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REVIEW

The new Italian SIDAPA Baseline Series for patch testing (2023): an update according to the new regulatory pathway for contact allergens

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ABSTRACT

Allergic contact dermatitis (ACD) is a common inflammatory skin disease caused by delayed hypersensitivity to chemical and biotic contact allergens. ACD significantly affects the patients' quality of life negatively impacting both occupational and non-occupational settings. Patch testing is the gold standard diagnostic *in vivo* test to precise the ACD etiology and to correctly perform prevention. According to the Italian Medicines Agency (AIFA) legislative decree no. 178 of 29th May 1991, allergens are defined as medicines and therefore they are subject to strict regulation. In 2017, AIFA (decree no. 2130/2017) started a procedure to regulate contact allergens on the Italian market and actually the contact allergens temporarily authorized are reported in AIFA decree no. 98/2022, valid until November 2023. The availability on the market of contact allergens to diagnose ACD and continuous updating on the basis of new epidemiological trends are mandatory, jointly with the continuous update of the baseline and integrative series for patch testing. For this reason, the scientific community represented in Italy by the Skin Allergies Study Group of SIDeMaST (Italian Society of Dermatology and Venereology) and SIDAPA (Italian Society of Allergological, Occupational and Environmental Dermatology) are constantly working, in close relationship with the European scientific communities with large expertise in this important sector of the modern Dermatology. Herein, we report the setting up of regulatory legislation by AIFA and the new Italian Adult Baseline Series for patch testing.

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KEY WORDS: Allergic contact dermatitis; Allergens; Patch tests.

Contact dermatitis (CD) is a common inflammatory skin disease with acute, subacute, and chronic course caused by repeated contact with allergens and irritants.[1] Allergic contact dermatitis (ACD) is a delayed-type hypersensitivity mediated by T-cells mostly presenting with eczematous lesions negatively impacting on patients' quality of life.[2, 3] The ACD pathomechanism includes an induction phase during the first allergen exposure, leading to a clonal expansion of allergen-specific T-cells. Subsequently, a re-exposure of the subject to the same allergen or cross-reacting substances leads to the elicitation phase, causing eczematous skin manifestations.[3]

In occupational settings, ACD represents the majority of occupational skin diseases in several fields.[4] In fact, contact allergens can be found in many compounds in several occupational settings, such as textile, cosmetic, rubber industries and healthcare workers.[1, 3] Regarding non-occupational exposures, metals, dyes, and cosmetics are the most frequently involved allergens.[1, 3] Therefore, the identification of relevant allergens in subjects at risk for ACD in occupational and non-occupational settings is mandatory to develop and implement targeted primary, secondary, and tertiary prevention strategies.[5-8]

Patch testing is the gold standard procedure to diagnose contact allergy.[3, 8] Contact allergens mostly inducing ACD are comprised in the baseline series, while those less frequently involved are organized into supplementary series, codified according to the exposure source, both in occupational and in non-occupational fields. The series for patch testing are constantly evolving, due to changing population exposure, prevalence trend of contact allergy, introduction of new compounds such as preservatives and fragrances considered to have lower sensitizing potential or to be less expensive.[7] Therefore, a periodic updating by the scientific Dermatology community with large expertise in this topic, namely SIDAPA (Italian Society of Allergological, Occupational and Environmental Dermatology) and Skin Allergy Group of SIDeMaST (Italian Society of Dermatology), is required. In March 2022, a Technical Board based on selected dermatologists and physicians belonging to other specialties (pediatrics, immunology, occupational medicine) involved in patch testing, was created by the Italian Medicine Agency (AIFA) (decree no. 134/2022, March 30th, 2022) to establish the clinical use of contact allergens for patch testing and to draw up guidelines that meet the latest scientific criteria and regulatory requirements.[7]

To date, contact allergens are considered as medicines and therefore subject to a well-defined regulation.[9] According with the current regulatory legislation, contact allergen medicines currently marketed in Italy are divided in three main categories: 1) medicines with regular marketing authorization (MA); 2) medicines with MA *ope legis*, including allergens already used in Italy before the legislative decree no. 178/1991 and for which marketing has been temporarily allowed; 3) medicines marketed pursuant to art. 5 of Legislative Decree 219/2006 as Named Patient Product (NPP).[7]

The aim of this review is to describe the continuous updating of the Baseline Series for patch testing and to illustrate the complex regulatory pathway for contact allergens in terms of benefit/risk and the current situation in Italy. Finally, we analyzed the new SIDAPA Italian Baseline Series for patch testing, emphasizing the new contact allergens and reviewing those already present in the previous one.

The contact allergen regulatory pathway for patch testing

Allergen medicines are pharmaceutical preparations obtained from extracts containing allergens with diagnostic and therapeutic purposes.[7] Allergen medicines currently on the Italian market are: 1) medicinal products with a regular MA: at present, only 3 diagnostic medicinal patch test has been authorized; 2) medicinal products authorized *ope legis* pursuant to the Decree of 13th December 1991 issued to harmonize the Italian legislation with European Union directives on medicinal products; 3) medicinal products marketed as Named Patient Product (NPP) pursuant to Legislative Decree 219/2006 Article 5, regulated by article 5 of law No. 94/1998.[7]

In order to avoid risks related to the unavailability of allergenic medicinal products, temporary provisions on allergens were provided (decree of 13th December 1991, giving indications aimed to ensure the alignment of the production and marketing of these medicinal products according to legislative decree no. 178 of 29th May 1991, which for the first time classified allergens as medicinal products. Following Italian transposition of the EU Community Code, AIFA started a process to verify the quality of allergen medicinal products on the Italian market, defining the procedures and timeframes to regulate their marketing and obtaining the related MA in accordance with the Directive 2001/83/EC. MA is issued following a scientific assessment of the quality, safety and efficacy requirements of the medicinal product. For this purpose, a complex dossier containing information on chemical-pharmaceutical, pre-clinical and clinical aspects, is required.[7] In 2017, AIFA concluded the transitional phase

to obtain MA for allergen medicinal products (decree no. 2130 of 22 December 2017) admitting to registration only a part of the allergen products that had been on the market *ope legis* up to December 1991. Since unmet clinical needs emerged, AIFA opened a second phase of the procedure. Until the end of this phase, the allergens admitted to the dossier technical evaluation will remain on the market *ope legis*. Article 5 of Legislative Decree 219/2006 allows an exception to the MA provisions for medicinal products "prepared industrially after written and unsolicited request of the physician, who undertakes to use the aforementioned medicinal products on a specific patient under his direct and personal responsibility."[7] In this case, article 5 of law no. 94/1998 (Di Bella Law) is adopted. This law states that "physicians may prescribe magistral preparations exclusively based on active ingredients described in EU pharmacopoeias or contained in industrial medicinal products authorized in Italy or in another EU country" and that "the prescription of magistral preparations based on active ingredients already contained in medicinal products whose marketing authorization has been revoked or not confirmed, is permitted."[7] Article 5 of the EU Directive 2001/83 provides that "a Member State may exclude from the scope of this Directive medicinal products supplied in response to a *bona fide* unsolicited order, formulated in accordance with the prescriptions of an authorized healthcare professional and intended for a particular patient under the direct personal responsibility of the prescribing physician." Nevertheless, the EU Court of Justice has placed limits on this freedom: "the power deriving from article 5 of Directive 2001/83 to exclude the application of the provisions of that law, may be exercised only in cases of necessity, taking into account the specific needs of patients."[7] However, if a product with a MA is on the market, the manufacture of a corresponding medicinal product as a NPP is not permissible.[7]

The production of contact allergens is only allowed for manufacturing plants located in EU territory with regular GMP (Good Manufacturing Practices) certification. Companies intending to produce contact allergens are required to send formal notification to AIFA before marketing, providing information on the contact allergen, the production site and the relative authorization.

The evolution of the Italian baseline series for patch testing

A baseline series should include contact allergens of greatest importance and relevance for the majority of patients. Across Europe, different national CD groups are active, many of these using electronic data collection of patch test results. Moreover, a high degree of methodological standardization had been achieved, as documented by the European Society of Contact Dermatitis (ESCD) patch test guidelines.[10]

The medical history together with physical examination may address to a possible sensitizing exposure, and should address the choice of patch test series. Unfortunately, it is not sufficient patch testing with only suspected sensitizers, because unsuspected ones frequently turn out to be relevant. This is the reason why a "baseline series" of test allergens should be applied in the evaluation of all patients suspected of having CD.[10] The current version of the Italian Adult Baseline Series consists of 33 contact allergens, including negative control (petrolatum) and it is currently recommended by SIDAPA.[7, 8]

The baseline series is often insufficient, and additional patch test substances or series, based on the patient's history and exposure, should be considered.[7] The SIDAPA baseline series is dynamic and subject to continuous evaluation and modifications, depending on population exposures and the prevalence of contact allergy. The use of a baseline series in all tested patients was adopted worldwide in the 1980s;[4] previously many authors preferred to apply "selected patch test" based on anamnestic data, with a special focus on the occupational dermatology.[4] Bruno Bloch acted as a group leader for promoting and disseminating the idea of applying a limited baseline series on each patient. Finally, Poul Bonnevie, professor of occupational medicine in Copenhagen, expanded Bloch's embryonic baseline series of tests and published it in 1939 (Table I) in his famous textbook of environmental dermatology. Some allergens (such as colophony, balsam of Peru, formaldehyde, potassium dichromate, nickel sulfate and phenylenediamine) are used in the current baseline series, since they still appear to be employed in different occupational sectors.

