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REVIEW

CONTACT DERMATITIS WILEY

One hundred years of allergic contact dermatitis due to oxidized terpenes: What we can learn from old research on turpentine allergy

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Abstract

Although in recent years the focus on sensitizing terpene oxidation products has been on oxidized limonene and linalool, the autoxidation of terpenes in relation to allergic contact dermatitis is not new and dates back to the early part of the 20th century with the use of turpentine causing occupational contact dermatitis in painters. This review is written in a way as to allow us to get closer to the work of the scientists in earlier days, to participate in the successes, and also to observe the weak points. The researchers concluded that the main culprit in Scandinavian turpentine was Δ^3-carene hydroperoxides. This explains its high sensitizing effect compared with French turpentine which is of the Iberian type with no or only traces of Δ^3-carene. Historical exposure to turpentine showed that ending the industrial exposure stopped the occupational skin sensitization. Patch test studies demonstrated that monoterpene hydroperoxides, far from being an obsolete source of contact allergy solely related to turpentine, is a common cause of contact allergy in the population. A hundred years of extensive chemical and clinical studies worldwide should be sufficient to meet the evidence requirement regarding allergic contact dermatitis caused by terpenes.

KEYWORDS
air-oxidized terpenes, allergic contact dermatitis, hydroperoxide, oil of turpentine, occupational contact dermatitis, Δ^3-carene

1 | INTRODUCTION

The contribution of air-oxidized terpenes to allergic contact dermatitis (ACD) has generated a lot of interest over the past two decades (over 300 entries in Contact Dermatitis based on the keywords terpene and oxidation) mainly in connection with fragrance allergies. Although numerous articles have clearly demonstrated that terpenes can react with air to form oxidation products,[1,2] that these oxidation products (mainly hydroperoxides) are very potent skin allergens,[3] that these oxidized chemicals can elicit positive skin reactions in patients by either patch testing[4-8] or repeated open application test (ROAT),[9,10] the contribution/relevance of these terpene oxidation products to fragrance skin allergy remains a matter of debate.[11] As very often, the critical point and/or the missing link is the exposure assessment! Difficulties in tracing exposure, based on analysis of fragrance products, are often used to challenge the contribution of these oxidation products to the induction of skin allergies.[12,13] Indeed, it is very difficult to trace and assess the exposure of the general population to chemicals ubiquitous in our environment and to which we are all constantly exposed.

Although in recent years the focus has been on oxidized limonene and linalool, the autoxidation of terpenes in relation to ACD is not something new and dates back to the early part of the 20th century with the use of turpentine causing occupational contact dermatitis in painters. The added value of "occupational" contact dermatitis over "consumer" contact dermatitis is that the link between exposure on one side and pathology on the other side can be established more easily. Indeed, the decrease in use of turpentine as a solvent for occupational and household settings during the second half of the 20th

century resulted in a noticeable decrease in the cases of ACD caused by turpentine[14] and we can learn a lot from the turpentine (hi)story! This review is written in such a way as to allow us to get closer to the work of the scientists in earlier days, to participate in the successes but also to observe the weak points.

For decades, turpentine has been one of the most common causes of occupational contact dermatitis, especially among painters. In the 1950s it was shown by patch testing of sensitized patients that oxidation in air increased the "eczematogenic" effect of Swedish turpentine and also to a lesser extent that of French turpentine. The investigations demonstrated the same difference in effect for the bicyclic monoterpenes α-pinene and Δ^3-carene (Figure 1) when patch tested pure and after autoxidation. α-Pinene is a major compound in both Swedish and French turpentine, while Δ^3-carene is only present in large amounts in Swedish turpentine. As Δ^3-carene has been shown to autoxidize much faster than α-pinene, the conclusions drawn were that the main culprit in Scandinavian turpentine was oxidized Δ^3-carene.

2 | METHODS

A selective literature search among publications from the beginning of the 20th century up to recent days yielding a narrative review of chemical and clinical aspects of contact allergy to turpentine with a focus on the breakthrough in the research that took place in Scandinavia in the middle of the 20th century.

