Received: 20 February 2019 | Revised: 2 March 2019 | Accepted: 4 March 2019
DOI: 10.1111/cod.13263

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REVIEW

# *Myroxylon pereirae* resin (balsam of Peru) – A critical review of the literature and assessment of the significance of positive patch test reactions and the usefulness of restrictive diets

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In this article, contact allergy to *Myroxylon pereirae* resin (MP) (balsam of Peru) is reviewed. The topics presented include the uses, the chemical composition, the frequency of sensitization, the relevance of positive reactions, the MP-containing products causing allergic contact dermatitis, co-reactivity with other fragrance and non-fragrance materials, the sensitizers, the usefulness of MP as a "marker" of fragrance allergy, and the effectiveness of, and indications for, "balsam-restrictive" diets. Sensitization to MP occurs in 4% to 8% of patients routinely tested for suspected contact dermatitis. There are few adequate data on relevance. Topical pharmaceuticals were formerly, but are not today, important sources of sensitization. Cosmetics and foods or drinks are hardly ever products responsible for sensitization to MP. Positive patch test reactions in the large majority probably result from previous sensitization to MP constituents because of their presence in fragrances and fragranced products, MP thereby acting as marker (or "indicator") of fragrance allergy. However, fragrance mix I is a more sensitive marker, and the added diagnostic value of testing with MP is unknown. The allergenic ingredients of MP include isoeugenol, eugenol and cinnamyl alcohol, but there are other—largely unknown—chemicals that are responsible for contact allergy. Suggestions are given for further research to address questions thus far unanswered and to improve patient care.

KEYWORDS
balsam of Peru, balsam-restrictive diet, chemical composition, eugenol, cinnamyl alcohol, coniferyl benzoate, fragrance, isoeugenol, *Myroxylon pereirae* resin, perfume, fragrance marker, contact allergy

## 1 | INTRODUCTION

*Myroxylon pereirae* resin (MP) is a botanical balsam that has a long history of medicinal use, especially as an antiseptic and for wound healing. Bonnevie, at the Finsen Institute in Copenhagen, began routine testing with MP in 1939 to detect sensitization to topical preparations containing the balsam.[1] Since the 1960s, MP has been used as a marker for fragrance sensitivity, as it was discovered that half of the patients with positive reactions to MP are also sensitive to one or more toilet soap perfumes and vice versa.[2–4]

In this article, various aspects of contact allergy to MP are reviewed, including its chemical composition, the frequency of sensitization, the sensitizers, the relevance of positive reactions, the MP-containing products causing allergic contact dermatitis, the use of restrictive diets in patients reacting to MP, and co-reactivity with other fragrance and non-fragrance materials. An attempt is made to establish the significance of positive patch test reactions to MP and the value of testing MP in the baseline series. This article is an abbreviated but strongly adapted version of the chapter "*Myroxylon pereirae* resin (balsam of Peru)" published in the author's book *Monographs in*

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*Contact Allergy, Volume II—Fragrances and Essential Oils.*[5] The literature on contact allergy to MP up to 1961 was reviewed by Hjorth in his famous PhD Thesis "Eczematous allergy to balsams."[2]

### 1.1 | What is *Myroxylon pereirae* resin?

MP (INCI name United States *Myroxylon pereirae* (balsam Peru) resin; balsam Peru; balsam of Peru; Peruvian balsam; CAS no. 8007-00-9; EC number 232-352-8) is the balsam obtained from the bark of *Myroxylon balsamum* (L.) Harms var. *pereirae* (Royle) Harms. This tree grows between 300 and 700 m above sea level in the coastal regions of El Salvador and also in Nicaragua, Honduras, Guatemala, Cuba, Mexico, Costa Rica, and Panama.[3,6–8]

To remove the bark from the tree, it is alternately scorched and beaten. The balsam in the bark is obtained by boiling. Following removal of strips of bark from the tree, the exposed wood also secretes balsam. This material is absorbed into rags wrapped around the tree, which are then boiled in water. The balsam sinks to the bottom and is then collected.[7] Crude MP is a dark brown, viscous liquid that is transparent and yellowish-brown when viewed in a thin layer. It has an aromatic smell of cinnamon and vanilla, and a bitter taste. The name balsam of Peru is misleading. Most MP in worldwide circulation comes from El Salvador, not Peru, where the source tree does not grow. The misnomer does not originate, as is often stated, from El Salvador belonging to the Viceroyalty of Peru in the 16th century, but from the fact that, at that time, the Spanish originally packed and shipped the balsam to Europe from the port of Callao in Lima, Peru, one of the main ports of that time in the New World.[9]

### 1.2 | Uses

MP has a long history of medicinal use. In the 17th century, the "drug" appeared in German pharmacies. It was included in the United States Pharmacopeia from 1820, and MP has been described in many other national pharmacopoeias. Indications for its topical use have included chronic ulcers, poorly healing wounds, decubitus, eczema, pruritus, haemorrhoids and anal pruritus (in the form of rectal suppositories), scabies (later replaced with its ingredient benzyl benzoate), frostbite, nappy rash, and intertrigo. However, in 2016 the European Medicines Agency concluded that "There is no documentation available for Peru balsam to support a well-established use indication."[10]

The main buyers of pure MP are or were pharmaceutical companies, perfume manufacturers, the food industry, and stores selling natural or herbal products. MP as a complete mixture has been replaced more and more by single constituents or fractions of MP that are now used in foods, sweets, bakery goods, chocolate, pastries, and medicinal ointments.[11] MP or its ingredients may also be added, or have been added, to tobacco. Formerly, MP was present in many topical pharmaceuticals, for example, in countries such as France, Denmark and Belgium. Currently, however, it is not used in such products in Denmark,[12] and it is only rarely used in Belgium.[13]

Crude MP as such has not been used in perfumery and, as a consequence, not in perfumes in cosmetics, since 1982 (or 1974?[14]), when the International Fragrance Association (IFRA) banned its use in fragrances.[15–17] The possibility that some cosmetic products contain MP as a non-fragrance ingredient cannot be excluded, but, as the sensitizing properties have been well known for decades, it seems unlikely that many cosmetic manufacturers would use it. Indeed, in February 2019, MP was present in only 6 of 70 893 (0.008%) cosmetic products for which the composition is known in the Skin Deep Cosmetics Database of the Environmental Working Group (EWG), United States.[18] Extracts or distillates are allowed, and the current IFRA Standard restricts the use of these products to a level of 0.03% to 0.7% in consumer products, depending on the product category.[19] However, neither material is used at high volumes, and the "oil" was present in only 17 of 70 893 (0.02%) cosmetic products products in the United States.[18] Whether these products are[17] or are not[16,20] less allergenic than the crude material is controversial, but, with EC3 values in the murine local lymph node assay of 4% for the oil and 2.5% for the absolute,[17] these materials are still "weak-to-moderate" sensitizers.

## 2 | CHEMICAL COMPOSITION

Surprisingly little information is available on the qualitative and quantitative chemical composition of MP and its derivatives (oil, essential oil, and absolute).[2,6,7,11,17,21] The oleoresin is said to contain some 250 ingredients with a resin content of 20% to 40%[2,6]; the rest is a high-boiling volatile oil (often incorrectly called "essential oil") named cinnamein (which is also a synonym for benzyl cinnamate).[22] The quantitatively most important chemicals in MP appear to be benzyl cinnamate (up to 40%), benzyl benzoate (up to 30%), cinnamic acid (3%-30%), benzoic acid (1.5%-11%), coniferyl benzoate (only in fresh MP up to 8.5% [probably a mistake, should be 1.5%[5]]), nerolidol (2%-7%), benzyl alcohol (1%-2%), vanillin (0.2%-1.3%), cinnamyl cinnamate (0.5%), cinnamyl alcohol (0.4%), ferulic acid (0.1%-0.4%), benzyl isoferulate (0.2%), and coniferyl alcohol (0.2%).[6,11] These and other ingredients of MP or its derivatives identified with gas chromatography, gas chromatography-mass spectrometry or other analytical methods are shown in Table 1.[2,6,7,11,17,21,23] The concentrations for most are not mentioned, as they have been presented as percentages of various fractions of MP, have been identified in MP derivatives (the composition of which greatly depends on the mode of production), or have been identified only qualitatively. In contrast to what is often stated, cinnamal does not appear to be an ingredient of MP (products). According to the European Pharmacopeia, MP should contain 45% to 70% mass/mass of esters, mainly benzyl benzoate and benzyl cinnamate.[24]

MP derivatives used in perfumery are prepared either by vacuum distillation (Peru balsam oil) or by solvent extraction (Peru balsam absolute/oil); it can also be hydrodistilled to obtain Peru balsam essential oil. In nearly all materials, the most important chemicals are benzyl benzoate (at least half of the composition), benzyl cinnamate, cinnamic acid, benzoic acid, *E*-nerolidol, benzyl alcohol, and vanillin.[21,23,25] In one investigation, nerolidol was the major constituent in a hydrodistilled essential oil sample and in an oil obtained by solid-phase micro-extraction.[7]

