitis in the same patient.[83,84]

***Ketoprofen*** ((RS)-2-(3-benzoylphenyl)-propionic acid), an important cause of photocontact dermatitis, has also been described as responsible for CoU.[85] It is one of the propionic acid class of non steroidal anti-inflammatory drugs (NSAID) with analgesic effects.

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***. The latter is a first-generation antihistamine of the phenothiazine family. It is a chiral compound and is found as a mixture of enantiomers. Among the many professional areas where case reports of CoU 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.[86]

However, main drugs responsible for occupational CoU are antibiotics and, particularly, penicillin, ampicillin, amoxicillin, and cephalosporins. Antibiotics are very often associated to ICoU.[87]

The term ***penicillin*** is often used to refer to benzylpenicillin (penicillin G, found in 1928), procaine benzylpenicillin, benzathine benzylpenicillin and phenoxymethylpenicillin. The core of the molecule has the formula R-$C_9H_{11}N_2O_4S$, where R is a variable side chain that differentiates the penicillins from one another. The key structural feature is the four-membered β-lactam ring, essential for antibacterial activity. Thus, all penicillin antibiotics contain a common nucleus (6-aminopenicillanic acid) composed of a β-lactam ring fused with 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. Allergic reactions are estimated to occur in approximately 2% of patients treated with penicillin. Severe reactions to penicillin such as anaphylaxis can occur and are potentially life threatening. 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 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. Alternatives to benzylpenicilloyl-poly-L-lysine and minor determinant mixtures are commercially available for skin testing.[88] Penicillin skin testing is believed to be safe if done properly, although severe reactions such as anaphylaxis have been reported, these were produced because violation of the test protocols such as doing intracutaneous testing without first doing prick testing.

After penicillins, ***cephalosporins*** are the most important β-lactams inducing IgE mediated reactions.[89] Allergy has been reported with use of a specific cephalosporin, as a cross-reaction between different cephalosporins or as a cross-reaction to other β-lactam antibiotics. Unlike determinants derived from penicillins, cephalosporin allergenic determinants have not been well

identified and thus, standardized diagnostic skin testing is not available. Nevertheless, skin testing with diluted solutions of cephalosporins can be valuable in confirming IgE-mediated hypersensitivity reactions.[90,91]

***Pyrazolone*** is a five-membered ring lactam. It is a derivative of pyrazole that has a keto (=O) group. There are three isomers, 3, 4 and 5-pyrazolone. Pyrazolones are NSAIDs and the most frequent drugs inducing selective reactions thought to be mediated by specific IgE. Sensitivity of diagnostic tests is poor probably due to the incomplete knowledge of the structures involved. Research is today ongoing on pyrazolone metabolites and its relevance on hypersensitivity reactions.[92]

***Steroids*** are organic compounds with four rings arranged in a specific molecular configuration. The core structure is composed of 17 carbon atoms, bonded in four fused rings: 3 cyclohexane rings (A, B, C) and one cyclopentane ring (D). Steroids vary by the functional group attached to this core and by the oxidation state of the rings. Corticosteroids (i. e. cortisol or hydrocortisone) are potent anti-inflammatory and immunomodulator agents used in treatment of various inflammatory diseases including allergic diseases. They can in some cases induce immediate or delayed hypersensitivity reactions. Topical corticosteroids are well-known contact sensitizers. However, diagnosing an allergic reaction is still a challenge for clinicians. While knowledge of delayed hypersensitivity as a secondary effect of topical use is improving, little is known about immediate reactions to systemic corticosteroids.[93] Urticaria to hydrocortisone cases have been reported, in atopic patients after hydrocortisone injection or infusion, and in patients treated with hydrocortisone sodium succinate. All cases are thought to be IgE-mediated.[94,95]

## Other Chemicals

Chemicals not belonging to the families of compounds described above but necessary to mention are shown in Fig. 5.

***Epoxy resins*** are LMW pre-polymers, which normally contain at least two epoxide groups. The epoxide group is also known as glycidyl or oxirane group. 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, tetrahydrophthalic, methyl tetrahydrophthalic, hexahydrophthalic, methyl hexahydrophthalic, maleic and trimellitic anhydrides. Cyclic acid anhydrides often cause allergic respiratory diseases, and in the literature only single case reports of CoU of few patients were found. However, occupational CoU has been described by a Finnish study as workers may be exposed in powder or liquid form during manufacturing processes.[96] Data are presented for 21 subjects who had been exposed to organic acid anhydrides and examined during the period 1990-2006. 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.