3 | RESULTS

Oil of turpentine, commonly known as turpentine, is the volatile part of the oleoresinous material of conifers. The source of all large-scale production of turpentine is the trees of the genus *Pinus*. Industrially, turpentine can be classified into three types: gum turpentine, wood turpentine, and sulfate turpentine. The essential oil gum turpentine (CAS # 8006-64-2) is obtained by steam distillation of oleoresin collected from wounds or scars of living pine trees, the nonvolatile residue consisting of gum rosin or colophonium. It is by far the largest volume of essential oil found in nature. Like rosin (colophonium), the main production of gum turpentine comes from China (*Pinus massoniana* Lamb.) but Iberian turpentine from *Pinus pinaster* Aiton is also important. In order to facilitate assessment of quality, the international standard ISO 21389:2004 specifies certain characteristics of oil

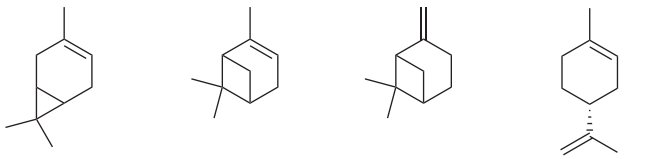


FIGURE 1 Chemical structures of some monoterpenes suspected to be involved in oil of turpentine allergic contact dermatitis

of turpentine, Chinese type (mainly from *P. massoniana* Lamb.), while ISO 11020:1998 specifies certain characteristics of oil of turpentine, Iberian type (*P. pinaster* Sol.). Wood turpentine is obtained from the distillation of the extract of virgin pine stumps (nonvolatile residue: wood rosin). Sulfate turpentine (not essential) is obtained by condensation of the vapours generated in the kraft (sulfate) pulping process for the production of paper (compare tall oil rosin). It is mainly produced in countries with high paper and pulp production (eg, Scandinavia, Russia, and Northern America).[15] Gum turpentine and sulfate turpentine are the products in use today. No distinction between these two types of turpentine is usually made in the reported cases of contact allergy to turpentine.

The chemical composition of turpentine varies depending on, for example, tree species, method of isolation, geographic region, and time of year for harvesting. This is in agreement with other essential oils and colophonium. In general, turpentine contains four main classes of components: hydrocarbons, terpene alcohols, ethers, and sesquiterpenes. Bicyclic unsaturated monoterpenes are the most common among all turpentine compounds and among these the most predominant is α-pinene (50%-90%) and to a lesser extent β-pinene (3%-28%); in some cases, Δ^3-carene is also predominant depending on the source of production. Δ^3-Carene is a major constituent found at concentrations of 15% to 40% in turpentine from the western United States, Canada, Scandinavia, Russia, and Eastern Europe including Austria. Turpentine from Indonesia, Southeast Asia, and India is also rich in Δ^3-carene; Indian (gum) turpentine can contain up to 65% of Δ^3-carene. Chinese gum turpentine and the Iberian type of gum turpentine from France, Spain, and Portugal contain no or only traces of Δ^3-carene.[15,16] Among the minor constituents of turpentine, limonene (dipentene) is of interest in connection to later publications and discussions regarding ACD from this terpene.

During the first part of the 20th century, the professional use of turpentine caused dermatitis in painters. From the start, this was assumed to be due to irritating impurities such as acetic and formic acid, formaldehyde, and furfuraldehyde formed in new distillation processes for production or from additives in poor-quality turpentine.[17,18] However, Perutz[19] suggested in 1926 that turpentine caused skin sensitization based on patch test results in four patients with turpentine eczema. In the 1930s, it was observed that the sensitizing effect of various oils of turpentine could be attributed to the terpene content with α-pinene as the main constituent being the most plausible culprit.[20] The same authors found in experiments on guinea pig that the sensitizing capacity of pinene was increased upon addition of soft soap at induction by repeated application to the skin. In addition, the old oxidized turpentine that had caused dermatitis in factory workers induced eczematous reactions in the animals.[21] The authors also found an increase in the number of cases of dermatitis after using oil of turpentine which had been exposed to light and air during prolonged storage and that the "eczematogenic" effect increased with oxidation.[22]