**TABLE 1** Ingredients identified in *Myroxylon pereirae* resin (MP), extracts, and essential oils (adapted from Ref. [5])

| |
|---|
| Acetic acid |
| Acetophenone |
| Acetovanillone (4-hydroxy-3-methoxyacetophenone) |
| α-Amorphene |
| Amyrin |
| Aristolene |
| Benzaldehyde |
| Benzoic acid (1.5%-11%) |
| Benzyl alcohol (1%-2%) |
| Benzyl benzoate (up to 30%) |
| Benzyl cinnamate (up to 40%) |
| Benzyl *p*-coumarate (benzyl-*trans*-4-hydroxycinnamate) |
| Benzyl ferulate |
| Benzyl formate |
| Benzyl isoferulate (*cis* and *trans*) (0.2%) |
| Benzyl vanillate (benzyl 4-hydroxy-3-methoxybenzoate) |
| *cis*-α-Bisabolene, β-bisabolene and *cis*-γ-bisabolene and *trans*-γ-bisabolene |
| β-Caryophyllene |
| 1,8-Cineole |
| *cis*-Cinnamic acid and *trans*-cinnamic acid (3%-30%) |
| Cinnamyl alcohol (0.4%) |
| Cinnamyl cinnamate (0.5%) |
| Coniferyl alcohol (0.2%) |
| *cis*-Coniferyl benzoate and *trans*-coniferyl benzoate (up to 1.5% in fresh MP) |
| Coniferyl cinnamate |
| α-Copaene |
| α-Curcumene |
| Cycloisosativene |
| *p*-β-Cymene and *trans*-β-cymene |
| Docosanoic acid |
| Dodecanoic acid |
| Eicosanoic acid (arachidic acid) |
| Ethylbenzene |
| Ethyl benzoate |
| Ethyl cinnamate |
| Ethylhexanoic acid (tentatively identified) |
| Eugenol (0.2% in fraction BP3) |
| α-Farnesene and β-farnesene |
| Farnesol (traces) |
| Ferulic acid (0.1%-0.4%) |
| Formic acid |
| Geranyl acetone |
| Guaiacol |
| Heptadecanoic acid (margaric acid) |

**TABLE 1** (Continued)

| |
|---|
| Hexacosanoic acid (cerotic acid) |
| 1-Hexacosanol |
| Hexadecanoic acid (palmitic acid) |
| Hydroconiferyl benzoate |
| Hydroconiferyl cinnamate |
| Hydroxycinnamic acid |
| Isoeugenol (0.85% in fraction BP3) |
| Isoferulic acid (traces) |
| Lactic acid (2-hydroxypropanoic acid) |
| Limonene |
| Methoxyeugenol |
| Methyl benzoate |
| Methyl cinnamate |
| Methyl vanillyl ketone |
| α-Muurolene |
| Naphthalene |
| Nerolidol (2%-7%) |
| allo-β-Ocimene, *cis*-β-ocimene and *trans*-β-ocimene |
| 1-Octacosanol |
| Patchoulene |
| α-Phellandrene and β-phellandrene |
| 1-Phenylethanol (α-methylbenzyl alcohol) |
| 3-Phenylpropanol |
| α-Pinene and β-pinene |
| β-Sesquiphellandrene |
| Stearic acid (octadecanoic acid) |
| Styrene |
| α-Terpinene and γ-terpinene |
| 4-Terpineol (terpinen-4-ol) |
| α-Terpineol |
| 1-Tetracosanol (lignoceryl alcohol) |
| Tetradecanoic acid (myristic acid) |
| 1-Undecanol |
| Vanillic acid (4-hydroxy-3-methoxybenzoic acid) |
| Vanillin (0.2%-1.3%) |
| *p*-Vinylguaiacol |

Abbreviation: BP3, balsam of peru fraction 3; MP, *myroxylon pereirae* resin.

## 3 | CONTACT ALLERGY

Contact allergy to MP has been seen slightly more often in women in most studies[26–28]; in some investigations, the percentages of men reacting to MP were somewhat (although not significantly) higher.[29,30] In almost all studies, MP allergy occurred significantly more often in the older (>40 years) age groups.[26,27,29–31] In a large Information Network of Departments of Dermatology (IVDK) study, risk quantified by the prevalence ratio rose with increasing age vs reference (age

1-36 years) from 1.87 (age 37-50 years) and 2.79 (age 51-64 years) to 3.32 (age 65-99 years).[26]

## 3.1 | Frequency of sensitization

### 3.1.1 | General population

In a 2018 meta-analysis of 12 studies covering 8002 patch tested individuals from the general population, the pooled prevalence of sensitization to MP was 1.8%.[32] Estimates of the 10-year prevalence of contact allergy to MP in the general population of Denmark based on the clinical epidemiology drug-utilization research method in 2006 ranged from 0.57% to 0.77%.[33] In a similar study from Germany, the estimated prevalence in the general population in the period 1992 to 2000 ranged from 1.3% to 3.0%.[34]

### 3.1.2 | Patch testing in consecutive patients suspected of having contact dermatitis (routine testing)

As MP is present in most, if not all, baseline series used for routine screening testing worldwide, data on testing MP in consecutive patients are abundant. The results of nearly 55 such published investigations back to 2000 were shown in detail in 2019[5] and are summarized here. MP is nearly always tested at 25% pet. The test material from Chemotechnique contains 5% sorbitan sesquioleate. The TRUE Test system appears to be less sensitive for detecting sensitivity to MP than the petrolatum-based chamber systems.[35,36]

In 14 studies from the United States, 10 of which were performed by the North American Contact Dermatitis Group (NACDG), frequencies of sensitization have ranged from 6.6% to 13.7%.[5,37] Generally speaking, the rates appear to have decreased somewhat in the last decade, ranging in all NACDG studies between 7% and 8%. In Europe, 12 multinational multicentre studies have been performed by the European Surveillance System on Contact Allergy network, the IVDK in Germany, Switzerland, and Austria, the European Environmental and Contact Dermatitis Research Group, and other parties. The frequencies of sensitization have ranged in a very narrow band of 5.3% to 6.4% in most investigations[36,38–43], but were higher (6.8%-9.2%) in the IVDK studies.[5,26,44] Often, there was significant variability in the results per centre or country: 3.6% to 12.8%,[36] 1.6% to 10.6%,[38] 1.4% to 14.6%,[39] 2.3% to 12.9%,[40] and 2.8% to 10.9%.[41]

Concerning other European countries, four Danish studies with overlapping study periods and populations found frequencies of sensitization ranging from 2.8% to 4.4%.[5,45] In four investigations from the United Kingdom, frequencies of positive patch test reactions ranged from 2.9% to 6.4%, with lower rates in recent periods.[5,46,47] In Spain, positivity rates were 2.4%, 6.4%, and 5.8%.[31,48,49] In Sweden, 4.8% to 6.5% of routine patients reacted to MP.[27,30,50] Other European countries have also presented their patch test results with MP: The Netherlands, 2.8% (the low frequency probably resulting from the use of TRUE Test); Finland, 6.2%; Belgium, 6.1%; Switzerland, 7.8%; and the Czech Republic, 7.3%.[5]

Data on the frequencies of sensitization to MP are available from Thailand, Singapore, China, Australia, Iran, Israel, and Turkey. The rates ranged from 2.1% to 8.9%, with low rates in Turkey and Iran, and the highest rate in Australia.[51]

### 3.1.3 | Relevance and causative products

In the studies performed by the NACDG, generally 30% to 35% of the positive patch test reactions were sored as having "definite" or "probable" relevance, but very few reactions were considered to be definitely relevant.[5,37] Only six of the remaining 41 studies provided relevance data.[5,45,48,49,51] The percentages of positive reactions considered to be relevant ranged from 21% to 75%. In just one of the 55 investigations were products containing MP that caused dermatitis mentioned.[49] In this study from Spain, performed in the period 2002 to 2004, among 50 MP-allergic patients seen in one clinic, 32 reactions (64%) were considered to be relevant. In 19 patients, the culprit products were topical pharmaceuticals, and in 13 patients dermatitis had (apparently) been caused by cosmetics containing MP.[49]

### 3.1.4 | Patch testing in groups of selected patients

Many investigators have presented their results of patch testing with MP (and usually many other allergens) in groups of selected patients, for example, physical therapists, patients with eyelid/periorbital dermatitis, patients with allergic contact cheilitis, patients with stasis dermatitis/leg ulcers, patients suspected of having cosmetic intolerance or fragrance allergy, and patients with hand dermatitis. Most studies have been retrospective. These studies can be interesting when unexpected elevated frequencies are observed, which may indicate exposure to unknown sources of MP. Unfortunately, in by far most of the studies, there were no data on the frequency in a control group of patients routinely tested or other adequate controls. In addition, as MP is an indicator of fragrance allergy, any selection towards groups with an elevated risk of fragrance sensitization will inevitably lead to increased percentages of positive reactions to MP, not necessarily as an expression of (increased) exposure to the material itself. Other limitations of studies testing selected groups of patients are that data on relevance were provided in no more than 30% of the investigations, and that the culprit products were hardly ever mentioned.

In eight studies testing patients with stasis dermatitis and/or leg ulcers between 2002 and 2016, frequencies of sensitization to MP ranged from 13.6% to 50%; most found 30% to 40% positive reactions.[52–59] It is clear that, in all studies, the frequencies of sensitization to MP were higher than in routinely tested patients[53,55,58,59] or than expected. Relevance was mentioned in one study only: "definite" 0%, "probable" 6%.[52] Causative products were never mentioned. However, in a 2005 to 2008 study from France, where very high rates of sensitization to MP have been observed in the past in patients with stasis dermatitis and/or leg ulcers,[57] it was mentioned that, at that time, wound dressings with MP were still being used in France for leg ulcers.[54] In IVDK studies, the localization "feet/legs" was a risk factor

for a positive patch test reaction to MP, with a prevalence ratio of 1.45.[26]

In six studies in groups of patients with cosmetic allergy (allergic contact cheilitis, patients known to be allergic to cosmetics or fragrances, and patients with previous positive patch test reactions to deodorants, perfumes, eau de toilette, aftershave, bath or shower products, or skin creams), frequencies of sensitization to MP ranged from 14% to 45%, and were mostly between 17% and 24%.[60–65] These high frequencies are hardly surprising, considering the selection criteria. Relevance in three studies addressing this issue was 100%[62,63,65] (the latter selected on the basis of relevant reactions), but causative products were not mentioned.