In Italy, SIDAPA society was founded in May 1999 in the footsteps of GIRDCA (Gruppo Italiano di Ricerca Dermatiti da Contatto e Ambientali) in order to better promote, always in agreement with other dermatological companies, the field of allergological, environmental and professional dermatology. The first Italian baseline series was approved by SIDAPA in 2005. The Italian and the European baseline series are periodically updated replacing obsolete contact allergens with emerging ones. From 2005 To 2011, 3 new allergens have been introduced: fragrance mix II 14%, budesonide 0.01% and hydrocortisone

TABLE I.—*The first baseline series for patch testing by Poul Bonnevie (1939).*

Compound	Concentration (%)	Vehicle
Turpentine	50	Olive oil
Colophony	10	Olive oil
Balsam of Peru	25	Lanolin
Salycilic acid	5	Lanolin
Formaldehyde	4	Water
Mercuric chloride	0.1	Water
Potassium dichromate	0.5	Water
Silver nitrate	2	Water
Nickel sulfate	5	Water
Resorcinol	5	Water
Primula obconica	as is	
Sodium perborate	10	Water
Brown soap	as is	
Coal tar	pure	
Wood tars	pure	
Quinine chlorhydrate	1	Water
Iodine	0.5	Ethanol
Pyrogallol	5	Petrolatum
Phenylendiamine	2	Petrolatum
Aminophenol	2	Petrolatum
Adhesive plaster	as is	

21 acetate 1%, while desoximetasone, disperse yellow and corticosteroid (CS) mix have been eliminated. Budesonide 0.01% is considered the most suitable marker for CS hypersensitivity;[11] over the years, although there has been a reduction in the prevalence of allergy to budesonide, it was decided to keep it in the baseline series as good marker to detect the majority of patients sensitized to topical and systemic CSs. In fact, it has been verified that there is a cross-reactivity between budesonide and other CSs, both topical and systemic.[12]

Always within the framework of CSs, in recent years there have been added other two markers of CSs' hypersensitivity: hydrocortisone 21-acetate 1% before and now tixocortol 21-pivalate 1%. The latter takes over from hydrocortisone 21-acetate; in fact, many studies have demonstrated that tixocortol 21-pivalate is a better marker of allergy to hydrocortisone rather than hydrocortisone 21-acetate, because the latter has a lower sensitivity.[13, 14] Of note, following the recommendations of the British Society Cutaneous Allergy and of ESCD, in 2015 2-hydroxyethyl-methacrylate (2-HEMA) 2% pet. was included in Italian baseline series, as a good marker of contact allergy to acrylates.[10, 15, 16] Subsequently, an Italian multicenter study confirmed these data.[17]

During 2015 also other 4 allergens have been introduced in the Italian baseline series:

- sorbitan sesquioleate 20% pet. was added as a single allergen in the baseline series because of its capacity to give numerous false positives within the fragrance mix I (FM I), leading patients to have a misdiagnosis of allergy to FM I;[18]
- textile dye mix (TDM) 6.6% pet.: given the high frequency of allergy to textile dyes there was a need to add a better marker than disperse blue 124 1% and disperse yellow 3 1% tested individually;[19]
- methylisothiazolinone (MI) 0.2% aq: although it was tested within the mixture methylchloroisothiazolinone (MCI)/MI, it has been decided to also test MI individually after its introduction as a stand-alone preservative in skin care products and cosmetics;[20]
- 3-dimethylaminopropylamine (DMAPA) 1% aq.

Regarding DMAPA, it was thought to have an important role in contact allergy to cocamydopropylbetaine (CAPB), so it was introduced in SIDAPA baseline series in 2015. However, because of the sensitizing power of other impurities contained in CAPB, like amidoamines, CAPB itself has now been added as a new component of the Italian baseline series besides DMAPA.[21-23]

Regarding isothiazolinone preservatives, also benzisothiazolinone (BIT) becomes part of the new baseline series, in addition to MCI/MI mixture and MI itself. BIT is a frequent allergen contained in many personal care products and industrial chemicals and the rate of sensitized people to BIT is increasing over the years. Moreover, although cross-reactivity between MCI/MI and BIT is possible, BIT seems also to act like an independent sensitizer; this was another good reason that led the Italian study group to add it in the new series.[24]

In addition, as recommended by EBS, other three allergens appear in the new Italian baseline series: caine mix III 10% (because the mix is more sensitive than benzocaine tested individually),[25] *Compositae* mix II 5%, which either definitely improves the capacity to detect any hypersensitivities instead of *Compositae* mix 2.5%, either includes parthenolide (0.1%) that represents a useful screen for allergy to *Compositae* plants,[26, 27] and sodium metabisulphite (SMB), an emergent allergen which is frequently used in the cosmetic, pharmaceutical, and food sectors.[28]

The new (2023) Baseline Series for patch testing

Twenty-seven contact allergens have been confirmed compared to the series in use since 2015 (Table II). The current version of the adult baseline series consists of 33 contact allergens including negative control (petrolatum)

TABLE II.—*The SIDAPA baseline series 2016 for patch testing.*

Compound	Concentration % (w/w)*
Fragrance mix II	14
Lyral	2.5
Citral	1
Farnesol	2.5
Citronellol	0.5
Hexyl cinnamal	5
Coumarin	2.5
Thiuram mix	1
Tetramethylthiuram disulfide	0.25
Tetramethylthiuram monosulfide	0.25
Tetraethylthiuram disulfide	0.25
Dipentamethylenethiuram disulfide	0.25
Potassium dichromate	0.5
Balsam of Peru	25
N-isopropyl-N'-phenyl-p-phenylendiamine	0.1
Methylchloroisothiazolinone/methylisothiazolinone	0.02 [a]
p-Phenylenediamine	1
Lyral	5 [a]
Colophony	20
Neomycin sulfate	20
Mercaptobenzothiazole	2
p-Tert-butylphenol formaldehyde resin	1
Nickel sulfate	5
Fragrance mix I	8+5
Amyl cinnamal	1
Cinnamal	1
Cinnamyl alcohol	1
Evernia prunastri extract (oak moss absolute)	1
Hydroxycitronellal	1
Eugenol	1
Isoeugenol	1
Geraniol	1
Hydrocortisone 21 acetate	1
Textile dye mix	6.6
Disperse blue 35	1
Disperse yellow 3	1
Disperse orange 1	1
Disperse orange 3	1
Disperse red 1	1
Disperse red 17	1
Disperse blue 106	0.3
Disperse blue 124	0.3
Paraben mix	16
Methylparaben	4
Ethylparaben	4
Propylparaben	4
Butylparaben	4
Benzocaine	5
Cobalt chloride	1
Dimethylaminopropylamine	1 [a]
Budesonide	0.01
Lanolin alcohols (wool alcohols)	30
Methylisothiazolinone	0.2 [a]
2-Hydroxy ethyl methacrylate	2
Sorbitan sesquioleate	20

*All in petrolatum except those in aqua ([a]).

(Table III). Therefore, 6 new emergent contact allergens have been introduced, as a result of a review of the literature on emerging contact allergens: benzisothiazolinone (0.1% pet.), caine mix (10% pet.), cocamidopropylbetaine (1% aq), *Compositae* Mix II (5% pet.), sodium metabisulfite (1% pet.), and tixocortol-21-pivalate (1% pet.). In the new Italian baseline series 2 allergens have been removed from the previous baseline series (2005): hydrocortisone 21-acetate (1% pet.) and benzocaine (5% pet.) (Table II and Table III).

TABLE III.—*The SIDAPA adult baseline series 2023 for patch testing.*

Compound	Concentration % (w/w)*
Balsam of Peru	25
1,2-Benzisothiazolin-3-one, sodium salt	0.1
Budesonide	0.01
Caine mix	10
Benzocaine	5
Cinchocaine hydrochloride	2.5
Tetracaine hydrochloride	2.5
Cobalt(II) chloride hexahydrate	1
Cocamidopropyl betaine	1 [a]
Colophony	20
Compositae mix II	5
Anthemis nobilis flower exctract	1.2
Chamomilla recutita flower exctract	1.2
Achillea millefolium flower exctract	1
Tanacetum vulgare	1
Arnica montana flower exctract	0.5
Partenolide	0.1
3-Dimethylamino-1-propylamine	1 [a]
Textile dye mix	6.6
Disperse blue 35	1
Disperse blue 106	0.3
Disperse blue 124	0.3
Disperse yellow 3	1
Disperse orange 1	1
Disperse orange 3	1
Disperse red 1	1
Disperse red 17	1
N-isopropyl-N'-phenyl-p-phenylenediamine	0.1
Formaldehyde	2 [a]
2-hydroxyethyl methacrylate	2
Wool alcohols	30
Lyral	5
2-Mercaptobenzothiazole	2
Mercapto mix	2
2-Mercaptobenzothiazole	0.5
N-Cyclohexyl-2-benzothiazyl-sulfenamide	0.5
Dibenzothiazyl disulfide	0.5
Morpholinyl mercaptobenzothiazole	0.5
Methylchloroisothiazolinone/ Methylisothiazolinone	0.02 [a]
2-Methyl-4-isothiazolin-3-one	0.2 [a]
Neomycin sulfate	20
Nickel sulfate	5

(To be continued)

TABLE III.—*The SIDAPA adult baseline series 2023 for patch testing (continues).*

Compound	Concentration % (w/w)*
Paraben mix	16
Methylparaben	4
Ethylparaben	4
Propylparaben	4
Butylparaben	4
p-Phenylendiamine	1
Potassium dichromate	0.5
Fragrance mix I + Sorbitan sesquioleate	8
α-Amylcinnamic aldehyde	1
Cinnamic aldehyde	1
Cinnamic alcohol	1
Oakmoss absolute	1
Hydroxycitronellal	1
Eugenol	1
Isoeugenol	1
Geraniol	1
+ Sorbitan sesquioleate	5
Fragrance mix II	14
Lyral	2.5
Citral	1
Farnesol	2.5
Citronellol	0.5
α-Hexylcinnamaldehyde	5
Coumarin	2.5
Bisphenol A epoxy resin	1
p-tert-Butylphenol formaldehyde resin	1
Sodium metabisulfite	1
Sorbitan sesquioleate	20
Thiuram mix	1
Tetramethylthiuram disulfide	0.25
Tetramethylthiuram monosulfide	0.25
Tetraethylthiuram disulfide	0.25
Dipentamethylenethiuram disulfide	0.25
Tixocortol 21-pivalate	1
Petrolatum	100

*All in petrolatum except those in aqua ([a]).

Nickel sulfate (CAS 7786-81-4) (5% pet.)