It was well known to Swedish painters and physicians that French turpentine (Iberian type) had a greatly reduced tendency to cause dermatitis compared with Swedish sulfate turpentine. Based on these

observations, the dermatologist Sven Hellerström from Stockholm was able to show that the greater "eczematogenic" power of Swedish turpentine must be linked to the presence of Δ^3-carene. The results of Hellerström's first investigations[23] on this subject were presented in a 1939 publication included in a discussion among dermatologists on the applicability and sources of error regarding hypersensitivity tests when it comes to compensation for occupational dermatoses. Its aim was to demonstrate from the example of turpentine that occupational ACD was also possible to prove and should be compensated. A more detailed description of the work was published in 1951 as a background in a paper on the pursuit of turpentine research.[24] In his initial investigation in the 1930s, Hellerström examined the "skin irritating" properties of turpentines and various substances present in different samples of turpentine in 80 patients with dermatitis (nature not specified). The test series included French turpentine oil; Swedish sulfate turpentine; a fraction consisting of unspecified monocyclic terpenes; and the specific terpenes α-pinene, β-pinene, and Δ^3-carene. Liquid paraffin was used as the solvent. Up to 10% of individuals responded to some of the tests. Sulfate turpentine and Δ^3-carene consistently gave the highest rate of positive tests and the strongest reactions while the percentage of response to French turpentine was "strikingly lower" and the reactions were weaker. α-Pinene, β-pinene, and the monocyclic terpenes caused weak reactions which usually appeared somewhat later than the others, similar to reactions with French turpentine. No solitary reaction to French turpentine was observed. The results were confirmed by analogous experiments performed by Rokstad in Denmark using test material from Hellerström.[25]

Although oxidation was observed in both Swedish and French turpentine during storage, it was speculated that the difference in sensitization potential could be due to the oxidation of Δ^3-carene over time, because it oxidizes much faster than α-pinene, the main constituent in both turpentines. As Δ^3-carene is a constituent in Swedish sulfate turpentine (30% to 35%) while no or only traces could be detected in French gum turpentine, it was considered that it could be possible to obtain less sensitizing Swedish turpentine by extracting Δ^3-carene. However, because the Δ^3-carene content was so high and Δ^3-carene at that time was not used for other purposes, this was not economically possible.

After the war, Hellerström, along with a chemist from the paper industry in Sweden (Lundén) continued his investigations on the cause of turpentine allergy.[24] α-Pinene and Δ^3-carene, pure, freshly distilled, "weakly oxidized," and "strongly oxidized," were tested in individuals sensitive to Swedish sulfate turpentine. They were also tested with sulfate turpentine (freshly steam-distilled, stored in air for 10 days, aerated at 60°C for 10 days, stored in air for 50 days) and with French turpentine from a drug store with and without distillation. The results of this study showed a link between the degree of oxidation and the positive results of the patch tests. They found that the "eczematogenic" component of turpentine was apparently not related to the pure hydrocarbons, the $C_{10}H_{16}$ terpenes, but to products formed by their oxidation. However, both Swedish and French turpentine gave positive reactions after oxidation, showing that not only oxidation products of Δ^3-carene but also oxidation products of other substances were sensitizing (strongly oxidized α-pinene gave positive reactions). No reaction was observed in the controls but unfortunately, the study does not give the number of positive individuals and controls tested. The conclusions drawn from this study were "… one may examine subjects with strong so-called terpene sensitivity by patch testing with turpentine and its fractions without obtaining positive reactions, provided the substances used in the tests are pure and freshly distilled. Hence the oxidation products seem to play a highly significant part in the provocation of the supersensitiveness reactions."[24] In parallel, sensitization experiments with turpentine fractions were performed in 30 guinea pigs by "energetic application to the skin in toxic dosage" for 6 months. The applications totally failed in sensitizing the animals. It was later discovered that the turpentine used was pure, freshly distilled, and directly supplied by the chemical company in well-filled ampoules made of brown glass, which were stored in a dark room. In other words, the turpentine used was as far as possible free of oxidation products.[24]