In six studies in groups of patients suspected of having cosmetic or fragrance allergy,[66–71] frequencies of sensitization ranged from 9.4% to 19.6%. Relevance was mentioned in one study only (95%), but this investigation had certain weaknesses.[66] There was a control group in only one study: the frequency of sensitization in the group suspected of having cosmetic/fragrance allergy (7.9%) was significantly higher than in a control group undergoing routine testing.[70]

In seven studies in which patients with eyelid dermatitis or periorbital dermatitis were patch tested with MP, frequencies of sensitization ranged from 1.7% to 17%, but in five of the seven studies, the frequency was <7%.[72–78] In three investigations in which relevance was addressed, rates of relevant reactions were 43%,[77] 58%,[78] and 75%,[74] but the culprit products were not mentioned. In four studies with a control group, the frequency of sensitization to MP was significantly lower than in routine testing.[73–75,78]

In hairdressers, the prevalence of sensitization to MP in most studies was not or only slightly elevated,[79–83] which also applies to healthcare professionals, including nurses.[84–86] However, adequate control groups are largely lacking. Other indications for patch testing with MP have included individuals suspected of having photodermatoses, children, physical therapists, and patients with pure allergic hand dermatitis, with poikiloderma of Civatte, and with facial allergic contact dermatitis; convincingly elevated rates of sensitization to MP were not observed.[5]

## 3.2 | Case reports and case series

### 3.2.1 | Pharmaceuticals

In the past, MP was widely used in topical pharmaceutical preparations, and these were important sources of sensitization. In Hjorth's investigations, published in his 1961 PhD Thesis,[2] for example, of 126 balsam of Peru-allergic patients who had reported having used preparations containing MP, 111 (88%) had used the official 10% pet. Balsamum Peruvianum of the Danish pharmacopoeia, approximately half of them for burns. Forty-eight of 230 MP-positive individuals had been referred because of allergic contact dermatitis caused by MP preparations. Most reactions were caused by pure MP or MP in topical pharmaceutical preparations, including ointments, gauzes, and suppositories.[2] Eight patients from France in the mid-1970s had allergic contact cheilitis caused by MP in "Dermophil Indien," a pharmaceutical lip stick.[87] Quite remarkably, this product is still available, and even now contains MP.[88]

In the period 1990 to 2016, in a clinic in Belgium, 125 patients were investigated for allergic contact dermatitis caused by a medicinal herbal preparation.[13] In 30 (24%) patients, MP was the active principle in these preparations. Currently, these preparations are only rarely used in Belgium (although some preparations still contain MP[88]), and the majority of positive reactions were observed before the year 2000.[13] In the period 1978 to 2008, in the same clinic, 16 patients had allergic contact dermatitis caused by MP in topical pharmaceutical preparations, 13 for wound healing, two for the treatment of haemorrhoids, and one antiseptic/disinfectant.[89] There is very likely overlap with the data from Ref. [13]

Two patients presented with cheilitis and perioral dermatitis. Patch testing showed positive reactions to MP and to an ointment used as a lip balm, and for minor burns, cuts, nappy rash, sunburn, rash, and scalds. MP was not listed as an ingredient in this ointment, but the manufacturer confirmed that a small amount of MP was present in the product.[90] A man presented with a 12-week history of non-healing perianal erosions. He was prescribed a "healing spray" containing trypsin, MP, and castor oil, and the sores progressed to ulcerations. Use of the spray was discontinued, and the patient was patch tested; this showed positive reactions to MP, eugenol, and the spray. During the patch test, the perianal area became indurated.[91] A woman developed severe weeping dermatitis of the face after the application of an MP-containing ointment. This was followed by dissemination to the legs, where the ointment had not been applied. The eruption on the legs resembled vasculitis, with diffuse redness and numerous partly purpuric papules and some slightly haemorrhagic bullae. Patch testing showed the patient to be allergic to MP, fragrance mix (FM) I, colophonium, wood tars, eugenol, isoeugenol, oil of cloves (main ingredient: eugenol), and lavender oil. Although the authors suggested that systemic spread of the allergen was plausible, they did not, quite curiously, consider the possibility of systemic allergic dermatitis resulting from the ingestion of food or drinks.[92] One other patient apparently also had purpuric vasculitis-like lesions caused by allergy to MP.[93] A veterinarian had occupational allergic contact dermatitis of the hands caused by MP-containing ointments that he used for treating animals.[11]

### 3.2.2 | Cosmetics

MP was stated to be the (or an) allergen in 71 patients in a group of 603 individuals (11.8%) suffering from cosmetic dermatitis, seen in the period 2010 to 2015 in Leuven, Belgium.[94] In the period 1996 to 2013, in a tertiary referral centre in Valencia, Spain, 628 individuals had allergic contact dermatitis caused by cosmetics. In this group, MP was stated to be the responsible allergen in 17 (2.7%) cases (Ref. [95]overlap with Ref. [96]). In the period 2000 to 2007, 202 patients with allergic contact dermatitis caused by cosmetics were seen in the same clinic in Valencia, Spain. In this group, MP was the allergen in four (2%) individuals, resulting from its presence in moisturizing cream

(n = 2), deodorant (n = 1), and perfume (n = 1) (Ref. [96] overlap with Ref. [95]).

In Belgium, between 1985 and 1990, 3970 patients with dermatitis were patch tested. Four hundred and sixty-two of these reacted positively to patch tests with "cosmetic allergens." The reactions were considered to be relevant in 68%, probably relevant in 25%, and doubtfully relevant in 7%. In the list of "most common allergens", MP had rank number 2, with 114 reactions (24.7% of the positively tested patients).[97] In Belgium, in the years before 1986, of 5202 consecutive patients with dermatitis who were patch tested, 156 were diagnosed with pure cosmetic allergy. MP was the "dermatitic ingredient" in 52 (33%) patients (frequency in the entire group: 7%).[98]

In the late 1980s, MP was present in several popular over-the-counter nappy products in the United States, and may have caused allergic contact dermatitis in children or resulted in fragrance sensitization.[99] Balsam of Peru was responsible for three of 399 cases of cosmetic allergy for which the causal allergen was identified in a study of the NACDG in 1977 to 1983.[100]

Hjorth, in 1961, mentioned perfumed soaps, perfumes and fragranced cosmetics (including a toothpaste containing oil of cinnamon and a hair lacquer containing benzoin) as causative products in a number of patients with allergy to MP, but the presence of MP in those products was never verified. However, some patients did react to one of more fragrance chemicals that are also present in MP.[2]

The author has not been able to find a single case report of proven cosmetic allergy caused by MP (contact dermatitis caused by cosmetic products, positive patch test reaction to MP, a positive patch test, repeat open application test or use test result with the product, the presence of MP in a cosmetic verified, and resolution or improvement of dermatitis after cessation of use of the product).

### 3.2.3 | Foods and drinks

In several case histories of MP-allergic patients, the development of dermatitis or exacerbations thereof,[2,11,101–105] ulcerations of the tongue[106] or glossodynia[11] have been ascribed to foods and drinks such as cola, vermouth, vanilla, chocolate, cinnamon cakes, wine gums, liqorice, marzipan, caramels, cream toffees, ice cream, and other sweets/candies. In some individuals, avoidance of these products resulted in improvement or healing of the symptoms[2,104,107]; in others, the dermatitis resolved or improved after use of a MP-restrictive diet,[105,106,108–110] sometimes combined with other measures, such as the avoidance of fragranced products.[106,108] In a number of these patients, oral administration of MP resulted in exacerbation of dermatitis.[104,105,110]

### 3.2.4 | Miscellaneous products

Twenty-five case reports of contact allergy to MP mentioning the patients' sex, age, profession, site of skin lesions, co-reactions, reactions to constituents, individual habits, possible aetiologies and comments/remarks were reported in the mid-1990s in Germany.[11] The most important possible aetiologies were plastics, consumption of sweets, smoking (in those days, MP and various of its ingredients were added to tobacco in the manufacture of cigarettes), and wound healing/herbal ointments.[11] Plastics were considered to be relevant in patients reacting to resorcinol monobenzoate, which is an ultraviolet stabilizer in cellulose acetate and other plastic materials. This chemical has not been identified in MP, but frequently reacts, for unknown reasons, in MP-positive individuals (cross-reaction with coniferyl benzoate?). However, plastic as a cause of allergic contact dermatitis in MP-allergic patients and resorcinol monobenzoate was not well substantiated, as the chemical has never been shown to be present in MP, and its presence in the plastic was never ascertained by the author.[11]

A factory worker preparing copper mirrors for carbon anhydride lasers developed dermatitis of the fingers of his right hand. He had positive patch test reactions to MP and a cutting fluid. The manufacturer did not provide data on the composition of the fluid, but other MP-allergic patients also reacted to the product. In addition, neither the patient nor other MP-allergic individuals had positive test reactions to the non-perfumed variety of the same brand of cutting fluid.[111] Although this does not prove that MP was present in the cutting fluid, this possibility cannot be excluded. One or more separate ingredients of MP may also have caused the reaction in the cutting fluid.