Nickel is the most common cause of contact allergy in the general population and the most frequently detected allergen in patients patch tested for suspected ACD.[29] Nickel is a ubiquitous metal added to jewelry, household products and cosmetics for its abstract hardening properties and because it is inexpensive.[30] A great variety of occupational exposures have been described, such as contact with cutting fluids, keys, coins, electrical components, dental tools, guitar strings and others, although nickel allergy is mostly caused by non-occupational exposure, such as jewelry and clothing decorations, medical devices, pigment for paint, cosmetics and food (mainly legumes, chocolate, salmon, peanuts).[29, 30]

Nickel ACD is often characterized by eczematous dermatitis although non-eczematous-patterns are reported, including lichenoid dermatitis, vitiligo-like lesions, dyshidrosiform dermatitis, granuloma annulare-like lesions and vasculitis.[29] A systemic CD can occur in case of systemic nickel exposure.[29]

In Europe, the prevalence of nickel allergy has declined in some countries following implementation of the EU Nickel Directive; in fact, in 1994, legislation on nickel was implemented in the EU, legislation that had already been in place in the Nordic countries for some years, which came into force in 2000.[31] Later, in 2009, the EU Nickel Directive was included in REACH, the EU Chemicals Regulation (EC) No 1907/2006, Annex XVII Section 27.[31] This directive led to a decrease in the prevalence of nickel contact allergy in Europe, averaging 15.5%, it was lower in Sweden (8.3%) and higher in Portugal (18.5%) as shown by an epidemiological study performed in 2010 on 3119 patients in five European countries.[32] Exposure reduction aiming to prevent nickel allergy in the general population is possible through regulations, education and information campaigns to educate consumers and retailers, decontamination of exposed skin surfaces, use of protective creams or the use of protective gloves.[30]

Potassium dichromate (CAS 7778-50-9) (0.5% pet.)

Chromium is a relatively common element, occurring naturally in rock, soil, plants, animals, and volcanic dust and gases.[33] The most stable valence states are trivalent Cr (Cr[III]) and hexavalent Cr (Cr[VI]). Chromium is chiefly found as Cr(III) in nature, whereas Cr(VI) is generally produced by industrial processes.[33] In many countries, cement remains a major cause of ACD.[34] Occupational groups such as construction workers and bricklayers are therefore at risk of developing chromium allergy. Workers within the metal and tanning industry, offset printers and lithographers may also be exposed to chromium and develop chromium allergy.[34] Regarding chromium, a European regulation on leather (No. 301/2014) was implemented in May 2015, restricting the content of chromium(VI) to a maximum level of 3 ppm; this led to a reduction of chromium contained in the EU cement, but not in India, a country with similar regulation, where dichromate levels in cement are still high.[35] Leather products are also an important source of non-occupational chromium ACD. Hexavalent chromium may be present in tattoo inks with skin exposure and systemic risk.

The prevalence of chromium sensitization in a review by Alinaghi *et al*. based on data from 2007 to 2017 was 1.8% in 19 included studies and 13,250 individuals tested.[36] Potassium dichromate is tested at 0.5% in pet. In

2014, legislation was implemented (Commission Regulation (EU) No. 301/2014 of March 25, 2014 amending Annex XVII of Regulation (EC) No. 1907/2006) limiting the dichromate content to less than 3 mg/kg of leather. The medium- and long-term effect of this preventive measure will be evaluated in the coming years.

Cobalt chloride (CAS 7791-13-1) (1% aq)

Cobalt is a potent skin sensitizer and a frequent cause of contact allergy.[37] The hard metal industry is believed to represent the main source of occupational cobalt exposure. Cobalt is also used as a component of cement, ceramics, fertilizers.[38] On the other hand, leather shoes and gloves, piercing, tattoos, medical devices (such as prothesis) and cosmetics (like eyeshadows) are an important source of cobalt non-occupational exposure.[38]

About cobalt allergy, Alinaghi *et al.* reported in their review, which included 24 studies in the period 2007-2017, a prevalence of contact sensitization of 2.7% of 15389 individuals tested.[36] Cobalt ACD is often characterized by eczematous dermatitis of the involved contact body sites (frequently back of hands and forearms), although cases of lichenoid dermatitis and dyshidrosiform dermatitis are reported. Moreover, vapors and fumes derived from welding can cause airborn CD.[38] Cobalt chloride hexahydrate is tested at 1% in pet. To limit skin sensitization to cobalt and allergic cobalt dermatitis, identification of the cobalt elicitation threshold level is warranted.[37]

N-isopropyl-N'-phenyl-p-Phenylenediamine (CAS 101-72-4) (0.1% pet.)

N-isopropyl-N'-phenyl-p-Phenylenediamine (IPPD) has antioxidant and ozonant properties.[39] It is used in the prevulcanization phase by rubber industry to prevent deterioration of objects subjected to mechanical stress, especially those used in industrial activities and tyres (black rubber).[39] IPPD is also found in steering wheels, knobs, boots and shoes, diving equipment, gloves, masks and other black or gray rubber objects, as well as in lubricating oils and greases.[39] IPPD ACD is predominantly represented by palmar eczema, especially in the occupational environment.[39] Cases of purpuric CD have also been described.[13]

The prevalence of positive patch test reaction to IPPD in the two-year period 2019-2020 is about 0.79% in Europe (Italy 0.84%).[10] Furthermore, despite rubber chemicals are currently among occupationally relevant allergens, occupational sensitization to IPPD shows a downward trend.[40] IPPD 0.1% has been also tested (along with N-cyclohexyl-N'-phenyl-paraphenylenediamine 0.25% and N-N'-diphenyl-paraphenylenediamine 0.25%) in black rubber mix (BRM) 0.6% pet., eliciting 0.88% positive reaction.[10, 39] The prevalence of sensitization to BRM, therefore, is similar to that to IPPD.[10] This data suggests that IPPD is the main sensitizer among paraphenylenediamine-derivatives rubber compounds, and seems to be able to identify most patients with sensitization to black rubber. In patients with primary relevant sensitization to IPPD cross-reactions with paraphenylenediamine and other para compounds are infrequent.[39]

Patients with IPPD contact sensitization should avoid contact with black or gray rubber objects, especially in occupational setting and for a long time; black rubber gloves may be substituted with vinyl gloves.[39] It has been suggested that dimethylbutyl-phenyl-p-phenylendiamine may be an alternative in rubber manufacturing process; however, cross-reaction has been described.[39]

p-Phenylenediamine (CAS 106-50-3) (1% pet.)

p-Phenylenediamine (PPD) is a strong sensitizer contained in hair dyes and temporary tattoos (black henna tattoo); it can be also found in textiles, rubber, cosmetics, or inks.[39] Permanent hair dyes are the most common source of contact sensitization.[39] Furthermore, PPD is the main allergen in occupational ACD of hairdressers.[41] PPD ACD develops some hours or a few days after the exposure. Typical localizations from ACD due to hair dyes are face, ears or neck; more rarely it occurs on the scalp; it may also widespread to the chest and upper arms.[42] When located at the eyelids, an angioedema-like appearance can occur.[42] Temporary tattoo dermatitis instead is usually located at the contact area. In addition to classical eczematous appearance, other rare pattern of PPD contact allergy can occur: leukoderma, lichen planus-like, or erythema multiforme-like eruption.[39] An European multicenter study overall 2-year period (2019-2020) showed that patch test with PPD was positive in 3.61% of tested patients (Italy 4.72%).[10] The rate of sensitization was higher in central and southern Europe than in Scandinavia, probably due to the higher proportion of dark-haired people in those geographical areas and to the higher use of oxidative dark hair dyes containing elevated concentration of PPD.[10]

During the recent years there has been an increase in positive patch test reaction to PPD that could be related to the increased use of hair dyes even among young people.[42] It has been also reported that ACD to PPD occurs in about 2.5% of temporary tattoo, especially in children.[42] Many

of these patients then also develop ACD to permanent hair dyes.[42] PPD is tested 1% pet. in SIDAPA baseline series. Patients with temporary tattoo ACD may develop a strong, bullous reaction; therefore, testing with PPD 0.01% pet. has been suggested. PPD 0.3% pet. for 2 days or short-contact (1 hour) PPD 1% pet. patch test have been proposed for patients with severe clinical reaction.[42] Patients who are not reactive to either test on day 2 can then be tested with 1% PPD for the next 2 days.

Cross-reaction between PPD and other chemically related allergens containing an amine group in para position in benzene ring (para compounds) is reported.[39, 42] In Europe, the proportion of patients with positive patch tests is similar between PPD and TDM 0.6% (3.61% *vs.* 3.23%), with more than one third of them reacting to both the allergens.[10] Orange 3 contained in TDM is considered as the main cause of this cross-rection.[10] PPD sensitized patients, especially with strong positive patch test reaction, seems to be more prone (up to 10%) to react to other -para allergens, such as IPPD or caine mix.[42]

Herbal hair dyes may be alternatives in PPD sensitized patient: derivatives like henna generally have low allergic potential; however, some of them may contain diaminotoluenes and diaminobenzenes as additives, which can lead to CD. Also semipermanent hair dyes may be alternatives in PPD sensitized patients; however, they may contain low PPD concentration.[39, 42]

Permanent PPD-free hair dyes containing p-toluene-2,5-diamine, hydroxyethyl-p-phenylenediamine, or 2-methoxymethyl-p-phenylenediamine are less allergenic than PPD and can be used by some PPD sensitized patients.[39, 42] However, patients should be advised that these dyes should only be used after they have been tested.[42] It would be necessary that, when dyeing the hair, the dye does not go beyond the scalp, using a petrolatum barrier on the scalp margin. Hairdressers with PPD ACD should wear nitrile, single-use gloves.[10, 39, 42]

Textile dye mix (Disperse blue 35 1%, CAS 12222-75-2; Disperse yellow 3 1%, CAS 2832-40-8; Disperse orange 1 1%, CAS 2581-69-3; Disperse orange 3 1%, CAS 730-40-5; Disperse red 1 1%, CAS 2872-52-8; Disperse red 17 1%, CAS 3179-89-3; Disperse blue 106 0.3%, CAS 12223-01-7; Disperse blue 124 0.3%, CAS 61951-51-7) (6.6% pet.)