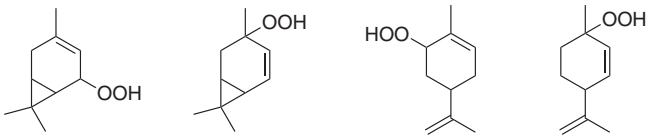
Swedish investigations continued with joint research between dermatologists from Karolinska Institutet and organic/analytical chemists from Stockholm University in a fruitful collaboration. In their first cooperative work, they investigated whether a difference in allergenicity measured by patch tests in an individual sensitized to turpentine depended on the purity of the terpenes previously identified in turpentine.[26] One individual with known allergy to Swedish turpentine was tested with chromatographic fractions of pure and oxidized terpenes as they eluted from the column and a plot was made between the fractions and the patch test reactions for each of the pure or oxidized compounds tested. For patch testing, 5 to 10 mm^3 of the test substance at a known concentration was applied on a patch together with a drop of olive oil. The intensity of the reactions (+ distinct persistent erythema, ++ erythema and swelling, and +++ distinct persistent erythema and vesiculation) was read first after 2 days and then daily for 5 days. The conclusions drawn from the study were that the intensity of the skin reaction was apparently consistent with the degree of oxidation of the terpene tested and that individuals who were hypersensitive to terpenes at earlier testing did not react to pure terpenes.[26] The result therefore corroborates the conclusions of the previous paper by Hellerström and Lundén.[24] The chemical part included purification of terpenes, synthesis of terpene oxidation products, and the isolation of the "eczematogenically" active substances from the oxidized turpentine. The development of a new method for the microscale separation of low-molecular-weight organic compounds by "displacement" was critical to the work. It was called microadsorption or (the micro sorption method) and is described as follows: One drop (40 μL) of oxidized turpentine or oxidized terpenes was loaded on top of a 25.0 cm long, narrow (i.d. 1.4 mm) column filled with active silica gel. Separation of the components were performed by displacement chromatography at a pressure of 1 atm. Absolute ethanol was used as displacer solvent and the compounds were separated unto fractions of 5.0 μL, with the most polar analytes in the last fraction. The identification was based on the differences in refractive indices between pure and oxidized compounds.[27,28] A clear difference in the refractive indices was measured between the fractions the last ones also being more "eczematogenic." Thus, this technique made it possible to collect the "eczematogenically"

active components. However, in this study only minute amounts were separated and therefore only a single subject was tested with the different fractions.

New studies by the Swedish group then tried to identify and isolate the specific eczematogenic component formed during the oxidation of Δ^3-carene.[29,30] The group used the same technique as before, that is, microadsorption with detection by a refractometer (a clear increase in refractive indices measured from the fractions of oxidized Δ^3-carene, which eluted last compared with the purest fractions, was evidenced). Attempts were made to concentrate the active component directly but failed due to its instability. Instead, various physicochemical investigations were carried out to elucidate its chemical structure. Patch testing the allergenic individuals with the last eluted fraction of oxidized Δ^3-carene gave an initial skin reaction when applying about 20×10^{-6} g, and a three plus reaction (described as distinct persistent erythema and vesiculation) was produced when applying about 300×10^{-6} g active ingredient. Based on the results obtained from patch tests with oxidized Δ^3-carene fractions after microadsorption and the physicochemical investigations, it was concluded that the allergenic effect was related to the process occurring in the first phase of autoxidation and could be attributed to a monomolecular Δ^3-carene hydroperoxide (Figure 2). However, the exact structure was not elucidated.

The chemists in the Swedish group continued their research into the autoxidation of the most common terpenes in Swedish sulfate turpentine, namely, Δ^3-carene, α-pinene, β-pinene, and limonene. By comparing their oxidation rates, they found that Δ^3-carene was by far the most easily oxidized, α-pinene and limonene followed, while β-pinene oxidized very slowly.[31] In a separate paper on the autoxidation of limonene, the experiments performed supported the hypothesis of a radical mechanism for the autoxidation of limonene, although it was not possible to isolate any hydroperoxide.[32] The author states that "it is not his intention to bring new physical evidence for the complex scheme of autoxidation, but to discuss how the experimental facts fit with the theory given by the British school of Farmer et al.[33] and reviewed by Bolland[34] and Bateman.[35] This school considers that autoxidation proceeds by a three-stage radical mechanism: initiation, propagation and termination. In the first two stages the formation of hydroperoxides from radicals dominates, and in the last the radicals are transferred to non-chain-reacting compounds."