## 4 | THE SENSITIZERS IN MP

Since Hjorth's classic study on balsam of Peru in 1961,[2] in which he found that 80% of his MP-allergic patients reacted to coniferyl benzoate, this has been considered to be the most important allergen in the product. However, coniferyl benzoate was first identified in MP in 1995, 34 years later![6] It was the strongest sensitizer of all MP ingredients tested in guinea-pigs.[2,6] Moreover, it was said that it can only be found when fresh samples of MP are investigated, as it is very unstable and degrades in MP and syringes very quickly.[6] In several studies, patients known to be allergic to MP have been tested with selected ingredients.[2,11,112–114] The results are shown in Table 2.

The results have varied widely. There were differences in the methodology of patch testing, the size of the populations tested, the number and nature of ingredients tested, the test concentrations, and, sometimes, the vehicles used; and, of course, different samples of MP were used with—most likely—different compositions. Therefore, reliably identifying the main sensitizers in MP on the basis of the available data is not possible.

The highest percentages of positive reactions were caused by coniferyl benzoate, isoeugenol, eugenol, cinnamyl alcohol, cinnamic acid, and cinnamyl cinnamate. Coniferyl benzoate is a potent sensitizer, and MP may contain up to 30% cinnamic acid. However, the other substances appear to be present in MP in low concentrations. Whether these are high enough in MP to induce contact allergy and/or elicit allergic contact dermatitis in previously sensitized individuals has not been investigated. There may be cross-reactivity between eugenol and isoeugenol, and between cinnamic acid, cinnamyl alcohol, and cinnamyl cinnamate, thereby enhancing the sensitizing/eliciting

**TABLE 2** Results of patch tests with components of *Myroxylon pereirae* resin (MP) in allergic patients (adapted from Ref. [5])

| Compound | No. of studies | No. of patients | Test concentrations | Percentage positive (range) | References |
|---|---|---|---|---|---|
| Coniferyl benzoate [a] | 2 | 184 | 0.5%, 1% and 2% pet. | 28-81 | 2,11 |
| Isoeugenol | 2 | 235 | 2% pet.; 5% pet. | 27-62 | 2,11 |
| Eugenol | 4 | 383 | 2% and 5% pet.; unknown | 0-62 | 2,11,113,114 |
| Cinnamyl alcohol | 4 | 349 | 5% and 10% pet.; unknown | 0-37 | 2,11,113,114 |
| Cinnamic acid | 4 | 387 | 5% pet.; unknown | 13-32 | 2,11,112,113 |
| Cinnamyl cinnamate | 2 | 114 | 5% pet. | 20-25 | 11,114 |
| Cinnamal[b] | 2 | 213 | 2% pet.; unknown | 10-21 | 2,113 |
| Benzoic acid | 2 | 241 | 5% pet. | 8-20 | 2,11 |
| Benzyl alcohol | 2 | 197 | 5% pet.; 10% eth. | 8-20 | 2,11 |
| Benzyl cinnamate | 4 | 366 | 5% pet.; unknown | 3-19 | 2,11,113,114 |
| Vanillin | 4 | 420 | 5% and 10% pet.; pure | 0-17 | 2,11,113,114 |
| Resorcinol monobenzoate[c] | 1 | 102 | 2% pet. | 16 | 11 |
| Coniferyl alcohol | 1 | 102 | 1% pet. | 14 | 12 |
| Benzyl benzoate | 4 | 371 | 5% pet.; unknown | 0-12 | 2,11,113,114 |
| Benzaldehyde | 1 | 100 | 5% pet. | 10 | 2 |
| Nerolidol | 2 | 153 | 1% pet.; 3% olive oil | 3-6 | 2,11 |
| Farnesol | 2 | 155 | 5% pet.; 50% olive oil | 2-4 | 2,11 |
| Methyl cinnamate | 3 | 259 | 10% and 25% pet.; unknown | 0-4 | 11,112,113 |
| Benzyl isoferulate | 1 | 102 | 1% pet. | 2 | 11 |
| Isoferulic acid | 1 | 102 | 5% pet. | 1 | 11 |
| Ferulic acid | 1 | 102 | 5% pet. | 0 | 11 |

[a]Coniferyl benzoate is an unstable chemical, and is swiftly degraded in MP and in commercial test syringes.
[b]Not a constituent of MP; may be a sensitizer after conversion in the skin of cinnamyl alcohol to cinnamal.
[c]Resorcinol monobenzoate has not been identified in MP; however, patients sensitized to resorcinol monobenzoate for unknown reasons almost invariably react to MP[11,115,116]; conversely, only 0% to 16% of patients sensitized to MP co-react to resorcinol monobenzoate [11,117].

potential. Alternatively, some patients may well have become sensitized to these substances because of their presence in other products. In other words, a reaction to an ingredient in these studies does not necessarily mean that the patient had become sensitized to it from contact with MP. However, the relationship with some ingredients is clear. In one study, the odds ratios of a reaction to MP were 51 in patients reacting to its ingredient eugenol, 25 in patients reacting to isoeugenol, and 13 in patients reacting to cinnamyl alcohol.[20] In two other investigations, 70%[118] and 73%[47] of patients reacting to eugenol, 36%[47] and 63%[118] of patients reacting to isoeugenol and 24%[47] and 42%[118] of patients reacting to cinnamyl alcohol co-reacted to MP. Moreover, of seven patients reacting to benzyl alcohol, which is also present in MP, four (57%) co-reacted to MP.[114]

It seems highly likely that at least a number of these patients, possibly most, had previously become sensitized to these fragrances from sources other than MP, and that the concentration of the fragrance in the 25% pet. patch test material was high enough, possibly together with the effect of other sensitizers, cross-reactors, and irritants, to elicit a positive MP patch test reaction. Similar phenomena are well known with fragrances and essential oils, whereby fragrance-allergic individuals have positive patch test reactions to essential oils containing these fragrances (eg, geraniol and rose and geranium essential oils, and limonene and tea tree oil), even when previous contact with the oils is unlikely.[5]

## 5 | CROSS-REACTIONS, PSEUDO-CROSS-REACTIONS, AND CO-REACTIONS

It is well known that fragrance-allergic patients often react to several or even many fragrances, indicators (FM I, FM II, MP, and colophonium), essential oils, and fragranced products (polysensitization[119]). Possible explanations are: (a) cross-reactivity (sensitization to fragrance A, inducing contact allergy to structurally related fragrance B, with which the patient had never had contact; almost impossible to prove); (b) pseudo-cross-reactions (the patch test substances contain the same hapten; also termed "false cross-reactivity"[26]); (c) metabolization or oxidation of one fragrance into another (eg, cinnamyl alcohol into cinnamal, and geraniol into geranial and neral); (d) concomitant sensitization from their presence in the same product (coupled exposure); and (e) independent sensitization over time in different products.

For co-reactivity (also termed coupled reactivity[26]) of indicators and their ingredients, pseudo-cross-reactivity is a very plausible explanation, and this also applies to many cases of positive patch test reactions to individual fragrances and essential oils containing them. Co-reactivity of individual fragrance chemicals may mostly be the result of concomitant or independent sensitization, facilitated by the extremely widespread use of perfumes and perfumed products

containing many different fragrance chemicals. One final explanation for co-reactivity between MP, FM I and its ingredients is not fragrance sensitization, but contact allergy to sorbitan sesquioleate, which may be present in all of these patch test materials (depending on the supplier) for proper emulsification. If sorbitan sesquioleate is not routinely tested, this possibility goes unnoticed and the patients may be advised improperly.

## 5.1 | Ingredients of MP

Co-reactivity of many fragrant chemicals with MP can be expected, when these are present in MP in concentrations adequate for elicitation of a positive patch test reaction (pseudo-cross-reactions). For eugenol, isoeugenol, cinnamyl alcohol, and benzyl alcohol, this has been discussed in the section "The sensitizers in MP" above. Elevated rates of co-reactivity between MP and fragrances are not specific for ingredients of MP. Geraniol-allergic patients, for example, had an odds ratio of 13.6 for reacting to MP in one study,[20] although MP does not contain geraniol or its aldehydes geranial and neral formed by oxidation. The chemicals that have been identified in MP are summarized in Table 1.

## 5.2 | Fragrance mix I

A high degree of co-reactivity between MP and FM I and vice versa has been observed in numerous studies. In groups of MP-allergic patients, 18%,[49] 25%,[120] 33%,[121] 36%,[48] 38%,[122] 39%,[123] 45%,[124] 48%,[11] 51%,[125] and 59%[126] co-reacted to FM I. Conversely, of patients reacting to FM I, 9%,[120] 15%,[121] 22%,[12] 27%,[127] 33%,[125,126] 34%,[128] 31% to 39%,[129] 44%,[123] 52%[48] and 59%[126,130] co-reacted to MP.

These two substances share common components, that is, eugenol, isoeugenol, and cinnamyl alcohol. FM I also contains cinnamal; MP does not, but cinnamyl alcohol in MP may be converted in the skin into cinnamal, which then acts as a sensitizer or reacts in cinnamal-allergic individuals. Indeed, cinnamal is patch test-positive in 10% to 20% of MP-allergic patients,[2,113] and, in cinnamal-allergic individuals, MP allergy is overrepresented.[20,47] In one study, even 14 of 27 (52%) cinnamal-allergic patients also reacted to MP.[123] MP (from Chemotechnique Diagnostics) and FM I both contain the emulsifier sorbitan sesquioleate, which may be an occasional cause of contact allergy and co-reactivity between the two patch test materials.