Disperse azo dyes (DAD) are the main cause of textile ACD.[19] They are mainly used for dyeing synthetic fabrics and not natural fibres[39] and are small lipophilic compounds that do not bind to textile, so they easily reach the skin.[19, 39] Clothing close contact and friction, along with sweating facilitate their release; therefore, ACD occurs mainly in the neck, upper thigs, and skin folds, with greater severity during summer.[39, 43] Eczematous (often xerotic) eruption is the main clinical feature; however, lichenoid, purpuric, lymphomatoid, psoriasis-like, nummular eczema-like, or atopic dermatitis-like eruption has been reported.[39] The prevalence of DAD contact sensitization seems to be decreasing in recent years in Europe, probably following the restrictions on their use introduced by European directives.[44] A European multicenter study performed in the two years period 2019-2020 showed a patch test positive prevalence of 3.58%.[10] In Italy, between 2018-2019 a prevalence of 1.5% was reported, with a positive clinical relevance of about 70% in patients with strong (++; +++) patch test reaction; occupational exposure accounted for 18.7% of cases.[44]

Patch testing with TDM 6.6% pet. has been recommended for the etiological diagnosis of DAD ACD, and is currently included in the SIDAPA baseline series.[19] Patch test reaction to TDM should be carefully evaluated, as both irritant reactions and a high rate of weak (+) reactions are reported.[19, 44] Due to similarity between disperse orange 3, contained in TDM and PPD, a high cross-reactivity rate between these two molecules, was reported.[10] Patients with positive TDM patch test should have individual components of the mix tested; furthermore, additional textile series and sometimes pieces of garments and their extracts should be tested in patients with suspected textile ACD.[39] Patients with ACD to DAD should only wear natural fiber clothing and any new garment, however, should be washed several times before being worn.[39] In case of demonstrated sensitization towards one of the components of TDM, the patient must be warned that several substances are used to color a garment and therefore it may not be sufficient to avoid wearing clothing of the color detected by patch test.[43]

Thiuram mix (tetramethylthiuram disulfide 0.25%, CAS 137-26-8; tetramethylthiuram monosulfide 0.25%, CAS 97-74-5; tetraethylthiuram disulfide 0.25%, CAS 97-77-8; dipentamethylenethiuram disulfide 0.25%, CAS 94-37-1) (1% pet.)

Thiurams and dithiocarbamates are chemically related accelerators used in the vulcanization of rubber and gloves and they constitute the main source of contact allergy to rubber chemicals.[45] Occupational exposure mainly concerns hairdressers, healthcare workers and others frequently using rubber gloves, farmers using pesticides, users of disinfectants or biocides, users of glues and adhesives.[45]

Sensitization to thiuram mix is rather frequent: a study of the North American Contact Dermatitis Group on 49,758 patch tests performed between 1994 and 2016 revealed 2034 positive results (4.09%),[46] and a more recent study performed from 2015 to 2017 with the European baseline series showed an only slightly lower prevalence (3.6%).[47] Italian data from the SIDAPA database on 7267 patch tests performed between 2018 and 2022 show a 2.06% of positive results, of which 62% with current or past relevance, 14.67% with uncertain relevance, 23.33% with unspecified or no relevance.[48]

Prevention measures primarily include reduction of contact with rubber and specific products used in agriculture.[48] This can be achieved through reduction of rubber (natural rubber, nitrile, neoprene) in products of common and professional use, replacing it where possible with vinyl, plastic, silicone, polyurethane or polyethylene, and use of alternative pesticides, fungicides and insecticides.[48] Moreover, allergic subjects must avoid direct contact with elastic bands/fibers or other rubber-containing parts of clothing items (including shoes) and common objects (condoms, rubber pillows, hot water bottles, swimming caps and goggles, masks, ear plugs, toys, balls, makeup sponges, mascara brushes, tires, knobs, handles, steering wheels, stickers, insulating tapes). Rubber may also be present in medical equipment such as catheters, devices used for kidney dialysis, elastic bands for the treatment of circulatory disorders.[48]

Mercaptobenzothiazole mix (mercaptobenzothiazole 0.5%, CAS 149-30-4; N-cyclohexyl-2-benzothiazolesulfenamide 0.5%, CAS 95-33-0; dibenzothiazyl disulfide 0.5%, CAS 120-78-5; morpholinyl mercaptobenzothiazole 0.5%, CAS 102-77-2) (2% pet.)

These organosulfur compounds are chemically related: dibenzothiazyl disulfide results from oxidative coupling of the thiol groups of two molecules of mercaptobenzothiazole, and its reaction with amines produces sulfonamide derivatives like morpholinyl mercaptobenzothiazole and morpholinyl mercaptobenzothiazole.[45] They are mainly used as accelerators in rubber vulcanization. Mercaptobenzothiazole may be also found in antifreezes, greases, anticorrosive agents, adhesives, detergents, leather, veterinary topical products and polyether polymers, dibenzothiazyl disulfide is a material used for construction (*e.g.* semi-permanent fixtures, flooring, tile, sinks, bathtubs, mirrors), morpholinyl mercaptobenzothiazole in corrosion inhibitors and releasing fluids.[45] Contact with rubber is the main cause of allergy; additionally, occupational risk exists for subjects involved in leather tanning and processing, metal machining, pulp/paper processing, photographic processing, plastic composites manufacturing, and those working with glues and adhesives or using disinfectants or biocides.[45]

The frequency of sensitization to mercaptobenzothiazole mix 2% was 0.49% in a study on 29,856 patch tests recorded in the European Surveillance System on Contact Allergies (ESSCA) between 2009 and 2012,[21] 0.44% in a study on 15,171 patch tests recorded in the Slovenian E-Surveillance System between 2008 and 2017.[24] SIDAPA data on 7268 patch tests performed between 2018 and 2022 show 0.54% of positive results (76.9% with current of past relevance, 10.3% with uncertain relevance, 12.8% with unspecified or no relevance).[48]

Prevention measures primarily include reduction of contact with rubber and other products containing components of mercaptobenzothiazole mix.[48] Possible actions include reduction of rubber (natural rubber, nitrile, neoprene) in products of common and professional use (replacements may be vinyl, plastic, silicone, polyurethane, polyethylene), use of alternative materials in industry, information campaigns to increase awareness of risk and use of individual protection devices by exposed workers.[48] Finally, allergic subjects must avoid direct contact with elastic bands/fibers or other rubber-containing parts of clothes (including shoes) and common objects (condoms, rubber pillows, hot water bottles, swimming caps and goggles, masks, ear plugs, toys, balls, makeup sponges, mascara brushes, tires, knobs, handles, steering wheels, stickers, insulating tapes). Rubber may also be present in medical equipment such as catheters, devices used for kidney dialysis, elastic bands for the treatment of circulatory disorders.[48]

Mercaptobenzothiazole (CAS 149-30-4) (2% pet.)

Mercaptobenzothiazole is an organosulfur compound. It is used for patch testing at 2% concentration, in pet.[45] The main source of exposure is rubber, as mercaptobenzothiazole is an accelerator in the process of vulcanization; other sources include antifreezes, greases, anticorrosive agents, adhesives, detergents, leather, veterinary topical products.[45] It is also an antioxidant and stabilizer, added to polyether polymers to improve air aging and ozone resistance.[45] Past uses, where it has been completely/almost completely replaced, included metalworking fluids and photometric determination of some heavy metals.[45]

Contact with rubber is the most frequent cause of allergy to mercaptobenzothiazole; additionally, a higher

risk of occupational allergy exists for subjects involved in leather tanning and processing, metal machining, pulp and paper processing, and those working with glues and adhesives.[45] Large studies on the frequency of sensitization to mercaptobenzothiazole 2% were published by Warburton *et al.*, who reported a 0.58% prevalence in 57,186 patch tests recorded in the ESSCA between 2009 and 2012,[49] and by Dugonik *et al.*, who reported a 0.46% prevalence in 15,171 patch tests recorded in the Slovenian E-Surveillance System between 2008 and 2017.[50] SIDAPA data on 7266 patch tests performed between 2018 and 2022 show 0.55% of positive results (87.5% with current of past relevance, 5% with uncertain relevance, 7.5% with unspecified or no relevance).[48]

Prevention measures primarily include reduction of contact with rubber and other products containing mercaptobenzothiazole.[48] This can be achieved through reduction of rubber (natural rubber, nitrile, neoprene) in products of common and professional use (possible replacements are vinyl, plastic, silicone, polyurethane, polyethylene), use of alternative materials in industry, and information campaigns to increase awareness of risk and use of individual protection devices by exposed workers.[48] Finally, allergic subjects must avoid direct contact with elastic bands/fibers or other rubber-containing parts of clothing items (including shoes) and common objects (condoms, rubber pillows, hot water bottles, swimming caps and goggles, masks, ear plugs, toys, balls, makeup sponges, mascara brushes, tires, knobs, handles, steering wheels, stickers, insulating tapes).[48] Rubber may also be present in medical equipment such as catheters, devices used for kidney dialysis, elastic bands for the treatment of circulatory disorders.[48]

Fragrance mix II (citral 1%, CAS 5392-40-5; farnesol 2,5%, CAS 4602-84-0; coumarin 2,5%, CAS 91-64-5; citronellol 0,5%, CAS 106-22-9; alpha-hexyl cinnamal 5%, CAS 101-86-0; hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) 2,5%, CAS 31906-04-4) (14% pet.)

Fragrance mix II (FM II), consists of six individual synthetic substances tested in a total concentration of 14% pet.[51] The six individual ingredients are tested at different concentrations, due to the necessity to maintain the sensitivity for detecting contact allergy to each individual fragrant ingredient while minimizing the risk of irritation from the combination of several constituents in one test preparation. The ingredient HICC, in fact, is tested in a lower concentration in the mix than when tested separately (5%).[51]

A recent paper showed that testing a FM II with a 5% HICC did not detect a significantly more positive patients than FM II with 2.5% HICC; the number of irritant reactions did not increase as well.[52] Since 2013 the frequency of positive reactions to FM II in Europe have been declining, yielding about 3% in 2018.[52, 53] The most common sensitizer in FM II is HICC.[54] Fragrances are ubiquitously used in perfumes and other perfumed cosmetic products, but also in detergents, fabric softeners, and other household products where fragrance may be used to mask unpleasant odors from raw materials.[51] Fragrances are also used in aromatherapy and may be present in herbal products. Due to different purported healing properties may also be used as topical medicaments in aromatherapy and alternative medicine.[51]

Myroxylon pereirae (Balsam of Peru) (CAS 8007-00-9) (25% pet.)