A cooperative research project between dermatologists and chemists in the field of turpentine allergy was also started in Finland. The project was led by Dr Veikko Pirilä from the Institute of Occupational Health in Helsinki. The group began to investigate oil of turpentine before and after autoxidation based on the knowledge that oxidized terpenes can cause positive reactions in individual allergic to oil of turpentine.[36] The research first confirmed that stored turpentine (source not specified) gave contact allergic reactions in patients with known allergy to turpentine at patch testing. After removal of the oxidation products by boiling and distillation, no reactions were observed in the same patients. In order to study more precisely the chemical nature of the eczematous agent, research continued with investigations on pure and autoxidized α-pinene. The starting material was



Δ^3-carene hydroperoxides limonene hydroperoxides

FIGURE 2 Chemical structures of Δ^3-carene and limonene hydroperoxides

α-pinene obtained by fractional distillation of Finnish sulfate turpentine but also from a brand of high-quality α-pinene from the United States. Samples of α-pinene from these two raw materials were stored for over 1 year after which the presence of oxidation products was evidenced by the iodine test. Samples of oxidized α-pinene of both types were patch tested at concentrations from 50% and below in 12 individuals allergic to turpentine and all individuals reacted. By fractional vacuum distillation, the group managed to concentrate a more allergenic residue, as demonstrated by patch testing of two individuals. Positive reactions were demonstrated in one of them down to a concentration of 0.001% of the distillation residue. The autoxidation of α-pinene was well known and studied since the beginning of the 20th century. It had already been concluded that peroxide is the primary oxidation product of α-pinene.[37] The Finnish group therefore wanted to study whether peroxide or other oxidation products could be specifically linked to the observed "eczematogenic" reactions. No peroxide was isolated but on the basis of the chemical and clinical knowledge obtained, the conclusions drawn were that the "eczematogenic" agent and α-pinene peroxide are either identical or at least closely related substances.[36]

After the Swedish publication stating that Δ^3-carene hydroperoxides (Figure 2) should be the main culprit in turpentine from Scandinavia,[29] the group in Finland focused its efforts on carene considering that their results obtained on the autoxidation of α-pinene were due to contamination with Δ^3-carene.[38] In their next study,[39] they compared the oxidation of Δ^3-carene at room temperature with that of oxidation at 60°C and found that if the first takes several weeks or months, the increase in the temperature reduces the oxidation time to a few days. A maximum content of peroxides of 18.5% was found in both cases. Patch testing six individuals with known turpentine allergy with samples of autoxidized Δ^3-carene taken at different time points showed a clear correlation between the hydroperoxide content and the patch test reactions.

The irritant effects of pure and oxidized terpenes (Δ^3-carene, α-pinene, β-pinene, and limonene) were compared in a separate paper.[40] Here also the patch test technique was described a little more in detail. The terpenes were first purified by distillation and then autoxidized at room temperature from 3 weeks to 5 months. The peroxide content was measured with the iodine method according to Wagner et al.[41] The test preparations were diluted with olive oil and applied on 7×7 mm patches on a Whatman 3MM filter paper disc, 7 mm in diameter. Serial dilutions of one or more samples of freshly distilled, non-oxidized terpenes were tested in 28 patients with various skin diseases but not sensitized to turpentine. Concentrations of

70% to 80% gave irritation, 50% gave weak reactions while 20% to 35% gave no reactions. No significant difference in irritant effects was observed between terpenes. Serial dilutions of oxidized terpenes were tested in 30 patients not sensitized to turpentine. The lowest hydroperoxide concentrations giving irritant reactions ranged from 1% to 8% with 2% for most individuals. A strictly standardized amount of substance (0.02 mL) was applied. Likewise for oxidized terpenes, no significant difference in irritant effects was observed between terpenes.

The Finnish researchers continued with patch testing 100 patients sensitized to turpentine with a serial dilution of oxidized Δ^3-carene with measured concentrations of Δ^3-carene hydroperoxides (0.5% [5000 ppm] to 0.0001% [1 ppm]).[42] They found frequent reactions down to a concentration of 0.01% (100 ppm) of Δ^3-carene hydroperoxides in 75 "less sensitive cases" who did not react to other terpenes. In the 25 additional patients who also reacted to other terpenes, they could see individuals reacting down to a concentration of 0.0001% (1 ppm; Figure 3).