## 5.3 | Propolis

Chemicals present in both propolis and MP include benzoic acid, benzyl alcohol, benzyl benzoate, benzyl caffeate, benzyl cinnamate, benzyl ferulate, benzyl isoferulate, caffeic acid, cinnamic acid, cinnamyl alcohol, coniferyl benzoate, farnesol, nerolidol, and vanillin.[131] Therefore, a certain degree of co-reactivity based on pseudo-cross-reactions may be anticipated. Indeed, 19 of 21 (90%)[114] and six of seven (86%)[132] propolis-allergic patients co-reacted to MP 25% pet. Conversely, of 11 MP-positive patients who had never come into contact with propolis, five (45%) also reacted to propolis.[114] In a large German study, however, of 102 MP-allergic patients, only nine (9%) co-reacted to propolis.[11] This asymmetrical co-reactivity pattern suggests that most of the sensitizers in propolis are also present in MP, but that some sensitizers in MP are not present in propolis or are present in concentrations too low to elicit a positive patch test reaction. Obviously, both are botanical products, and the composition of the samples used by the various investigators may have differed considerably, thereby influencing the results.

## 5.4 | Essential oils

Of 31 MP-allergic patients, 18 (58%) had positive patch test reactions to one (n = 12), two (n = 3), five (n = 1), six (n = 1) or nine (n = 1) of 35 essential oils. Most positive reactions were observed to cassia oil (high concentration of cinnamal) and to clove oil (high concentration of eugenol).[133]

## 5.5 | Other resins and balsams

Co-reactivity to other resins and balsams in MP-allergic individuals was investigated by Hjorth in 1961[2] and by Hausen et al in 1995.[6] In MP-allergic patients, frequent co-reactions were observed to balsam of Tolu (INCI name: *Myroxylon balsamum* resin) (47%), styrax/storax (INCI name: *Liquidambar orientalis* resin) (43%), Siam benzoin (INCI name: *Styrax tonkinensis* resin; contains 75% coniferyl benzoate and 10% benzoic acid) (80%), Sumatra benzoin (INCI name: *Styrax benzoin* gum) (43%), and compound tincture of benzoin U.S.P (contains styrax, benzoin, and balsam of Tolu) (90%).[2,6] In a group of 21 patients allergic to tincture of benzoin, 13 (62%) co-reacted to MP.[13] These products all have (many) ingredients in common with MP.

A number of resins and balsams were tested 10% in ethanol in a small series of MP-allergic patients. Six of 11 (55%) reacted to opoponax (*Commiphora erythrea glabrescens* gum), seven of 13 (54%) to Copaiba balsam (*Copaifera reticulata* balsam), and three to galbanum (*Ferula galbaniflua* gum).[2] In addition, three of 14 MP-allergic patients (21%) reacted to an extract of poplar buds (the source material for propolis, which often co-reacts with MP and in which caffeates are the main sensitizers), seven of 20 (35%) to ginger resinoid 10% pet., and all five tested with Tiger Balm.[2]

## 5.6 | Other co-reactions

Positive patch test reactions to MP (and to FM I) are very frequently observed in patients who are photoallergic to ketoprofen; the mechanism behind this has not been elucidated.[134,135] Patients sensitized to resorcinol monobenzoate almost[136] invariably react to MP[11,115,116]; conversely, only 0% to 16% of patients sensitized to MP co-react to resorcinol monobenzoate.[11,117] Resorcinol monobenzoate has not been identified in MP, and the mechanism behind the co-reactivity is unknown.

Of 11 patients with contact allergy to oranges (peel), five (45%) co-reacted to MP. Eight patients known to be sensitive to MP were patch tested with an ether extract of orange peel 10% pet., and five (63%) had strong reactions to the extract.[22] Of 73 patients sensitive to MP, 34 (47%) co-reacted to vanilla. This is not entirely attributable to vanillin being present in both products, as vanilla has only a low concentration of vanillin, and reactions to vanillin 10% pet. and vanillin pure were less frequent than reactions to vanilla.[2] A statistically significant overrepresentation has been found of simultaneous patch test reactions to MP and phenol-formaldehyde resins (PFRs).[125] Approximately 20% of those allergic to MP co-react to PFRs. It was suggested that this was attributable to the presence of low-molecular-weight phenols in both substances.[137]

## 6 | MP AS AN INDICATOR OF FRAGRANCE ALLERGY

MP has been used as a "marker" (or "indicator") of fragrance sensitivity in the European baseline series for patch testing since it was discovered in the 1960s that half of the patients with positive reactions to MP were also allergic to one or more toilet soap perfumes and vice versa.[2,3] MP was the most important marker until FM I was introduced in the late 1970s; in 2008, FM II and its separate fragrance ingredient hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) were added to the baseline series.[138] Currently, in most patients reacting to MP, fragrance allergy appears to be already detected by other fragrance indicators, notably FM I, and it has been shown that the composition of FM I is a good reflection of actual exposure to fragrances.[121,139] Therefore, some authors have suggested that MP may be of limited value in detecting cases of clinically relevant fragrance allergy, and that consideration should be given to the replacement of MP with more well-defined markers of fragrance allergy in order to detect cases not identified by FM I.[9,13,114,120,140,141] Nevertheless, now, 20 years after these studies, MP is still part of most (if not all) baseline series, and, when fragrance markers have been discussed in recent literature, MP has always been mentioned. Indeed, it was recently concluded that "Exposure to *M. pereirae*, or to some of the single constituents, is apparently frequent, so this 'historical' screening agent is still important for detecting fragrance sensitivity."[20]

Contact allergy to MP 25% in the baseline series occurs frequently; in most countries, rates of positive reactions are 4% to 8% or higher in routine testing (see section "Patch testing in consecutive patients suspected of having contact dermatitis [routine testing])." Many patients with positive reactions to MP (41%-72%) do not react to FM I (see section "Fragrance mix" above). In addition, there can be no doubt that MP is indeed a marker of fragrance allergy. In studies in which patients were patch tested with MP and with other fragrances such as individual fragrance chemicals, essential oils,[142] perfumes from cosmetic products, or fine fragrances, 24% to 74% of the patients reacting to MP also had positive patch test reactions to one or more of the fragrance test substances: 24% and 25%,[143] 29% and 35%,[140] 41%,[144] 42%,[121] 48%,[48] and 74%.[47] Conversely, in the groups of patients reacting to one or more fragrances, fine fragrances, or perfumes, only 15%,[141] 22%[121] and 10% and 38%[140] co-reacted to MP. Thus, there appears to be an asymmetrical co-reactivity pattern; the percentages of fragrance-positive individuals reacting to MP are low, whereas the percentage of MP-allergic individuals reacting to fragrances is high. A possible explanation—on the assumption that co-reactivity is caused by common ingredients—is that strong allergies induce positive patch test reactions to both MP and the fragrances, but weaker sensitivity only manifests as reactions to the fragrances, and not to MP, because of (too) low concentrations of the latter. Another possibility is that a large proportion of reactions to MP are caused by (unknown) components that are not present in the perfumes/essential oils/common fragrances tested (hence low co-reactivity to MP in fragrance-allergic individuals), but that allergy to these components does point at sensitivity to other fragrances (hence high co-reactivity to other fragrances in MP-allergic patients). Coniferyl benzoate might qualify for this, as this chemical has been an important sensitizer in MP in some studies, but is not used in fragrances.[145]

In all investigations, the percentages of patients reacting to FM I who also reacted to specific fragrances/perfumes and fine fragrance/essential oils, and the reverse situation, the percentage of patients allergic to fragrances who also reacted to FM I, were higher or far higher than the corresponding percentages for MP (ie, FMI is the more sensitive marker). In the case of the perfumes and fine fragrances, this can probably be attributed to the fact that all of these products proved to contain at least one and most often more than one of the ingredients of FM I.[121,140,141,143] In the studies in which a fragrance series was tested, it can be explained by the fact that the series always contained all ingredients of FM I.[47,143,144] It can be concluded that, although FM is clearly the more sensitive marker for fragrance allergy, MP is also a—slightly ill-defined[26]—"natural fragrance mix" acting as a fragrance marker.

### 6.1 | Added value of testing with MP: number of cases identified

The added value of testing with MP in the baseline series can be debated, if fragrance sensitization is indeed, in most cases, already picked up by a positive FM I reaction. In other words, how many cases of fragrance sensitization does a positive MP patch test reaction identify that are not already shown by FM I positivity or one of the other indicators (colophonium and FM II)? Only few data are available to help in answering this question, and they are limited to FM I.

In a study from Denmark, 335 female patients were patch tested with 10 popular women's perfumes, FM I, and MP. There were 23 reactions to one or more commercial perfumes. Twenty of them co-reacted to FM I, and five to MP; these five also reacted to FM I. No additional cases were detected by MP.[121] In another study from the same investigators, of 33 patients reacting to one or two fine fragrances, 20 co-reacted to FM I and five to MP. All MP-responsive individuals were also allergic to FM I.[141] In a third study from this group, of 21 patients reacting to one or more fragrances used in rinse-

off products, 11 (52%) co-reacted to FM I and two (10%) to MP (TRUE Test, lower sensitivity for detecting FM I and MP allergy). In the same study, of 16 patients reacting to one or more fragrances used in leave-on products, 13 (81%) co-reacted to FM I and six (38%) to MP. When testing with MP was performed, only one case of fragrance allergy was identified that was not already detected by FM I.[140]

These studies show that testing with MP detects very few cases of sensitization to fine fragrances (perfumes) and fragrances in rinse-off and leave-on cosmetic products that have not already been detected by a positive patch test reaction to FM I. A study from Spain, however, suggests that some fragrance allergies that are not detected by FM I can indeed be detected by MP.[48] In this investigation, 86 patients among 1253 routinely tested individuals, selected on the basis of one or more positive fragrance indicators or suspicion of fragrance contact allergy despite negative markers, were patch tested with a fragrance series. This series included the eight ingredients of FM I, the six ingredients of FM II, nine essential oils or botanical extracts (jasmine and lavender), and several ingredients of MP (eugenol, isoeugenol, cinnamyl alcohol, benzyl alcohol, vanillin, and farnesol). Twelve patients in the group of 86 tested with the fragrance series had single MP reactivity, and no reactivity to any other marker. Of these, three (25%) had positive reactions in the fragrance series. In the total population of 1253 patients routinely tested, 80 (6.4%) reacted to MP. Of these, 48 were single positives, not reacting to FM I or FM II. If 25% of these were to indicate fragrance allergy, 12 (ie, 0.96% of the total test population) patients with fragrance sensitization would have been missed by not patch testing with MP.[48] It should be realized, of course, that this calculation is based on only three positive reactions to MP, so the evidence is rather weak.