Another important constituent of epoxy resins that has been incriminated as producing immediate reactions is ***bisphenol A***. It is an organic synthetic compound belonging to the diphenylmethane derivatives group and bisphenols, with two hydroxyphenyl groups. It is a colorless solid soluble in organic solvents, but poorly soluble in water. Specific IgE cases have been reported.[97,98]

***Acrylates*** are the salts, esters and conjugated bases of acrylic acid and its derivatives. They are common monomers (i. e. methyl methacrylate) in polymer plastics. Acrylates easily form acrylate polymers due to the high reactivity of the constituting double bonds. Monomers such as 2-ethylhexyl acrylate, acrylic acid, cyanoacrylates and methyl methacrylate have been reported to cause immediate skin reactions.[99]

***Aromatic amines*** are a broad group of chemicals used in a variety of applications, such as hair dyes, ink for printers, photographic products, paper and textile industries, among others. According to their large spectrum of application, skin exposure of the general population to these compounds is high. Safety aspects and toxicity studies have shown that *para*-amino aromatic compounds and their derivatives are strong skin sensitizers, generally related to dyeing products. One of the most known is ***para-phenylenediamine*** (PPD). PPD is one of the most common primary intermediates of oxidative hair dyes and is usually reported as the main sensitizer in hair dye dermatitis. PPD is therefore included in the European Standard Series for diagnostic patch testing of eczema patients and is generally regarded as the screening agent for contact allergy to *para*-amino aromatic compounds but also to azo aromatic compounds used in textile dyes.[100-102] It can also induce immediate-type reactions going from local urticaria to fatal systemic reactions and anaphylactic shock.[103-105]

Other chemical compounds of LMW reported as inducing ICoU are aliphatic polyamides, methyl ethyl ketone, widely used as solvent in plastic manufacture, and monoamylamine, a vehicle ingredient of topical medicaments. Also, benzonitrile, a useful solvent and versatile precursor to many derivatives, carbamate-constituting groups of polyureythanes and diethyl fumarate.

Finally, metals and metallic salts can also cause occupational CoU. Aluminum, chromium, cobalt, iridium salts, nickel, 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.[106-111]

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**TABLE 7.1**

Chemical compounds reported as triggering NICoU and ICoU skin reactions [1,12]