Myroxylon pereirae resin (MP), also known as balsam of Peru, is a botanical resin derived from the bark of a tree *(Myroxylon balsamum var. pereirae)* which grows in central America.[55] MP, a viscous liquid with an intense vanilla and cinnamon smell, has a complex chemical composition with more than 200 ingredients (among them benzyl cinnammate, benzyl benzoate, eugenol, cinnamic acid, benzyl alcohol, vanillin and cinnamyl cinnamate) and the composition varies depending on geographical area and the production method.[55] The main sensitizers in MP are difficult to ascertain.[50] MP was used in the past for medicinal purposes as an antiseptic and antiscabietic, in wound healing and in the treatment of different itching dermatoses.[55] It was also used in cosmetics (now banned from this use) and food industry.[55]

Due to its well-known sensitizing potential, MP is no more used "as such" on the market.[55] Estimates of the last 10-year prevalence of contact allergy to MP in Europe, in general population ranges from 1.3% to 3%. About 4%-8% of patients show positive reactions to MP[56] when it is tested within the baseline series at 25% pet.[57]

Since the 1960s, it has been used as a marker for natural fragrance sensitivity, as it was found that about 50% of patients with positive reactions to MP are also sensitive to perfumes.[57] MP and Fragrance Mix I (FM I) are partly cross reactive as they share certain constituents such as cinnamal, cinnamic alcohol and eugenol as well as other compounds.[58] Even if many cases of contact allergy to fragrances may be detected testing FM I, about 50% of patients sensitized to MP do not react to FM I.[58]

A recent Italian paper confirmed the utility of testing MP along with FM I in baseline series as it allows de-

tection of a remarkable number of fragrance allergies, mostly relevant, which would be otherwise missed.[58] The presence of MP in pharmaceutical, cosmetic or consumer products is nowadays very limited and in scented products it is not declared.[56] It must be regarded as a marker of fragrance allergy towards scented cosmetics (deodorants, perfumes, hair lotions, aftershaves, hair sprays, lipsticks), resins, and insect repellents.[56] Scented MP components may be present in over-the-counter medicaments such as balsams, anti-scabies ointments, suppositories or in plasters.[56] Foods and drinks such as vermouth, cola, licorice, chocolate and candies may contain MP constituents; avoidance of these products may improve symptoms in allergic patients who complain of stomatitis or burning oral symptoms. MP components may also be present in scented tobacco.[56]

Fragrance mix I + sorbitan sesquioleate 5% (cinnamyl alcohol 1%, CAS 104-54-1; cinnamal 1%, CAS 104-55-2; hydroxycitronellal 1%, CAS 107-75-5; alpha-amyl cinnamal 1%, CAS 122-40-7; geraniol 1%, CAS 106-24-1; eugenol 1%, CAS 97-53-0; isoeugenol 1%, CAS 97-54-1; *Evernia prunastri* (oakmoss absolute) 1%, CAS 90028-68-5) (8% pet.)

All the components are synthetic fragrance ingredients while *Evernia prunastri* is of natural origin.[59] In 1990 sorbitan sesquioleate (a non-ionic surfactant) was added to the mix at the 5% concentration as an emulsifier in order to assure a satisfactory dispersion of the 8 constituents of the mix in the petrolatum vehicle.[59] This oil-soluble emulsifier is a rare cause of contact allergy but can induce false positive reactions to FM I; the need to maintain sorbitan sesquioleate as a single allergen in the baseline series has been recently demonstrated.[60]

The frequency of positive reactions to FM I in the decade 2009-2018 in Europe is about 5-6%.[53, 54] The most common sensitizer is no longer oakmoss absolute (less used commercially), but Isoeugenol.[54] Patch testing with fragrances is an important step in the diagnosis of fragrance allergy. The composition of FM still seems reflect the most common constituents of personal care products.[53] Fragrances are contained in cologne, eau de toilette, aftershave etc. They are also present in cosmetics (for skin, nails, hair, eyes), toothpastes, sunscreens, cleansing products, wet wipes and insect repellents.[52] Perfumes can also be found in household products such as dishwashing and clothing detergents, fabric softeners, polishes for furniture. Toilet paper, sanitary napkins and paper handkerchiefs may have perfumes in their composition. Metalworking fluids and cleaning chemicals frequently contain fragrances with the purpose of masking unpleasant odors. Before using a cosmetic product, therefore, it is always necessary to check its composition on the label or leaflet.[61]

Attention should be paid to products defined as "hypoallergenic" and those labelled as "of natural origin".[61] Fragrances may be a source for occupational CD; hairdressers and beauticians are particularly at risk.[61] According to EU regulation No. 1223/2009, 26 fragrances that are regarded as significant allergens have to be declared on cosmetic products.[61]

Sorbitan sesquioleate (CAS 8007-43-0) (20% pet.)

Sorbitan sesquioleate (SSO) is an oil-soluble and non-ionic surfactant derived from sorbitol and oleic acid.[60] It is used as a water-dispersible emulsifier in several cosmetics and pharmaceutical preparations, including moisturizers, personal care products, nail treatments, toothpastes and topical medications such as CSs, antibiotics, and antifungals.[60] At a concentration of 5% has been added as an emulsifier to FM I in order to ensure satisfactory dispersion of the eight constituents of the mix in the petrolatum vehicle.[60]

The frequency of SSO-induced ACD in Europe is relatively low, and SSO is not yet included in either the classic or comprehensive European baseline series.[62] The prevalence of contact allergy to SSO in Europe was from 0.2% to 1.5% and seemed to be higher in other continents.[62] The reported rates are for Denmark 0.2% (2010-2014) and Italy 0.5% (2019), lower than rates for Germany 0.8% (2016-2018), Belgium 1.5% (2002-2011) and the Netherlands 2.7% (1996-2013).[59, 63, 64] Usually, the patch test preparation with SSO is 20% in pet.[62, 63]

Hydroxyisohexyl 3-cyclohexene carboxaldehyde (CAS 31906-04-4) (5% pet.)

Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), also known as Lyral®, is a highly allergenic synthetic fragrance found in many commercial products.[65] It is widely used as fragrance ingredient in cosmetic products and non-cosmetic products such as household cleaners due to its low cost and its pleasant lily of the valley scent.[65] The prevalence of HICC contact sensitization ranges from 1.9 to 2.7% in European countries (2000-2001).[65] Due to the increasing prevalence of sensitization, the European Commission banned the presence of HICC in 2017; this law was fully implemented in 2021.[66] This has led to a significant decrease of the cases of sensitization, reflecting a change of the composition of the products on the market.[67] HICC is tested worldwide at 5% pet.; it is included in the Italian SIDAPA baseline series since 2005.[68]

A decreasing trend in sensitization from 2016 to 2021 has been demonstrated also in Italy, where the prevalence registered is 1%.[68] About 72-80% of the positive reactions found at patch testing are considered relevant.[65] Contact allergy frequently involves the facial area, the hands or armpits.[68] HICC is one of the components of FM II and is the most common sensitizer of this mix.[68] A recent study has demonstrated that 22.9% of HICC positive reactions would have been lost if only FM II had been tested.[68] This finding emphasizes the necessity to maintain HICC as a single allergen in the baseline series. HICC may be found in perfumes, deodorants, aftershave, lip products, wet wipes, detergents, household cleaners and detergents.[68] Therefore patients allergic to HICC should be advised to avoid the contact with all these products, especially if they buy online products outside Europe, potentially containing HICC and with misleading labeling on packs.

Paraben mix (methylparaben 4%, CAS 99-76-3; ethylparaben 4%, CAS 120-47-8; propylparaben 4%, CAS 94-13-3; buthylparaben 4%, CAS 94-26-8) (16% pet.)

Parabens are para-hydroxybenzoic acid esters that have been widely used as preservatives in the cosmetics, food, and pharmaceutical industries for more than 70 years.[69] Paraben mix consists of four substances tested in a total concentration of 16% in pet. Sensitivity to parabens is continuously monitored since they are patch tested in the baseline series as early as 1940.[69] The frequency of sensitivity to this widely used biocide has remained low and remarkably stable for many decades despite extensive use and progressive expansion of utilization worldwide.[69] The actual prevalence of paraben sensitivity in the general population is unknown and is suspected to vary by geographic location because of genetic and exposure degree differences.[70] Since 1998, data based on weak scientific evidence have attributed to parabens carcinogenic, infertility, and endocrine disruption effects.[69] Genuine phobia toward these compounds and adoption of "paraben-free" labeling on cosmetic products lead to their banning from most cosmetic products.[69]

The frequency of ACD to paraben mix is less than 0.5% in most clinical series, although it most frequently occurs in patients with long-lasting stasis dermatitis, disruption of skin integrity, and high use of topical drugs. A retrospective observational study including patients sensitized to parabens found a mean sensitization rate of 0.58% over a period of 39 years,[71] and these results are in line with those of other European studies performed in the period 2009-2012.[21]

Cocamidopropylbetaine (CAS 86438-79-1) (1% aq) and dimethylaminopropylamine (CAS 109-55-7) (1% aq)

CAPB is an amphoteric (betainic) surfactant that is commonly used in the cosmetic industry, because of its low potential for irritating the skin, together with its thickening power.[72] It is prepared by reacting fatty acids (obtained from coconut oil) or coconut oil itself with 3-DMAPA, yielding cocamidopropyl dimethylamine, which is subsequently allowed to react with sodium monochloroacetate to give the end-product cocamidopropylbetaine.[72] Anyway, this latter may contain varying amounts of the reactants and intermediates involved in its synthesis and among these DMAPA.[70] DMAPA is a well-known sensitizer and may be contained as a contaminant in personal care products and several industrial products (such as agricultural chemicals, fabric softeners, water-resistant textile fibers, synthetic dyes and paints, etc.).[72]

In a recent Italian study performed between January and December 2018, the authors showed a prevalence of 1.3% of contact allergy to DMAPA analyzing the data from 5140 consecutively patch tested patients.[72] Of note, the authors highlighted that the majority of the DMAPA-positive patients with clinical relevance reported the onset of the dermatitis during the last 2 years thus demonstrating that DMAPA is still present at sensitizing concentrations in many products as an impurity.[72] The North American Contact Dermatitis Group reported a 1.7% prevalence of positive reactions to DMAPA between 2009 and 2014,[22] while Finnish Institute of Occupational Health reported a 1.0% prevalence of occupational contact allergy due to DMAPA between 2002 and 2009.[23] in 2019 the Cosmetic Ingredient Review Expert Panel advised industry to keep minimizing the presence of DMAPA at concentrations lower than 0.01%.[73]