Taken together, the Scandinavian researchers concluded that the main culprit in Scandinavian sulfate turpentine was Δ^3-carene hydroperoxides. This also explains its high sensitizing effect compared with French turpentine because the latter is of the Iberian type with no or only traces of Δ^3-carene. In response to this, German researchers demonstrated the possibility that other compounds in turpentine also caused allergic reactions. Their research pointed at epoxides from oxidized pinene and limonene.[43,44] In a subsequent paper, the Finnish group compared the sensitizing capacity of different terpenes and showed that the more the terpenes were purified, resulting in a low Δ^3-carene content, the lower was the "eczematogenic" effect of their oxidation products, again highlighting the importance of Δ^3-carene hydroperoxide as the main culprit.[45] On this basis, it was concluded that that the pattern of sensitivity to different terpenes could vary depending on the type of exposure.

A radical change in the use of turpentine occurred between the 1930s and the 1970s, ending research and discussion on the allergenic effect of turpentine. Table 1 shows the decrease over time in the use of turpentine when it was replaced by cheaper petroleum-based solvents such as white spirit for use as, for example, paint thinner, and as the major constituent of varnishes, shoe- and floor-polishes and in various adhesives used both at work and at home. It is assumed that the figures given are representative for most countries in the world.[46]

The cause of skin sensitization due to turpentine, especially from Scandinavia, had been interpreted and resolved. The reduced use of turpentine also reduced turpentine dermatitis and the researchers became professors and turned their minds to other areas of research.

4 | DISCUSSION

As the main skin exposure disappeared, turpentine dermatitis was also reduced and turpentine was no longer considered a problem.[14] Of the research that had taken place, it was only remembered that the allergy to turpentine was due to Δ^3-carene hydroperoxides present in Scandinavian turpentine but not in French turpentine.

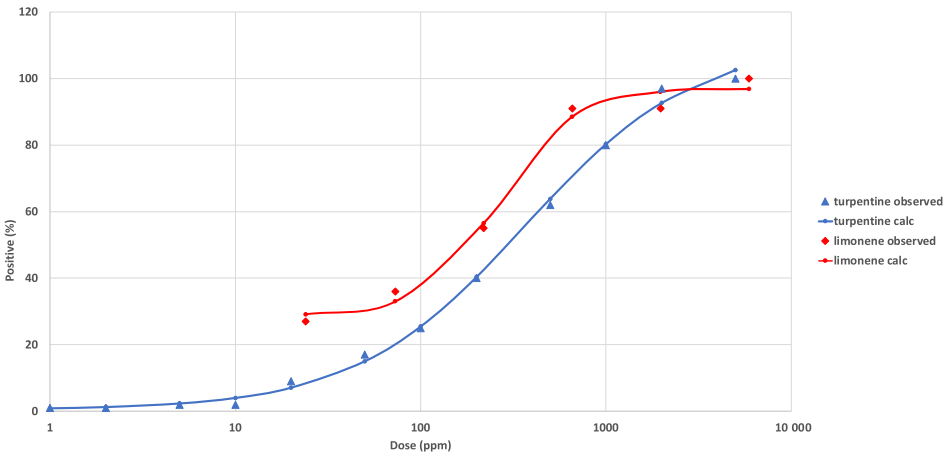


FIGURE 3 Observed and calculated dose-response curves in individuals sensitized to turpentine and limonene following exposure to serial dilution of Δ^3-carene hydroperoxides[42] or limonene hydroperoxides,[10] respectively

TABLE 1 Utilization of turpentine in the United States (1000 metric tonnes [% of total]) between 1935 and 1979[46]

Purpose	1935-1939	1955-1959	1975-1979
Chemicals	3.7 (5.5)	59.6 (60.1)	76.7 (95.5)
Solvent, industrial use	12.8 (18.9)	1.7 (1.7)	1.0 (1.3)
Solvent, in specific products	51.2 (75.6)	37.8 (38.2)	2.6 (3.2)
Total solvents	64.0 (94.5)	39.5 (39.9)	3.6 (4.5)
TOTAL	67.7	99.1	80.3

The massive use of petroleum-based solvents, especially chlorinated hydrocarbons (eg, chlorofluorocarbons), was soon questioned from a health point of view and because of its bad impact on the environment. Citrus oil which contains about 98% *R*-limonene was launched as a more environmentally friendly (alternative) solvent in the industry. Thus, the circle was closed and again the skin-sensitizing effect of autoxidized terpenes was demonstrated.[47]