| Compound Name | Product Category | NICoU | ICoU | Unclassified[a] |
|---|---|---|---|---|
| Acetic acid | Other | | | × |
| Acetyl acetone | Other | | × | |
| Acetylsalicylic acid | Drugs | | | × |
| Acid anhydrides | Other | | × | |
| Acrylic acid[b] | Other | | × | |
| Acrylic monomers | Other | | × | |
| Aescin[b] | Drugs | | × | |
| Albendazole | Drugs | | × | |
| Alcohols (amyl, ethyl, propyl, isopropyl, benzyl) | Biocides-Preservatives | | | × |
| Aliphatic polyamide | Other | | × | |
| Allantoin[b] | Fragrances-Cosmetics | | × | |
| Aluminium (metal) | Other | | | × |
| Aminophenazone | Drugs | | | × |
| *p*-Aminodiphenylamine (dye) | Other | | × | |
| Aminothiazole[b] | Other | | × | |
| Ammonia | Biocides-Preservatives | | × | |
| Amoxicillin | Drugs | | | × |
| Ampicillin | Drugs | | × | |
| α-Amyl cinnamaldehyde | Fragrances-Cosmetics | × | | |
| Anisyl alcohol | Fragrances-Cosmetics | × | | |
| Aziridine | Other | | × | |
| Azithromycin | Drugs | | × | |
| Bacitracin | Drugs | | × | |
| Balsam of Peru | Fragrances-Cosmetics | × | | |
| Basic blue 99 (hair dye) | Other | | × | |
| Benzaldehyde | Fragrances-Cosmetics | × | | |
| Benzocaine | Drugs | | | × |
| Benzoic acid | Biocides-Preservatives | × | | |
| Benzonitrile | Other | | × | |
| Benzophenone | Fragrances-Cosmetics | × | | |
| Benzoyl peroxide | Drugs | | × | |
| Bisphenol A | Other | | × | |
| Bronopol | Biocides-Preservatives | × | | |
| Butylated-hydroxytoluene[b] | Biocides-Preservatives | | × | |
| Butylhydroxytoluol | Other | | | × |
| Camphor | Biocides-Preservatives | × | | |
| Capsaicin | Drugs | × | | |
| Carbamates | Other | | | × |
| Cassia oil | Fragrances-Cosmetics | × | | |
| Cephalosporins | Drugs | | × | |
| Cetyl alcohol (emulsifier) | Fragrances-Cosmetics | | | × |
| Chloramine | Biocides-Preservatives | | × | |
| Chloramphenicol | Drugs | | × | |
| Chlorhexidine | Biocides-Preservatives | | × | |
| Chlorocresol | Biocides-Preservatives | × | × | |
| Chloroform | Other | × | | |
| Chlorothalonil | Other | | × | |
| Chlorpromazine | Drugs | | | × |
| Chromium (metal) | Other | | × | |
| Cinnamaldehyde | Fragrances-Cosmetics | × | | |
| Cinnamic acid | Fragrances-Cosmetics | × | | |
| Cinnamic alcohol | Fragrances-Cosmetics | × | | |
| Cinnamon oil | Fragrances-Cosmetics | | | × |
| Cisplatin (platinum salts) | Drugs | | × | |
| Cobalt (metal) | Other | | × | |
| Colophony (plant derivative) | Other | | × | |
| Copper (metal) | Other | | | × |
| Coumarin | Fragrances-Cosmetics | × | | |
| Dibutylphthalate | Other | | × | |
| Di-(2-ethylhexyl) phthalate | Other | | × | |

| | | | | |
|---|---|---|---|---|
| Diethylfumarate | Other | | | × |
| Diethyltoluamine | Other | | × | |
| Dimethylammonium chloride | Other | | | × |