Methylisothiazolinone (CAS 2682-20-4) (0.2% aq) and methylchloroisothiazolinone/methylisothiazolinone (CAS 55965-84-9)

MI and the mixture MI/MCI are two derivatives of isothiazolinones widely used as preservatives in rinse-off cosmetics, household detergents, water-based paints and industrial products. Sensitization to both isothiazolinones takes place both in the domestic sphere, mainly due to exposure to cosmetics and household detergents, and in the workplace, especially in cleaning workers.[74]

Formerly, MI was employed in a fixed combination (Kathon CG®) 1:3 with MCI. However, MI has been increasingly used alone, or in combination with other preser-

vatives, in industrial applications (*e.g.* paints) and household detergents at much higher concentrations.[74] The use of MI in cosmetics also increased after its use was permitted in the EU several years ago, allowing concentrations of up to 100 ppm in the finished product.[75] Contact allergy to isothiazolinones in Europe peaked during 2013 and 2014, with MCI/MI positivity reaching 7.6% (ESSCA) and 5.4% (Information Network of Departments of Dermatology [IVDK]).[76]

Considering these data, the European Scientific Committee on Consumer Safety stated that no safe concentration of MI was identified for leave-on cosmetics, whereas for rinse-off ones a maximum concentration of 15ppm was considered safe.[77] From then on, a slower decline has been observed in Europe during 2017 and 2018 by ESSCA (4.4%) and IVDK (3.2%).[76] On the contrary, the North American Contact Dermatitis Group (NACDG) still recorded high prevalence during 2017 and 2018 with 15.3% of patients sensitized to MI and 11% to MCI/MI, thus suggesting that differences in regulation may be contributing to the different trend.[78] In view of the relatively large number of patients testing positive to MI but not to MCI/MI, both MI and MCI/MI are present in the SIDAPA baselines series for patch testing respectively at 0.2% aq. and 0.02% aq. Recently, Isaksson *et al.* compared patch testing a new aqueous mix of MCI 0.015% and MI 0.2% with MCI/MI 0.02% and MI 0.2%.[79] This new mixture allowed to detect significantly more positive reactions, so the authors suggested replacing the preparations MCI/MI 0.02% aq and MI 0.2% aq. with the new mixture MCI/MI 0.215% aq.

Benzisothiazolinone (CAS 2634-33-5) (0.1% pet.)

BIT is a preservative commonly found in industrial products to preserve the water content of paints, varnishes, adhesives, and sealants, and other products.[80] It can also be found in household cleaning at high concentrations: this includes also products in spray form that can lead to an airborne pattern of contact allergy including facial dermatitis.[81] There is no legislation limiting isothiazolinones use in these settings, but it is not permitted in personal care products.[80] Uter *et al.* have conducted a multicenter study in a 2019-2020 European group, which showed a frequency of sensitization to BIT of 4.7%, so that the authors conclude that its inclusion in the European standard series appears suitable.[10] The NACDG reported even higher percentages (7.3%) in 2017 to 2018, but this may be due to the use of BIT in cosmetics, which is allowed in the US but not in the EU.[82] The trend of contact allergy to BIT seems to be increasing over the last 6 years, probably as a consequence of the increased use in household products.[24]

Neomycin sulfate (CAS 1405-10-3) (20% pet.)

Neomycin is an antibiotic that belongs to the aminoglycoside family and is effective against both gram-positive and gram-negative organisms, except *Pseudomonas aeruginosa*.[83] Its percutaneous absorption is minimal, and it is used in topical formulations for skin (creams, powders, and ointments), ear treatments, eye drops, vaginal suppositories, in solutions for urinary instillation, and solutions for peritoneal irrigation. It is also commonly found in dental and veterinary care products.[84] Currently, the recommended patch test concentration of neomycin sulphate is 20% in pet. Cross-reactivity may occur with the administration of other aminoglycosides, such as kanamycin, tobramycin, framycetin, gentamicin, amikacin, and streptomycin, sharing similar structures.[84] There is also a high-rate cosensitivity to bacitracin. If patients are sensitized to neomycin, mupirocin can be used since its chemical structure is unique among the topical antibiotics.[84]

Small quantities of neomycin absorbed from the gastrointestinal tract can produce the dissemination of dermatitis, the onset of lesions in previous dermatitis sites, reactivation of the positive reaction to the patch test, or systemic CD.[83] According with data of the NACDG, the incidence of neomycin ACD was 7.2% in 1985-1989 and peaked in 1996-1998 at 13.1% before declining to 8.4% in 2013-2014.[85] Neomycin sensitization rates in Europe have decreased compared to the past. Studies from major European centers from 1996 to 2006 reported neomycin sensitization rates varying from 1.1% to 3.8% and averaging approximately 2.6%.[83] Occupational dermatitis to neomycin usually affects the hands and face and occurs in healthcare professionals, pharmacists, dentists and veterinarians,[83] Reduction in the free availability of these drugs, together with careful prescriptions, will lead to a decrease in the sensitization rate to the European levels, with neomycin use being reserved for strictly indicated cases.[83]

Tixocortol-21-pivalate (CAS 55560-96-8) (1%)

Tixocortol-21-pivalate is a C-21 thioester of hydrocortisone.[86] It is an anti-inflammatory topical CS used in the treatment of rhinitis (as a nasal suspension or aerosols), pharyngitis (as lozenges), ulcerative colitis (as enema or rectal solution), and oral, inflammatory conditions (as a suspension or a powder).[86]

Tixocortol pivalate is used in patch testing to detect al-

lergy to hydrocortisone and to other CSs.[86] Patch testing performed with hydrocortisone is associated with a high rate of false negatives, especially when hydrocortisone is tested on a pet. vehicle but also occurs with an ethanol vehicle.[84] For these reasons, tixocortol-21-pivalate is now a new component of the Italian baseline series and it is patch tested at 1% in pet. Cross-reactivity may occur with other related CSs (amcinonide, budesonide, cloprednol, desonide, fludrocortisone acetate, fluocinolone acetonide, fluocinonide, flurandrenolide, halcinonide, hydrocortisone, hydrocortisone 17-butyrate, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone probutate, hydrocortisone buteprate, hydrocortisone valerate, methylprednisolone, micronized fluocinonide, prednicarbate, prednisolone, prednisolone acetate).[84] Although hypersensitivity to CS was previously thought to be infrequent,[85] during the1990s several studies showed high prevalence of sensitization to topical CSs, in the UK and Belgium >5%.[87] Data from the NACDG (2013-2014) on CS reported the incidence of ACD due to tixocortol pivalate of 2.1%.[88]

Budesonide (CAS 51333-22-3) (0.01% pet.)

Budesonide is used for the treatment of asthma, hay fever and other allergies, and for treatment and prevention of nasal polyposis.[84] Additionally, it is used for inflammatory bowel disease. In 2000, budesonide 0.01% in pet. was included in the European Baseline Series (EBS)[14] and several multicenter studies demonstrated a decreasing trend in the following 15 years in Europe and North America.[11, 87, 88] Over the last 5 years, two multicenter studies performed by the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC) (2015-2016) and the ESSCA (2015-2018) showed a further decreasing trend of this prevalence (0.62% and 0.67%, respectively).[87, 88]

An Italian retrospective study performed in the period 2018-2019 on 14,544 patients showed an ACD to budesonide 0.01% pet. in 0.6% of patients patch-tested.[11] Concerning the best patch test preparation, both the vehicle and the concentration are involved. Either ethanol or petrolatum is recommended for tixocortol pivalate and budesonide since studies have shown equivalent patch-test results with either vehicle.[89] Another concern is the optimal patch test concentration: a high patch test concentration of a potent CS may yield a negative test result on an early reading occasion whereas a low concentration may yield a positive test result.[89] This can be explained by the anti-inflammatory action of the CS itself, which influences patch test results at early readings (when the anti-inflammatory effect prevails), leading to a false-negative test result if the anti-inflammatory action predominates over the elicitation of the allergy test eczema.[89] This phenomenon has been demonstrated in European comparative studies, in which lower concentrations detected more allergic patients than did higher concentrations; therefore, budesonide 0.01% in pet. and tixocortol pivalate 0.1% in pet. are included in the EBS.[14]

Caine mix (benzocaine 5%, CAS 94-09-7; tetracaine-hydrochloride (HCl) 2.5%, CAS 136-47-0; cinchocaine-(syn, dibucaine)-HCl 2.5%, CAS 61-12-1) (10% pet.)

Local anesthetics (LAs) derived from caines are widely used, mainly in injectable preparations, but also in topical preparations.[90] ACD has frequently been reported following exposure to creams used for pruritus ani, hemorrhoids and insect bites, lotions for sunburn relief, and anesthetic eye and auricular drops.[90] Depending on their intermediate chain, caine molecules are usually classified into two major groups: esters (benzocaine, procaine, tetracaine, and amylocaine) and amides (cinchocaine or dibucaine, lidocaine, bupivacaine, mepivacaine, and prilocaine).[90] Conversely to amides, esters are metabolized by plasmaesterases top-aminobenzoic acid (PABA), which is responsible for the greater allergenic potential and cross-reactivity between anesthetics in this group.[90]

In the past, benzocaine has recommended within the EBS as a screening allergen to show ACD to LAs.[91] Nevertheless, its efficacy has been repeatedly questioned since the1980s. Indeed, benzocaine is not the best single agent in a baseline patch testing series to screen for LAs allergy since up to 70% of allergic reactions to LAs may be missed.[91] In the 2019 version of the EBS, benzocaine 5% pet. had been replaced by caine mix III 10% pet., which contains 5% benzocaine, 2.5% tetracaine-hydrochloride (HCl), and 2.5% cinchocaine-(syn, dibucaine)-HCl.[81] A study of the NACDG involving 10,061 consecutive patients overall the 5-years period 2001-2004 examined reactivity to single LAs ingredients with 1.7% positive to benzocaine 5% pet. with very limited overlap to other LAs, 0.95% positive to dibucaine (syn. cinchocaine) 2.5% pet., and 0.38% positive to tetracaine 1% pet.[90] A study from Coimbra, Portugal, analyzed 2736 patients consecutively patch tested over the period 2000-2010 with caine mix III 10% pet., yielding 4.0% positive reactions.[92]

Formaldehyde (CAS 50-00-0) (0.2% aq)

Formaldehyde (FA) is widely present in our environment and it is an important cause of ACD although to a much lesser extent than in the past.[93] FA can be found in prod-

ucts containing formaldehyde-releasers,2,6 which release FA in the presence of water.[94] FA is commonly present in food, cosmetics, pharmaceuticals, house-hold detergents, and many other consumer products, as well as in chemical (industrial) products.[93] FA solution is well known as a fixing agent to fix cells during immunofluorescence imaging and for cross-linking cells during chromatin immunoprecipitation (ChIP) assay.[93] The textile industry uses formaldehyde-based resins as finishers to make fabrics crease-resistant. When treated with phenol, urea, or melamine, FA produces, respectively, hard thermoset phenol FA resin, urea FA resin, and melamine resin.[93] These polymers are permanent adhesives used in plywood and carpeting. They are also foamed to make insulation, or cast into molded products.