## 6.2 | Added value of testing MP: ingredients

Another approach to assess the added value of MP as fragrance indicator is to look at its ingredients. Coniferyl benzoate, which has been considered to be the most important sensitizer in MP,[2,11] is not used in fragrances.[145] This means that any reaction to it is, by definition, not relevant as far as fragrance allergy is concerned, unless cross-reactivity is a possibility. The ingredients eugenol, isoeugenol and cinnamyl alcohol are present in FM I, and farnesol is present in FM II. In order to identify other possible allergens, studies performing routine testing with the other ingredients of MP that have previously shown positive reactions in patients reacting to MP (Table 2) were searched for; their results are shown in Table 3.

No data were found for cinnamyl cinnamate, coniferyl alcohol, benzaldehyde, methyl cinnamate, benzyl isoferulate, and isoferulic acid. The last three of these are very unlikely to be important allergens in MP, as they caused only 0% to 4% (methyl cinnamate), 2% (benzyl isoferulate) and 1% (isoferulic acid) positive reactions in a group of 102 MP-allergic patients.[11] Most of the other ingredients have had very low frequencies of sensitization, in the range of 0% to 0.4%, in routine testing (Table 3). Benzoic acid caused 4.9% and 5.7% positive reactions in two studies from the same clinic in the United States, but the test substance used (5% pet.) is known to cause irritant reactions,[5] and there were many ?+ reactions, which were counted as positive, in disagreement with international convention. In one investigation,

**TABLE 3** Frequency of contact allergy to ingredients of *Myroxylon pereirae* resin (MP) in routine testing

| | | Studies performing routine testing (reference numbers in parentheses)[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Compound** | **MP-positive[b]** | **(47)** | **(118)** | **(146)** | **(46)** | **(45)** | **(147)** | **(148)** | **(35)** | **(5)** |
| Cinnamic acid | 13%-32% | | | | | | | | | 1.5%[c] |
| Cinnamyl cinnamate | 20%-25% | | | | | | | | | |
| Benzoic acid | 8%-20% | | | | | | | | | 4.9%-5.7%[d] |
| Benzyl alcohol | 8%-20% | 0.1% | 0.3% | 0% | 0.2% | 0.1% | 0.3% | 0.1% | 0.4% | 0.2%-1.0% |
| Benzyl cinnamate | 3%-19% | 0.05% | 0.3% | 0.3% | 0.2% | 0.1% | 0% | 0.02% | 0% | |
| Vanillin | 0%-17% | | | | | | | | | 0.3% |
| Coniferyl alcohol | 14% | | | | | | | | | |
| Benzyl benzoate | 0%-12% | 0.1% | 0.0% | 0.3% | 0.1% | 0% | 0% | 0% | 0% | |
| Benzaldehyde | 10% | | | | | | | | | |
| Nerolidol | 3%-6% | | | | | | | | | 3.5%[e] |
| Methyl cinnamate | 0%-4% | | | | | | | | | |
| Benzyl isoferulate | 2% | | | | | | | | | |
| Isoferulic acid | 1% | | | | | | | | | |

[a]In the table, the percentages of positive reactions are shown; a blank means that the substance has not been tested in these (or any other) studies.
[b]Percentages reacting among patients allergic to MP (details in Table 2).
[c]Three positive reactions in 200 patients.
[d]Two studies from one US clinic; the test substance used (5% pet.) causes irritant reactions; there were many ?+ reactions, which were counted as positive (in disagreement with international convention); a large number of substances were tested, increasing the risk of false-positive reactions resulting from excited skin syndrome.
[e]Probably some irritant reactions; nerolidol was tested at 50% pet.

nerolidol caused 3.5% positive reactions (seven positives in 200 patients tested), but the test concentration was extremely high (50% pet.), and a number of the reactions are likely to have been irritant. Most interestingly, the quantitatively most important chemicals in MP, that is, benzyl cinnamate (up to 40%) and benzyl benzoate (up to 30%), have shown very low frequencies of sensitization, with a range of 0% to 0.3% for benzyl cinnamate (average, 0.12%; median, 0.08%) and a range of 0% to 0.3% for benzyl benzoate (average, 0.06%; median, 0.0%). This means that probably at least half of the MP used for patch testing is almost completely non-sensitizing.

A few other ingredients of MP are known allergens; these are shown in Table 4, with a summary of contact allergy reports. Three (β-caryophyllene, β-pinene, and α-terpineol) have been patch tested in routine testing, and have yielded low rates of sensitization. Most others have been shown to be (minor or major) allergens in tea tree oil or turpentine oil. Limonene (as hydroperoxides) was recently shown to be a frequent contact allergen.[47,50,151–155] Of patients allergic to limonene hydroperoxides, 11% to 48% were also allergic to MP, which is a significant association. It is not very likely, however, that many of these reactions can be ascribed to limonene in MP: in all studies but one, the percentages of positive reactions to FM I, which does not contain limonene, were higher. Also, limonene has been found in MP in one study only, by the use of solid-phase micro-extraction, which is a method for extracting trace organic compounds.[7]

**TABLE 4** Other allergenic ingredients not previously tested in *Myroxylon pereirae* resin (MP)-allergic patients

| Constituent | Contact allergy reports[5] |
|---|---|
| β-Caryophyllene | Routine testing with caryophyllene oxide: 0.5%, 0.6%, and 1.1%; in one study, all three positive patients co-reacted to colophonium; two case reports: essential oils as causative products |
| *p*-Cymene | One positive reaction in 64 patients allergic to tea tree oil[149] |
| Eucalyptol (1,8-cineole) | Two case reports: causative products tea tree oil and topical pharmaceutical |
| Limonene | Limonene hydroperoxides are very important allergens; significant association between a history of rash resulting from skin contact with citrus fruits and a positive patch test reaction to MP[120]; limonene is the major ingredient in citrus peel oils[150]; MP co-reactivity in 11%,[47] 13.5%,[151] 18%,[152] 21%,[153] 24%,[154] 33%,[155] and 48%[50] (higher frequency than with fragrance mix I [32%] in patients reacting to limonene hydroperoxides) |
| α-Pinene | Major allergen in turpentine oil (>50% positive reactions); a few case reports regarding essential oils |
| β-Pinene | Routine testing: 0.2%, 9% and 37% positive reactions in patients allergic to turpentine oil |
| α-Terpinene | Important allergen in tea tree oil, reacting in three of four sensitized individuals[149] |
| 4-Terpineol (terpinen-4-ol) | Minor allergen in tea tree oil with 5% positive reactions[149]; six patients reacted to "terpineol" in topical pharmaceutical preparations |
| α-Terpineol | Routine testing: 0.1% and 0.2% positive reactions; minor allergen in turpentine oil; six patients reacted to "terpineol" in topical pharmaceutical preparations |

## 7 | RESTRICTIVE DIETS IN PATIENTS ALLERGIC TO MP

As early as 1961, it was noted that the oral intake of MP or its individual components, such as cinnamic acid, vanillin, or eugenol, which are present as aromas in food and drink items, can cause a flare of dermatitis in some MP-allergic patients.[2] Later, in a number of patients sensitized to MP, dermatitis was found to resolve or improve after they had followed an MP-restrictive diet.[105,106,108–110] Oral administration of MP (provocation test) sometimes resulted in exacerbation of dermatitis.[104,105,110] Various studies on oral provocation with balsam of Peru and the effect of balsam of Peru-restrictive diets in patients allergic (and also in dermatitis patients not allergic) to MP have been performed, mostly between 1981 and 1996 by one group of Danish investigators.[156–160]

In the first study,[156] the investigators observed that the eczema of several patients with negative patch test results with MP could flare following ingestion of food items containing "balsams." In a preliminary open study, 42 individuals with eczema, in whom neither history nor standard patch tests had shown the cause of the dermatitis (nine with perianal dermatitis, 17 with bilateral hand eczema, and 16 with eczema at other sites), were challenged with 900 mg of MP orally once daily taken as capsules. Nine patients (21%) had unequivocal flares 1 to 3 days after the challenge with (sometimes generalized) pruritus and aggravation at the usual sites of the eczema. These nine patients with a positive challenge test result were instructed to avoid food items suspected to contain balsams for at least 1 month. At the end of this period, five (56%) patients showed clearance of all symptoms and signs of eczema.[156]