| Dimethyl sulfoxide | Other | × | | |
| Dinitrochlorobenzene | Drugs | | | × |
| Diphenylcyclopropenone | Drugs | | × | |
| Diphenylmethane-4,4'-diisocyanate | Other | | × | |
| Donezepil | Drugs | | × | |
| Epoxy resins | Other | | × | |
| Eugenol | Fragrances-Cosmetics | × | | |
| Formaldehyde | Biocides-Preservatives | × | × | |
| Formaldehyde resin | Other | | × | |
| Fumaric acid | Other | | | × |
| Gentamicyn | Drugs | | × | |
| Geraniol | Fragrances-Cosmetics | × | | |
| Gold (metal) | Other | | | × |
| Hydroxycitronellal | Fragrances-Cosmetics | × | | |
| Imidazolidinyl urea | Biocides-Preservatives | × | | |
| Iodochlorhydroxyquin | Drugs | | × | |
| Iridium (metal) | Other | | × | |
| Isoeugenol | Fragrances-Cosmetics | × | | |
| Kathon CG | Biocides-Preservatives | × | | |
| Ketoprofen | Drugs | | | × |
| Levopromazine | Drugs | | × | |
| Lidocaine | Drugs | | | × |
| Lindane | Drugs | | × | |
| Mechlorethamine | Drugs | | × | |
| Menthol | Fragrances-Cosmetics | × | | |
| Mercurochrome | Biocides-Preservatives | | × | |
| Mercury (metal)[b] | Other | | × | |
| Methimazole | Drugs | | × | |
| Methyl ethyl ketone | Other | | × | |
| Mezlocillin | Drugs | | × | |
| Monoamylamine | Drugs | | × | |
| Neomycin | Drugs | | × | |
| Nickel (metal) | Other | | × | |
| Nicotinic acid esters | Drugs | × | | |
| Nylon | Other | | × | |
| Palladium (metal) | Other | | | × |
| Panthenol (hair product) | Other | | | × |
| Parabens[b] | Biocides-Preservatives | | × | |
| Penicillins | Drugs | | × | |
| Pentamidine isothionate | Drugs | | × | |
| Phenotiazides | Drugs | | × | |
| 2-Phenoxyethanol | Biocides-Preservatives | | | × |
| *p*-Phenylenediamine (hair dye) | Other | | × | |
| Phenyl mercuric acetate | Biocides-Preservatives | | × | |
| Phenyl mercuric propionate | Biocides-Preservatives | | × | |
| Pilocarpine | Drugs | | | × |
| Polyethyleneglycol | Biocides-Preservatives | | | × |
| Polypropylene | Other | | | × |
| Polysorbates (emulsifier)[b] | Fragrances-Cosmetics | | × | |
| Promethazine | Drugs | | | × |
| Propylene glycol | Fragrances-Cosmetics | × | | |
| Propyphenazone | Drugs | | | × |
| Pyrazolones | Drugs | | × | |
| Pyrrolidone carboxylate | Fragrances-Cosmetics | × | | |
| Resorcinol | Fragrances-Cosmetics | × | | |
| Rhodium (metal) | Other | × | | |
| Ruthenium (metal) | Other | × | | |
| Ryfamicin | Drugs | | × | |
| Sodium benzoate | Biocides-Preservatives | × | | |
| Sodium hypochlorite | Biocides-Preservatives | | × | |
| Sorbic acid | Biocides-Preservatives | × | | |
| Sorbitan monolaurate (emulsifier)[b] | Fragrances-Cosmetics | | × | |
| Sorbitan monostearate (emulsifier)[b] | Fragrances-Cosmetics | | × | |
| Sorbitan sesquiolate (emulsifier)[b] | Fragrances-Cosmetics | | × | |