FA is also a precursor to polyfunctional alcohols such as pentaerythritol, which is used to make paints and explosives.[93] Furthermore, FA can be useful as a disinfectant as it kills most bacteria and fungi (including their spores).[93] It is used as an additive in vaccine manufacturing to inactivate toxins and pathogens. FA releasers are used as biocides in personal care products such as cosmetics.[93, 94] Quaternium-15, diazolidinyl urea, DMDM hydantoin, imidazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol (bronopol) are the five main releasers of FA (FRs) frequently used in cosmetics, pharmaceuticals, medical devices, household detergents, and chemical (industrial) products. In Europe, contrary to the United States, the use of free FA in cosmetics is nowadays forbidden, mainly due to its carcinogenic properties, it can still be found as a hidden impurity in them. The recommended patch-test concentration of FA is 2% aq.[95] The prevalence of FA sensitization has been found in decreasing in the last 15 years. It is between 1.5% and 2.5%, yet occasionally somewhat higher figures were reported (*i.e.*, 4%).[21, 93, 94] Patients sensitized to FA, both FA and FRs should preferably be avoided, except for bronopol in case it tests negatively.[96] In patients sensitized to a releaser, such as imidazolidinyl urea or diazolidinyl urea and not to FA, contact allergy was most likely induced by the releaser itself; consequently, only this specific releaser should then be avoided.[96]

p-ter-Butylphenol-formaldehyde resin (CAS 25085-50-1) (1% pet.)

p-ter-Butylphenol-formaldehyde (PTBPF) resin is synthesized from phenol and FA by acidic or basic catalytic reactions.[97] The structure and properties of the phenol-formaldehyde resin is highly dependent on the reaction conditions, the type of catalysts, and the molar ratio of reactants.[81] Phenolic resin is classified into novolac or resol resin based on the pH and phenol to FA ratio used in the reaction.[97] Resol type resins are formed under basic conditions when the molar amount of FA exceeds that of phenol. The first commercial product made from PFR was "Bakelite", a wholly synthetic polymer manufactured in 1909.[97] PTBPF is a FA resin found in adhesives and glue formulations particularly used in products such as shoes, handbags, belts, watchstraps, glues, varnishes, lacquer resins, motor oil additives, rubber antioxidants, printing inks, masonry sealant, insecticides, deodorants, and commercial disinfectants could contain this substance.[97] As a rule, the sensitizing agent in PTBPF resin is p-ter-butylphenol and not the phenol or FA.[97] Contact allergy to PTBPF is mostly non-occupational, and occupational cases have only been reported in the shoe manufacture and car industry.

The prevalence of PTBPF resin contact allergy when tested at 1.0% in pet. varies from 0.8-2.6%, but from 2004 to 2013/14 the prevalence declined by ~50% in Europe.[98] In a recent multicenter study across Europe the prevalence of PTBPF resin was 0.47%.[10, 98]

Due to its carcinogenic properties, the presence of FA in resins and other industrial products has been a subject of great concern in recent years. Modern alternatives for the production of wood-based panels employ substitutes for FA in the production of amino and phenolic resins, as well as novel hardeners for FA-free wood adhesives.[99]

Lanolin alcohols (CAS 8027-33-6) (30% pet.)

Lanolin is the refined form of wool grease or wool wax, the natural waterproofing substance secreted by the sheep sebaceous glands and found on their wool, from which it is extracted by scouring.[100] It is a complex mixture of high molecular weight esters, aliphatic alcohols, sterols, fatty acids and hydrocarbons with a composition that varies depending on the source of the raw material and its refining process.[100] There are many types of "lanolin" with varying degrees of purity. These range from crude industrial grades to highly purified medical grade lanolin.[100] Because of its emollient properties, lanolin is largely used in all sorts of cosmetic products and in topical medicaments.[100] It is also found in lubricants, rust-preventive coatings, furniture polish, shoe polish, printing inks and other commercial products.[100] The reported prevalence of lanolin sensitization in referred dermatitis patients has varied from 1.2% to 6.9% in several studies but its allergenicity is debated. Based on the data of the ESSCA surveillance system, in 2019-2022 the prevalence of positive patch test reactions to lanolin alcohols in Europe was 1.38%.[10]

Considering the broad use of lanolin this frequency of sensitization is relatively low. It is generally agreed that lanolin is a week allergen that can cause ACD after repeated or prolonged topical exposure, especially on damaged skin.[101] Atopic dermatitis, leg ulcers, and lower-extremity venous stasis dermatitis have been identified as risk factors for the development of lanolin contact allergy. Children and the elderly are also at greater risk of developing contact allergy to lanolin, partly because of comorbidities (AD and stasis dermatitis/leg ulcers, respectively).[101] Detection of lanolin-induced CD in diseased skin by patch testing on normal skin may lead to false negative results.[101] On the other hand, many patients with a positive patch test to lanolin alcohols may tolerate use of lanolin-containing emollients. Thus, the clinical relevance of a positive patch test reaction to 'lanolin has been questioned, especially when a lanolin-containing product is applied to normal skin. As a result, repeated open application test (ROAT) may have special utility for questionable or 1+ reaction to lanolin alcohols and it is recommended to test patients' own products in case of a clinical suspicion of lanolin contact allergy and negative patch test result.[101]

Colophony (CAS 8050-09-7) (20% pet.)

Colophony, also known as rosin, is the non-volatile fraction of oleoresins obtained from coniferous trees, mainly pine trees.[102] Its composition varies depending on the source and the way it is produced. Based on the way of recovery, there are three types of rosin: gum rosin, wood rosin and tall oil rosin.[102] They all contain the same major chemical components, consisting of about 90% resin acids, divided into abietic types and pimaric acid types, and 10% neutral substances such as diterpene alcohols, aldehydes and hydrocarbons.[102] Natural rosin can be modified to obtain derivatives with improved technical properties and most rosins used today are chemically modified but contain a variable percentage of unmodified rosin.[102]

Rosin is a well-known skin sensitizer. Its main allergenic components in both unmodified and modified rosin are autoxidation products of abietic acid (in particular 15 hydroperoxyabietic acid) that are formed upon exposure to air. Modified rosins can contain further allergens (such as maleopimaric acid) that are formed during the modification chemical process. Because of their good tackifying and emulsifying properties, rosin and its derivatives have countless of applications in domestic, occupational and healthcare settings. Products that can contain colophony include: adhesive tapes, plasters and dressings, glucose sensors and ostomy devices, impression material in dental care, cosmetics such as epilating waxes and make up products (mascara, lipstick), diapers and sanitary pads, various glues and sealants, in particular shoe glues, surface coatings, printing inks, metalworking fluids, and soldering materials, wood and wood-derived materials, string instruments, and dancers' shoes.[102-104] By law, products/materials containing ≥0.1% colophony should be labeled with the statement EUH208 "Contains rosin; colophony. May cause an allergic reaction".[102]

The reported frequencies of patch test positivity to colophony 20% in the period 2002-2014 vary between 1.4% to 4.2% in consecutively patch tested European patients.[103] According to ESSCA data, in 2019-2022 the overall prevalence of sensitization in Europe was 3.32%.[10] Colophony can cross-react with FMs, MP, *Compositae* mix and propolis. Colophony allergy is found in only a small number of fragrance-allergic patients and is not a good indicator for fragrance allergy. However, colophony can co-react to *Evernia furfuracea* (tree moss), owing to the oxidized resin acids present in the extract resulting from the collection process of this lichen from conifer bark. Therefore colophony-allergic patients should be advised to avoid fragrances containing this compound, and vice versa.[10]

Epoxy resin (CAS 25085-99-8) (1% pet.)

Diglycidyl ether of bisphenol A (DGEBA) 1% pet. is the standard patch test agent used to detect epoxy resin contact allergy.[105] It is an epoxy resin monomer based on a combination of bisphenol A and epichlorohydrin and it is the most important skin sensitizer in epoxy resin systems (ERSs).[105]

ERSs are commercial thermosetting products that, owing to their strong bonding properties, chemical resistance, and toughness, are widely used in industrial applications where strong, flexible and lightweight construction materials are required.[105] They are used in fields such as flooring, concrete bonding, and aircraft and automobile manufacture. In the electronics industry, they are used as insulation material.[106] ERSs are made up of epoxy resin monomers and curing agents/hardeners.[106] They also contain additives such as organic solvents, fillers such as fiberglass or sand, and pigments. When ERSs are used, the epoxy resin monomers are reacted with the curing agent to form a hard polymer.[106] Fully cured epoxy resin is regarded as non-irritating and non-sensitizing, while exposure to the uncured resin components can cause both ACD and irritant CD.[106] Approximately 75-95% of all epoxy resins are polymerization products of DGEBA, whereas

1% are polymers of the diglycidyl ether of bisphenol F (DGEBF). DGEBA and DGEBF can cross-react.[106]

The prevalence of sensitization to DGEBA has been reported to vary from 0.2% to 0.5% in the general population, and up to 1.3% in patients with dermatitis and it can reach 9% in high-risk occupations. According to the ESSCA surveillance system, in 2019-2022 the prevalence of sensitization to epoxy resin in patch tested subjects in Europe was 1.29%.[10] Epoxy chemicals are among the most common causes of occupational ACD.[106] Skin sensitization is seen in workers who handle uncured or incompletely cured resins and the hands and face are predominantly affected by dermatitis, the face primarily through airborne exposure.[104] Skin contact with the resins may also occur when handwashing tools used in applying the product or from exposure to the epoxy resin sawdust. Epoxy resins can penetrate polyethylene rubber, neoprene, and polyvinyl chloride gloves while laminated multilayer plastic gloves and nitrile gloves or nitrile-butatoluene gloves seem to give protection.[107] Despite protection measures, the skin of workers handling epoxy resin systems is frequently contaminated.[107] Hence, there is clearly a need for intensified prevention efforts including raising awareness among exposed workers and intensive training in correct use of personal protective equipment, as well as development and usage of ERSs with a lower sensitization potential.[107]

2-Hydroxyethyl methacrylate (CAS 868-77-9) (2% pet.)