In a second study from these investigators,[157] during 1982 to 1984, placebo-controlled, double-blind oral challenges with MP 1 g once daily in 210 patients with various types of dermatitis were performed. Forty-five of them (21%) experienced a flare of their symptoms within 4 days after challenge with MP, but not after treatment with placebo. Of 17 patients with positive patch test reactions to MP, 10 (59%) had a positive challenge test result, including all four patients with vesicular hand dermatitis. Among MP-negative patients, the symptoms of 12 of 58 (21%) patients with vesicular hand eczema flared, as was the case in five of 18 (28%) individuals with anogenital dermatitis, and three of eight (38%) individuals with axillary eczema. Among individuals with other patterns of dermatitis, only six (9%) had a positive oral challenge test result. Patients with a positive reaction to MP but a negative result with placebo were instructed to avoid food items suspected to contain balsams. Dietary restriction was followed by marked improvement or clearance of the dermatitis in approximately half of the patients who adhered to the diet for at least

1 month; only one of these patients had a positive patch test reaction to MP.[157]

In a subsequent publication by this group of authors, the results of long-term dietary restrictions were reported.[158] Sixty-four patients participated in this study. Twenty-four were patients who had positive patch test reactions to MP, and, in 40 individuals, the dermatitis had previously flared after oral challenge with MP. All 64 patients were asked to avoid food items suspected to contain balsams for 1 to 2 months, and the dermatitis of 37 (58%) cleared or improved markedly. If an improvement had taken place, the patient was asked to continue to diet moderately; 6 months to 3 years later, 30 (47%) felt that there was a long-term effect, and 27 still followed the diet instructions to some degree. In the subgroup of the 24 patients with positive patch test reactions to MP, 15 (63%) reported benefit from the diet.[158]

In yet another study by the same group,[159] the long-term effect of dietary restrictions was investigated in 15 patients who reacted positively to MP and/or FM, 13 of whom had a positive oral challenge test result. Most had vesicular hand dermatitis. Nine of 15 (60%) reported long-term improvement resulting from dietary restrictions. However, in a group of 12 patients with a negative patch test result with MP, but a positive challenge test result, a higher percentage (67%, 6/9) reported long-term improvement.[159] In a final study from this group, in 1996,[160] it was investigated whether the results of oral challenge with MP can predict possible benefit from a low-balsam diet. Forty-six patients with positive patch test reactions to MP and/or FM I and chronic dermatitis with a morphology consistent with systemic dermatitis had experienced improvement after using a low-balsam diet for 1 to 2 months, and continued to use it. Twenty-eight of these (71%) stated in a questionnaire mailed after 1 to 3 years that they had experienced long-term benefits from the dietary treatment. In the group of 22 with a positive oral provocation test result, 16 (73%) reported benefit; three of 10 (30%) who had a negative challenge test result, and nine of 14 (64%) of the patients in whom no oral challenge test had been performed reported benefit. This indicated that the oral challenge procedure offers only limited assistance in selecting patients who are likely to benefit from dietary treatment.[160]

The food items most commonly mentioned in the Danish studies by patients as causes of flare of dermatitis were spices, cinnamon, curry, vanilla, liver paste, wine, bitters, pickled herring, citrus fruit and citrus drinks, cake, ice cream, vegetables, candy, chocolate, tomatoes, and ketchup.[158–160] It should be appreciated that, in all of these studies, the symptoms were interpreted largely by the patients themselves, and no objective signs were observed by the investigators.

In a 1984 study from Finland,[161] a group of 118 MP-allergic patients were patch tested with a series of (powdered) spices. There were positive reactions in 48 (41%) individuals: cloves (46%), Jamaica pepper (21%), cinnamon (15%), ginger (6%), curry (6%), cardamom (4%), white pepper (3%), vanilla (3%), and paprika (3%). In a control group of MP-negative patients, only a few reactions were seen. Seventy-one MP-allergic patients had oral provocation tests performed with spices and seven (10%) had reactions, notably a vesicular reaction of the hands, but also two urticarial reactions; in three, the patch test with spices gave a negative result. The author suggested that spices are potential but rare causes of contact dermatitis, and that they may also cause skin symptoms, most frequently a pompholyx reaction, as a consequence of internal exposure in patients with contact allergy to MP.[161]

Ten years later, the same author performed double-blind placebo-controlled peroral challenges with MP and spices in patients with delayed-type allergy to MP.[162] Twenty-nine patients previously reacting to MP 25% pet. were tested with MP and spices. The second patch test with MP gave positive reactions in 17 (59%) of the 29 retested patients. Positive reactions to one or more spices were seen in five individuals (17%), all reacting to cloves and Jamaica pepper, and two reacting to cinnamon. One of the patients with positive patch test reactions to the spices did not react to balsam of Peru in the second patch test. Twenty-two patients were challenged perorally with 1 g of balsam of Peru and a spice mixture with equal parts of cinnamon, Jamaica pepper, cloves, and vanilla sugar, in two capsules of 200 mg each, and glucose as placebo. Eight of the 22 patients (36%) reacted to the active substances, but not to placebo (of whom four were MP-positive and four were MP-negative). The eight patients with positive oral challenge test results showed an increase of at least 30% in the number of palmar vesicles caused by ingested balsam of Peru or spices. It was concluded that it seems possible that ingested MP and related spices cause systemic allergic reactions in patients with delayed contact allergy to MP.[162]

In a retrospective study from the United States[163] published in 2001, of 45 patients allergic to MP and/or FM I in whom balsam dietary avoidance was recommended, 21 (47%) reported complete or significant improvement primarily related to dietary modification. Nine of 45 did not follow the recommended diet, and, of these, only one (11%) had significant improvement. The food items most commonly mentioned as causes of flare-up of dermatitis were tomatoes (which contain coniferyl alcohol and cinnamyl alcohol,[164,165]), citrus, spices, cola or soda, chocolate, chili, cinnamon, beer or wine, and vinegar. This study relied entirely on patients' subjective opinions.[163]

## 8 | DISCUSSION

In this discussion, we will focus on the following questions: (a) how useful are restrictive diets in MP-allergic patients; and (b) what is the significance of positive patch test reactions to MP and what is the value of MP in the baseline series?

### 8.1 | How useful are restrictive diets in MP-allergic patients?

The answer to the question "What, if any, is the value of a low-balsam diet?"[166] in MP-allergic patients is, at this moment, not clear-cut. No prospective studies to support advice regarding dietary restrictions have been published in the last 25 years, and most of the work on this subject does not meet current scientific criteria. For example, almost all studies relied on the patients' own observations, exacerbations

were not verified by the investigators,[166] the placebo effect of following a diet is probably considerable, and provocation and elimination experiments after initial improvement on a diet have rarely been performed, or at least have not been published. In addition, there is a lack of validated evidence with regard to the content of MP, spices containing MP ingredients (eg, eugenol in cloves and cinnamon) or individual MP components in various foods, and, consequently, there is no objective scientific measure with which to quantify dietary balsam exposure. Oral provocation tests with MP may give positive results, but this may also occur in MP-negative patients, and the results of oral provocation tests do not reliably predict the benefit of dietary intervention. In one study, patients with a positive provocation test result but a negative patch test result with MP had the same chance of experiencing dietary benefits as MP-positive individuals.[159] Provocation tests with the spices cloves (containing eugenol) and cinnamon have given positive results in some MP-allergic individuals,[161,162] but these authors did not investigate the effect of dietary restrictions of these products.

From these studies, the following—tentative—conclusions may be drawn and suggestions made. Some patients with dermatitis, especially those with forms suggestive of systemic allergic dermatitis (vesicular hand dermatitis, other types of symmetrical dermatitis of the hands or feet, anogenital dermatitis, symmetrical dermatitis in the large skin folds, such as the axillae, and the groins[167]), may benefit from a diet that restricts foods containing balsams, and certain spices such as cinnamon, cloves, and vanilla. Especially, patients with positive patch test reactions to MP (and probably also some patients who not react to MP but react to FM I), but also patients with negative MP patch test results, [156,157] may benefit. An oral provocation test is not very helpful in predicting the results of a diet, although following a diet after a negative test result is less likely to be beneficial than following a diet after a positive provocation test result. As restrictive diets are difficult to adhere to and often disrupt normal social life, it is recommended that dietary treatment be limited to those individuals with severe, long-standing dermatitis who respond poorly to conventional treatment.[158] Initially, the patients can be placed on a restrictive diet for at least 4 weeks, and, if the dermatitis significantly improves, long-term compliance can be recommended. Subsequently, one food group can be reintroduced into the diet every several weeks to ascertain whether this particular substance exacerbates the dermatitis. Those foods worsening the eruption would then have to be avoided permanently.[168]

A recent, possibly useful, suggestion is to divide the food allergens in MP into the following groups: eugenol, cinnamate, vanillin, benzoate, ferulic acid, and coniferin.[169] By establishing to which of these the MP-allergic patient reacts, it will be possible to give more specific instructions which foods, drinks and spices are best avoided. The authors suggested the following screening allergens for this: eugenol and isoeugenol (eugenol group), vanillin (vanillin group), cinnamal, cinnamyl alcohol, and benzyl cinnamate (cinnamate group), benzoic acid and sodium benzoate (benzoate group), ferulic acid (ferulic acid group), and coniferyl alcohol (coniferin group). The authors of this article also provide a table with a large number of foods, drinks, and spices, indicating which of the food allergen groups are present in them (and therefore need to be avoided by allergic patients).[169] Studies on the efficacy of such measures appear not to have been published thus far.

Detailed lists of high-risk processed foods (foods and drinks that frequently contain ingredients high in MP) and of primary ingredients (vanillin, eugenol, cinnamon, etc.) can be found at https://www.dermatitisacademy.com/bop-diet/#toggle-id-6 (last accessed March 4, 2019). However, one might start with avoiding citrus peels, spices such as cinnamon, cloves, vanilla, and curry, and products containing them, ice cream, flavoured beverages and colas, and tomatoes.