| | | | | |
|---|---|---|---|---|
| Stearyl alcohol (emulsifier) | Fragrances-Cosmetics | | | × |
| Steroids | Drugs | | | × |
| Streptomycin | Drugs | | × | |
| Sulbactam | Drugs | | × | |
| Tin (metal) | Other | × | | |
| Trichloroethanol | Other | | | × |
| Turpentine (plant derivative) | Other | × | | |
| Vanillin | Fragrances-Cosmetics | × | | |
| Vinyl pyridine | Other | | | × |
| Virginiamycin | Drugs | | × | |
| Wool alcohol | Fragrances-Cosmetics | | × | |
| Xylene | Other | | | × |
| Zinc (metal) | Other | × | | |

[a] Immediate contact reaction, unclassified nonimmunological/immunological
[b] Described as (non-clear evidence)

## FIGURE LEGENDS

**Fig. 1.** NICoU and ICoU general mechanisms.
**Fig. 2.** Chemical structures of the components of FMI and FMII.
**Fig. 3.** Chemical structures of most important preservatives and biocides.
**Fig. 4.** Chemical structures of drugs involved in immediate skin contact reactions.
**Fig. 5.** Chemical structures of other LMW compounds involved in immediate skin contact reactions.

**Fig. 1.**

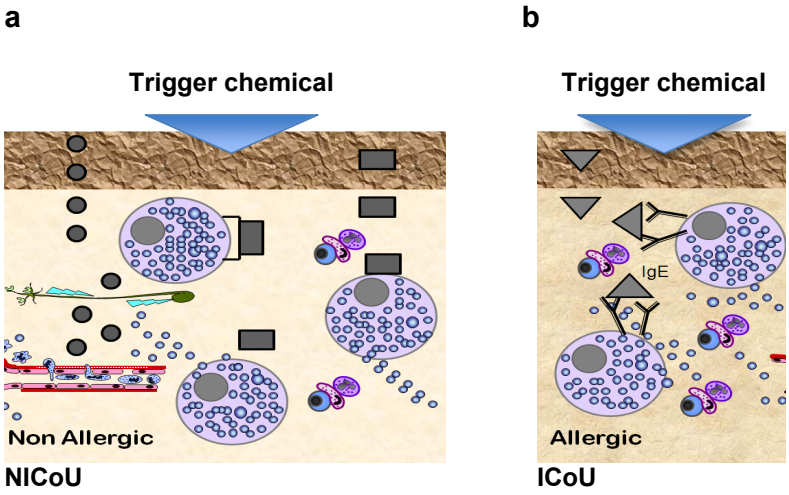

a
b
Trigger chemical
Trigger chemical
IgE
Non Allergic
Allergic
NICoU
ICoU

**Fig. 2.**

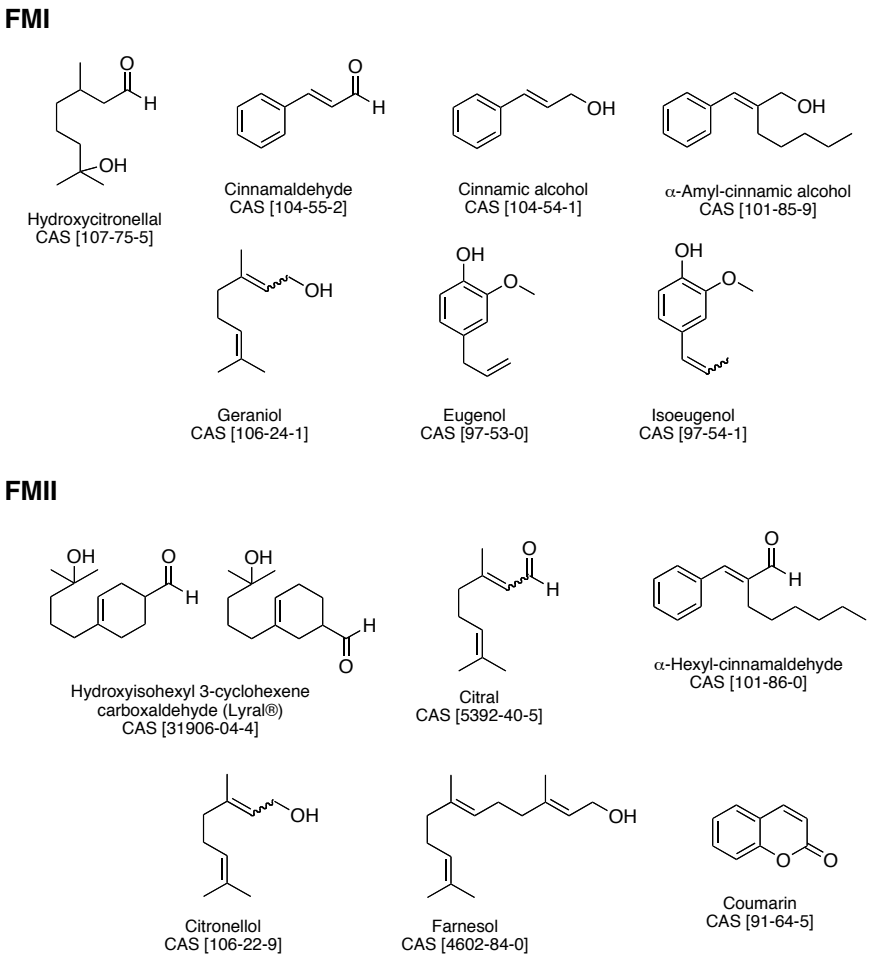

FMI
Hydroxycitronellal
CAS [107-75-5]
Cinnamaldehyde
CAS [104-55-2]
Cinnamic alcohol
CAS [104-54-1]
α-Amyl-cinnamic alcohol
CAS [101-85-9]
Geraniol
CAS [106-24-1]
Eugenol
CAS [97-53-0]
Isoeugenol
CAS [97-54-1]
FMII
Hydroxyisohexyl 3-cyclohexene
carboxaldehyde (Lyral®)
CAS [31906-04-4]
Citral
CAS [5392-40-5]
α-Hexyl-cinnamaldehyde
CAS [101-86-0]
Citronellol
CAS [106-22-9]
Farnesol
CAS [4602-84-0]
Coumarin
CAS [91-64-5]