2-Hydroxyethyl methacrylate (2-HEMA) is a water-soluble, modified methacrylate that is also a potent allergen when used as a monomer.[16] Under UV lighting, monomers quickly polymerize and in many industrial environments, including the plastic, glue, and painting industries, these compounds are frequently used.[17]

Historically, exposure came through the workplace (dental professionals), but as acrylate-containing nail products have become more popular, occurrences of non-occupational hand and facial dermatitis are on the rise.[17] Medical devices, including dental prostheses, are now a new source of acrylate allergy.[108-113] and 2-HEMA has been used in the past to identify methacrylate contact allergies.[17] SIDAPA has advised adding 2-HEMA 2% pet. to the baseline patch test series in Italy since January 2016. In one research, performed between November 2017 and October 2018 2-HEMA demonstrated a significant contact sensitization prevalence of 1.5% in a 4025 consecutively tested patients.[17] In light of the fact that this frequency of contact sensitization exceeds the 1% criterion, routine testing seems prudent.[17] In terms of sex, females had a 4-fold higher frequency than males, and 63.4% of non-occupational forms of exposure were found.[17] Allergy to artificial nails predominated among the relevant reactions in the examined individuals (80.5%), particularly in non-occupational setting (88.9%), corroborating the literature's recent findings that this reaction is on the rise.[109] Testing other acrylates, the issue of sensitization raises. The high frequency of reported sensitization was not due to 2-HEMA, but rather to other acrylates, such as ethyl acrylate, 2-hydroxy ethyl acrylate, etc.[114] However, some case reports described delayed patch test reactions at day 5 and day 10 and for this reason in cases of strong clinical suspicion of contact allergy late patch test readings are mandatory to avoid false negative reactions.[114]

The bulk of acrylate-related ACD events included nail products, which affected both customers and nail beauticians and called for more stringent regulation and preventative measures.[115-117] Beauticians are now more trained in the practices to use (vinyl gloves, face shields, wiping worktops) to reduce contact with acrylates.[115] However, the usage of gel polishes also occurs at home, when safety precautions are not taken and non-professional UV lights are utilized.[115] The biomedical industry will need to take into account the use of materials with a lower allergenic potential in the future due to the growth of contact allergies to medical devices, which are crucial for the health of many patients.

Compositae mix (*Anthemis nobilis* flower extract 1.2%, CAS 84649-86-5; *Chamomilla recutita* flower extract 1.2%, CAS 84082-60-0; *Achillea millefolium* flower extract 1%, CAS 84082-83-7; *Tanacetum vulgare* 1%, CAS 84961-64-8; *Arnica montana* flower extract 0.5%, CAS 68990-11-4; Partenolide 0.1%, CAS 20554-84-1) (5% pet.)

Compositae mix has been acknowledged as an effective addition to Sesquiterpene lactone (SL) mix 0.1% pet. for the identification of allergy to members of the *Compositae*/*Asteraceae* family of plants.[27]

SLs, a class of physiologically active compounds, are the sensitizing element of the Asteraceae family.[118] These lactones have a -methylene-lactone structure, which is necessary to induce *Compositae* sensitivity.[118] It has been demonstrated that the lactone ring interacts chemically and forms covalent connections with nucleophilic residues of proteins in the skin, inducing the inflammatory response that results in ACD.[118]

SLs are found in plants in a variety of compositions and quantities.[118] The bulk of type IV sensitizations to phytochemicals that have been diagnosed in Europe are caused

by the *Compositae*. The plant family also comprises food plants, including different salads, seeds, and vegetables, as well as medical herbs and flowers that are utilized in topical medications or cosmetics.[118] Cooks, farmers, florists, gardeners and horticulturists, and those in allied fields of the food processing industry are at risk to develop occupational and non-occupational *Compositae* ACD.[118] Direct skin contact with plants, as well as plant-based ingredients found in cosmetics and topical medications, can cause *Compositae* sensitivity. Aside from ACD and airborne ACD, other possible skin conditions include photo-ACD and chronic actinic dermatitis.[112] Typically, exposed body parts like the face, neck, 'V' of the neck, hands, and forearms are affected by *Compositae* dermatitis. Due to increased circulation of dried plant matter and exposed skin in hot temperatures, the risk of exposure is higher in the summer, when flare-ups are frequent, and acute vesicular reactions might happen.[118] Repeated exposure results in chronic and lichenified ACD.

Although some authors have pointed out in Sweden that the SL mix alone is not sufficient to support *Compositae* testing in a baseline series, the idea that SL mix alone is an inadequate screen that necessitates further research persists.[119] According to the literature, between 35% and 65% of *Compositae*-sensitized patients are detected by the commercial SL mix, which is now used in the European baseline series.[27]

The *Compositae* mix 6% pet. has a greater detection rate than SL mix, but there is a danger of false-positive reactions and, supposedly, active sensitization if it is given for 48 hours rather than the 24 hours recommended in one of the early reports.[27] In a Swedish multicenter study comparing the detection rates of SL mix and *Compositae* mix 5% pet. in 2818 patients (2006-2007), 0.9% of patients reacted positively to SL mix, while 1.1% of patients reacted positively to *Compositae* mix 5% pet.[119]

Given that *Compositae* are a common weed all throughout the world, avoiding direct exposure to them may be difficult. The preparation of edible varieties, most frequently lettuce and artichokes as well as leaves of chrysanthemum and marigold species, could also involve direct handling. Simple precautions include cleaning clothes frequently, taking a bath after being outside, and getting rid of *Compositae* weeds in home gardens.[118] *Compositae* flowers (such as dandelion or chrysanthemum spp.) kept indoors for decoration ought to be identified and replaced. If photosensitivity is suspected, a broad-spectrum sunscreen is recommended. It is advised to wear protective gloves, protective gear, and facial shield when there is occupational exposure, such as in gardeners. A further impairment of the skin barrier and exposure to irritants might result in refractory instances.[118]

Sodium metabisulfite (CAS 7681-57-4) (1% pet.)

Sulfites are a widespread class of sulfur-derived compounds that include the sulfite ion and are extensively employed in the cosmetic, pharmaceutical, and food sectors.[120]

The occurrence of contact allergy to SMB, which is also referred to as sodium disulfite or sodium pyrosulfite, has been documented on multiple occasions. However, establishing its relevance appears to be a challenging task.[120, 121] Sulfites are present in certain food and drink items due to the process of fermentation, while others are artificially produced and made available for commercial purposes.[114] Sulfites are utilized as growth regulators for microorganisms and as agents for bleaching, reducing, and antioxidant purposes.[120, 121] Additionally, they are incorporated into various pharmaceuticals to preserve the effectiveness and stability of certain medications, such as anesthetic preparations, antifungal and hemorrhoidal creams, rectal suspensions, parenteral, ophthalmic, nasal, and intravenous solutions.[120, 122] Subjects with an intolerance may experience various types of reactions, including asthma, rhinoconjunctivitis, and type I reactions leading to anaphylaxis and potentially fatal outcomes, when exposed orally, parenterally, respiratorily, or cutaneously. Symptoms such as malaise, dizziness, confusion, abdominal pain, and diarrhea have been also reported.[120, 122]

In addition to the frequently observed and thoroughly documented manifestations, sulfites have the potential to elicit cutaneous responses, such as flushing, urticarial or anaphylactoid reactions subsequent to ingestion and/or parenteral exposure, or ACD resulting from skin contact. Uter *et al.* have recently proposed the inclusion of SMB as an allergen in the European baseline series, warranting an audit.[123]

The importance of the vehicle in the evaluation of SMB is evident due to the compound's inherent instability in aqueous solutions. The aforementioned proposition has been suggested as a potential rationale for the comparatively limited incidence of positive responses to SMB, as well as the elevated frequency of uncertain or irritating reactions. In order to address this issue, numerous authors propose the utilization of petrolatum as a vehicle.[120] In 1994, a group of Italian researchers tested 2894 consecutive patients using potassium metabisulfite and sodium sulfite.[122] The results showed that 50 subjects (1.7%) exhibited posi-

tive reactions, only 12 positive reactions (24%) were clinically significant, with 5 of them being work-related.

According to a literature review, sulfite-induced ACD is a common occurrence and can be clinically significant when the medical history is accurate and well-directed.[122] It is imperative to acknowledge potential sources of exposure that may be relevant, particularly in professional environments such as the food industry and hairdressing, as well as in cosmetic and pharmaceutical products.[120, 121] Patch testing with SMB, which seems to be the best indicator for sulfite contact allergy, may also be useful in cases of immediate reactions to sulfite-containing products.[121]

Conclusions

The cornerstone of managing ACD is avoidance of allergens, and a key role in the identification of these culprit substances is played by patch testing. Hence the importance of a continuous updating of the baseline series based on the emerging contact allergens used in the occupational environments.[124] Moreover, as recommended by the ESCD[125] and SIDAPA[8] patch testing guidelines, it is important to have structured electronic documentation of patch test results, together with demographic and clinical information, in order to improve the periodic selection of emerging allergens.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Luca Stingeni and Katharina Hansel have given substantial contribution to the conception or the design of the manuscript and revised the manuscript critically; Leonardo Bianchi and Elena S. Caroppo have written most of the manuscript and have given contributions to literature research. All authors have participated to drafting the manuscript, read, and approved the final version of the manuscript.

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