## 8.2 | What is the significance of positive patch test reactions to MP and what is the value of MP in the baseline series?

Reactions to MP 25% pet. are frequent in most countries, and are generally found in 4% to 8% of patients routinely tested for suspected contact dermatitis. Many such studies have been performed, but only a few have provided data on the relevance of positive MP patch test reactions, and only in a single study after 2000 were culprit products mentioned: topical pharmaceuticals and cosmetics.[49] In case series and case reports, the most frequently mentioned products causing allergic contact dermatitis were also topical pharmaceuticals, cosmetics, and—to a far lesser degree—foods and drinks.

There can be no doubt that pharmaceuticals containing MP used to be frequent causes of MP allergy, especially preparations used for their alleged wound healing properties.[2] This may explain the high percentages of patients with leg ulcers and/or stasis dermatitis who reacted to MP,[52–59] especially in France, where wound dressings containing MP were still being used for leg ulcers 10 years ago.[54] In other countries, however, such preparations are rarely used any more (Belgium[13]) or are not used at all (Denmark[12]). The author's conclusion is that sensitization to MP in topical pharmaceuticals cannot explain the current high rates of positive patch test reactions to MP.

In three studies from Belgium,[94,97,98] MP was considered to be an important allergen in cosmetics, with 11.8% to 33.3% of the patients reacting to it. This may not, strictly speaking, be correct. Crude MP was banned by the IFRA in 1982, and is no longer used in perfumes (fine fragrances and perfumes in cosmetics and other products).[15–17] Extracts or distillates are allowed in low concentrations, but these products are little used.[5] Because of the well-known sensitization potential of MP, it is unlikely that cosmetic manufacturers would use crude MP. Indeed, in February 2019, MP was present in only six of 70 893 (0.008%) cosmetic products for which the composition is known in the EWG's Skin Deep Cosmetics Database.[18]There are no such data available in Europe. However, Belgian authors recently stated that pharmaceutical preparations containing MP are only rarely used in Belgium, and that few reactions to them have been observed after 2000.[13] Thus, the use of MP in cosmetics to some extent would be highly unlikely. Therefore, it was assumed that, in these Belgian studies, MP was considered to be a marker for fragrance allergy rather than a cosmetic ingredient, and that, in cases of allergy to fragrances

or fragranced cosmetics, the reaction to MP was scored as relevant; this has been confirmed by the main author (An Goossens, personal communication, January 2019).

In two Spanish studies, lower percentages (2% and 2.7%) of reactions to MP were stated to be the cause of cosmetic allergy.[95,96] However, products considered to be causative included a perfume and a deodorant,[96] which is highly likely to be incorrect, considering the long-standing IFRA ban on crude MP in fragrances and the impossibility of identifying MP derivatives in these products. The author's conclusion is that sensitization to MP in cosmetics cannot explain the current high rates of positive patch test reactions to MP.

The relationship between MP and foods and drinks has been discussed above. The oral route is not a very effective one for sensitization to occur, so most cases of dermatitis or exacerbations of dermatitis resulting from the ingestion of foods and drinks containing (or supposed to contain) MP or individual ingredients most result from, rather than being the cause of, sensitization to MP.

So, if topical pharmaceuticals, cosmetics and food and drinks are not responsible for MP sensitization, and other possible sources of contact with MP are not known, why then are there so many reactions to MP? The answer that is most likely to be correct is that people have previously become sensitized to one or more of its individual ingredients (most of which are fragrance chemicals), for example, by contact with perfumes, perfumed cosmetics, or non-cosmetic fragranced products, and this allergy subsequently becomes apparent by a positive patch test reaction to MP, which thus acts as an indicator of fragrance allergy. The notion that MP is a fragrance marker, a "natural fragrance mix," has existed since the 1960s,[2–4] and this is still the case, as, generally, 25% to 50% of patients with fragrance allergy proven by positive reactions to individual fragrance chemicals, essential oils, perfumes from cosmetic products or fine fragrances also react to MP.[48,121,140,143,144] However, FM I is a more sensitive marker than MP, and the key issue is how often MP shows relevant positive reactions, indicating fragrance sensitization, when FM I fails to do so. In other words: what is the added value of testing MP as well as FM I?

Although a high degree of co-reactivity between MP and FM I and vice versa is apparent, possibly because of common ingredients and well-known sensitizers such as eugenol, isoeugenol, and cinnamyl alcohol, generally, 50% to 75% of patients reacting to MP do not co-react to FM I (see the section "Cross-reactions, pseudo-cross-reactions, and co-reactions" above). Unfortunately, how many of these "single" reactions to MP are relevant has not been described in any investigation. However, in some well-designed studies from Denmark, testing with MP detected very few cases of sensitization to fine fragrances (perfumes) and fragrances in rinse-off and leave-on cosmetic products that had not already been detected by a positive patch test reaction to FM I.[121,140,141] From the data in a Spanish study,[48] the author calculated that nearly 1% of all routinely tested individuals may have had relevant MP reactions with negative results with FM I; however, the evidence for this is rather weak (see section "Added value of testing MP: number of cases identified" above). Thus, the data are currently insufficient to establish the added value of testing with MP.

Another approach to the subject of the usefulness of MP is to look at its ingredients. The exact spectrum of allergens in the MP materials used for patch testing that cause positive test reactions is currently unknown, but certainly includes isoeugenol, eugenol, and cinnamyl alcohol.[20,47,118] These cannot explain single positive reactions to MP, as they are also present, and in higher concentrations, in FM I. Coniferyl benzoate has been considered to be the most important sensitizer in MP.[2,11] However, assuming that patients with positive MP reactions have not had previous contact with the material itself, and because coniferyl benzoate is not used in fragrances[145] or other products except as an antifeedant (a substance that stops or inhibits feeding by a pest, and especially an insect),[170] it should not be a cause of positive reactions. Ingredients of MP that are possibly allergenic as shown by ingredient patch testing are shown in Table 2. None of these, or other ingredients of MP, appear to be important sensitizers (see section "Added value of testing MP: ingredients" above). In fact, the quantitatively most important chemicals in MP, that is, benzyl cinnamate (up to 40%) and benzyl benzoate (up to 30%), have shown very low frequencies of sensitization, with a range of 0% to 0.3%. This means that probably at least half of the MP used for patch testing is almost completely non-sensitizing. The author concludes that the ingredients of MP that cause single positive reactions to MP (and which therefore have added value if relevant) are unknown.

## 9 | CONCLUSIONS

MP 25% pet. in the baseline series causes many (4%-8%) positive patch test reactions in patients routinely tested for suspected contact dermatitis. Specific data on clinical relevance are largely lacking. Sensitization to MP in topical pharmaceuticals, cosmetics, foods and drinks or other known exposures cannot explain these high rates of sensitization. Most MP-positive patients have probably been sensitized previously by one or more of its ingredients, including isoeugenol, eugenol, and cinnamyl alcohol, because of their presence in fragrances or fragranced cosmetics or other scented products, and these sensitizations are subsequently shown by a positive reaction to MP, which thereby acts as an indicator of fragrance allergy, a "natural fragrance mix."

It is unknown to what degree MP identifies fragrance sensitizations that are not "picked up" by FM I, but there are indications that the added value of testing it as well as FM I is limited. Nevertheless, some 50% to 75% of patients with allergy to the MP test material do not react to FM I. How many of these reactions are relevant and what the sensitizers are is largely unknown. Benzyl cinnamate and benzyl benzoate, together making up approximately half of the substances, are probably hardly ever the culprit ingredients.

Regarding further research, the following studies may be helpful in determining the value of testing with MP in the baseline series and possibly improving patient care:

- Study 1 determines the percentage of single positive reactions to MP (ie, with negative results for FM I) and how many of these are

relevant, either by indicating fragrance allergy or from contact with products actually containing MP. These data can give an indication of the added value of MP and whether MP qualifies for—continued—inclusion in the European baseline series[171].

- Study 2 investigates the composition of the commercial MP substances used for patch testing, and preferably also of other samples, both qualitatively and quantitatively; the MP supplier Chemotechnique Diagnostics has provided no information on the composition of its MP material; for the material provided to SmartPracticeCanada/Europe, it was revealed by the supplier only that it complies with the European Pharmacopeia[24] and contains 48.1% (unspecified) balsamic esters (personal communications, February 2019).
- Study 3 tests groups of patients allergic to commercial MP test materials, preferably as shown by a positive patch test reaction on two occasions and with a negative patch test result with the emulsifier ingredient sorbitan sesquioleate (in Chemotechnique Diagnostics material) with a battery of its ingredients, as shown from study 2, to identify the most important causes of positive MP patch test reactions.
- Study 4 tests the chemicals most frequently reacting in study 3 in routine testing as an addition to MP, to determine the value of separate testing; if one to three chemicals appear to be the dominant haptens in study 3, they can be tested separately; if there are more allergenic ingredients, the formulation and testing of a "fragrance mix III" could be considered.

## CONFLICTS OF INTEREST

Anton de Groot is the author of the book *Monographs in Contact Allergy, Volume II—Fragrances and Essential Oils*, Boca Raton, FL, USA: CRC Press Taylor & Francis Group, 2019, which is referred to repeatedly in this article and of which this is a shortened but strongly adapted version.

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**How to cite this article:** de Groot AC. *Myroxylon pereirae* resin (balsam of Peru) – A critical review of the literature and assessment of the significance of positive patch test reactions and the usefulness of restrictive diets. *Contact Dermatitis*. 2019;80:335–353. https://doi.org/10.1111/cod.13263