**Fig. 3.**

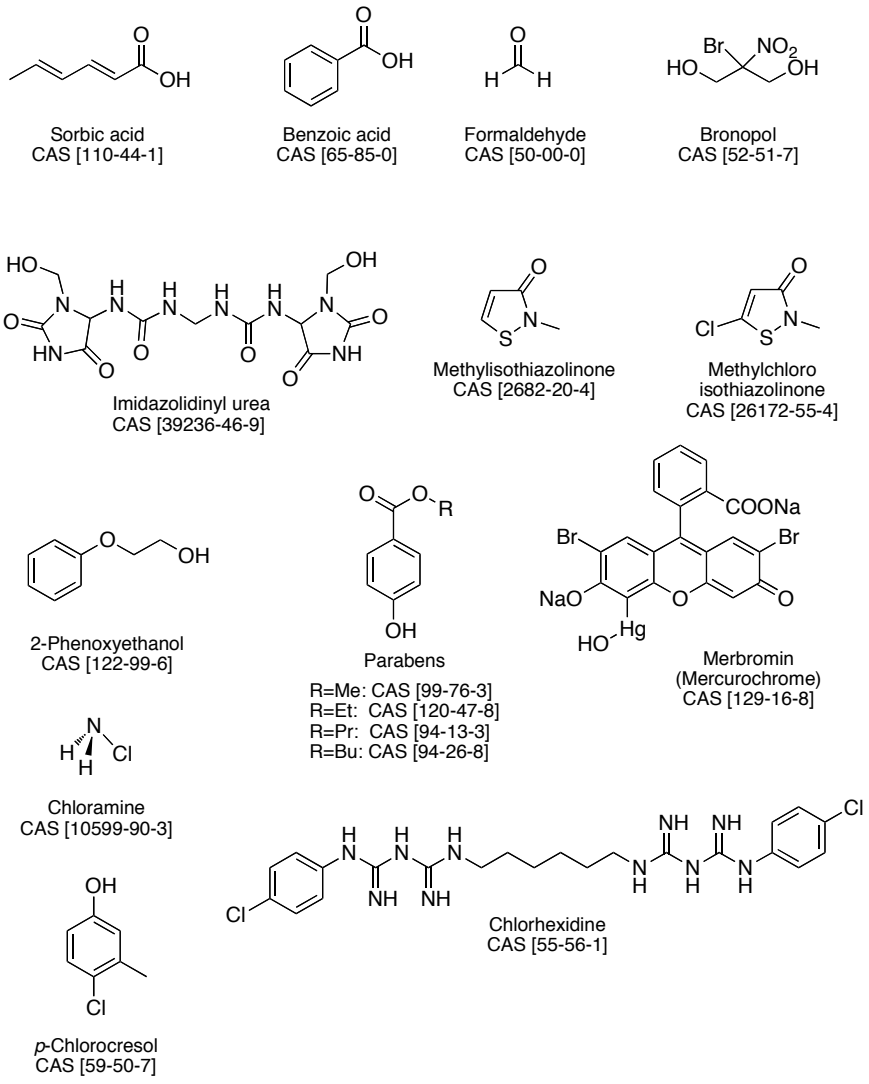

Sorbic acid
CAS [110-44-1]
Benzoic acid
CAS [65-85-0]
Formaldehyde
CAS [50-00-0]
Bronopol
CAS [52-51-7]
Imidazolidinyl urea
CAS [39236-46-9]
Methylisothiazolinone
CAS [2682-20-4]
Methylchloro
isothiazolinone
CAS [26172-55-4]
2-Phenoxyethanol
CAS [122-99-6]
Parabens
R=Me: CAS [99-76-3]
R=Et: CAS [120-47-8]
R=Pr: CAS [94-13-3]
R=Bu: CAS [94-26-8]
Merbromin
(Mercurochrome)
CAS [129-16-8]
Chloramine
CAS [10599-90-3]
Chlorhexidine
CAS [55-56-1]
p-Chlorocresol
CAS [59-50-7]

**Fig. 4.**

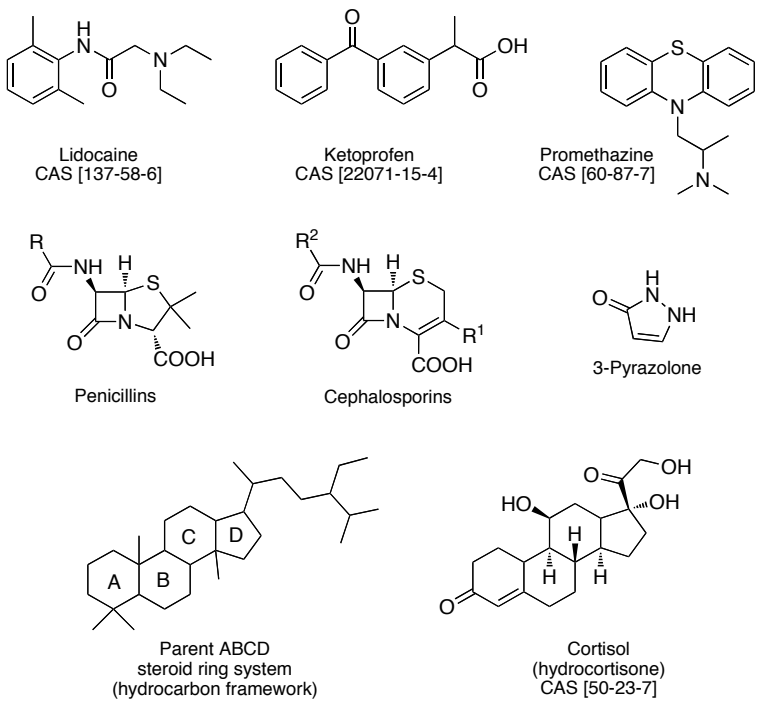
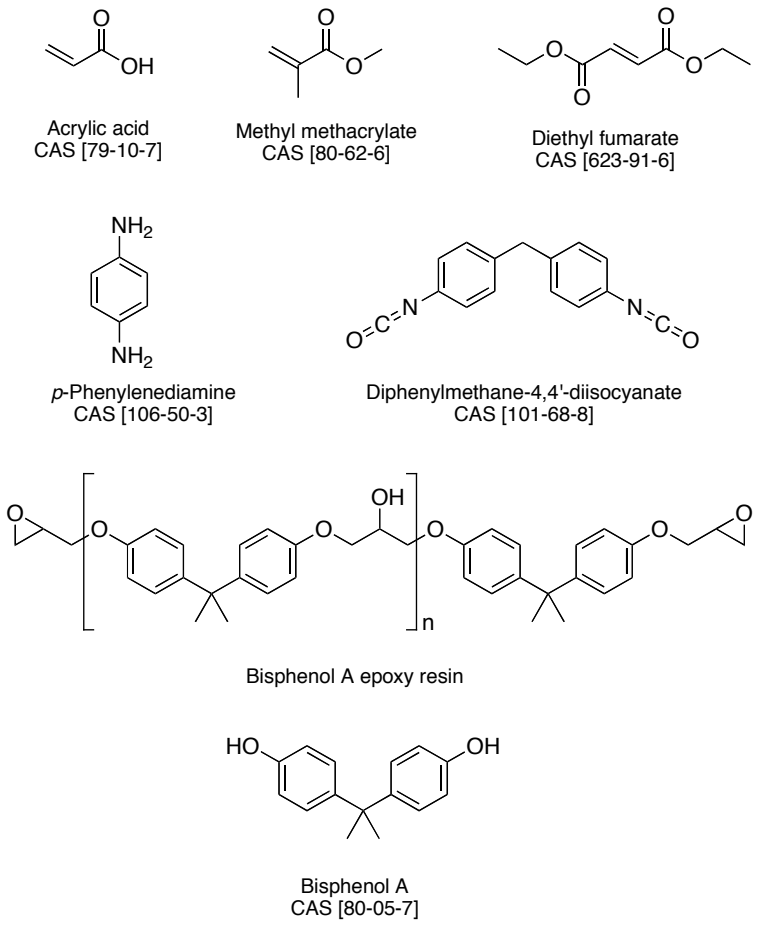

Lidocaine
CAS [137-58-6]
Ketoprofen
CAS [22071-15-4]
Promethazine
CAS [60-87-7]
Penicillins
Cephalosporins
3-Pyrazolone
Parent ABCD
steroid ring system
(hydrocarbon framework)
Cortisol
(hydrocortisone)
CAS [50-23-7]

**Fig. 5.**


Acrylic acid
CAS [79-10-7]
Methyl methacrylate
CAS [80-62-6]
Diethyl fumarate
CAS [623-91-6]
p-Phenylenediamine
CAS [106-50-3]
Diphenylmethane-4,4'-diisocyanate
CAS [101-68-8]
Bisphenol A epoxy resin
Bisphenol A
CAS [80-05-7]