The new in-depth and expanded investigations into the autoxidation of terpenes and its impact on skin sensitization and ACD confirmed the mid-20th century findings. Moreover, recent research on colophonium, the nonvolatile residue remaining after distillation of oleoresin from pine, had demonstrated that the major culprit in skin sensitization from colophonium is the hydroperoxide of its major resin acid abietic acid.[2,48]

The systematic experimental research and clinical investigations on turpentine which had started in Scandinavia are of high quality when considering the experimental technique available. However, descriptions of material and methods are not always up to modern standards, making it difficult to obtain complete information. The theory of autoxidation via a radical mechanism and the formation of hydroperoxides were well known by the time the investigation of turpentine allergy began.[33,34] Already in their first study, the Swedish researchers draw the conclusions that the so-called terpene sensitivity was due to oxidation products. Pure and air-exposed turpentine or isolated fractions were patch tested in patients with dermatitis and it was observed that the "eczematogenic" component of turpentine was apparently not linked to the pure hydrocarbons, terpenes $C_{10}H_{16}$, but to products formed by their oxidation. Research groups found that the Δ^3-carene hydroperoxides were the main culprit in oxidized turpentine from Scandinavia, but the exact structure of the most important hydroperoxide(s) was not elucidated. It was also shown that α-pinene, β-pinene, and limonene autoxidize, although the rate of oxidation of Δ^3-carene is far faster.[31] It was observed that Swedish and French turpentines gave positive reactions after oxidation, showing that Δ^3-carene and the oxidation products of other substances caused skin sensitization.[24] The Finnish group found that a low concentration of α-pinene peroxide gave positive patch test reactions in individuals with known contact allergy to turpentine.[36]

The discovery of a new analytic method called microadsorption, which utilizes displacement chromatography for polarity-based fractionation and measurement of refractive indices for identification, was crucial for the isolation of "eczematogenically" active substances from oxidized turpentine.[26-30] The fractionation of oxidized turpentine and various oxidized terpenes including Δ^3-carene was combined with patch testing in only a single patient allergic to turpentine due to lack of materials, which was of course a drawback in this first investigation.[26] The final structure elucidation for the identification of a Δ^3-carene hydroperoxide (the position of the hydroperoxide moiety is not specified) was carried out with physicochemical investigations, as the analytical tools that we use today were not present at that time. Let us recall that in general chemists possessed a know-how in this area which declined with the development and use of modern analytical instruments for identification. A maximum hydroperoxides content of 18.5% was observed after autoxidation at air exposure of Δ^3-carene,[39] which corresponds to concentrations observed in subsequent investigations of linalool and citronellol at air exposure.[49,50]

Patch testing and evaluation of the results were carefully carried out in a manner very similar to that recommended today. The amounts and concentrations of material applied appeared to be a major concern. A strictly standardized amount of substance (0.02 mL) was applied when irritation was investigated according to Pirilä et al.[40] We must remember that Professor Pirilä later developed a standardized patch test method with the so-called Finn chambers which are still used all over the world. The Swedish group also described a standardized patch test technique. For patch testing, 5 to 10 mm^3 of the test substance at a known concentration was applied on a patch with a drop of olive oil. The intensity of the reactions (+ distinct persistent erythema, ++ erythema and swelling, +++ distinct persistent erythema and vesiculation) was read first after 2 days, then daily for 5 days.[26]

The 1960s study showed no significant difference in irritant effects between the terpenes (α-pinene, β-pinene, Δ^3-carene, and limonene) investigated in pure or oxidized form. No irritation was found in concentrations up to 35% for pure terpenes.[40] However, oxidized terpenes were later shown to be more irritant than pure compounds. Subsequent research has demonstrated irritation for pure limonene at a concentration of 10% and a clear difference in irritant effect between limonene and linalool in pure and oxidized forms.[51] The different results could be due to a stricter definition for reading of irritant effects in later years.[52]

It is interesting to observe that the amounts of Δ^3-carene hydroperoxides in oxidized Δ^3-carene that caused elicitation in individuals sensitized to Swedish turpentine in the mid-1950s correspond to the amounts of limonene hydroperoxides in oxidized limonene that gave elicitation in individuals sensitized to oxidized limonene in a study from 2019 if we postulate the usage of approximately the same patch test area.[10,29,42] Investigations in Finland demonstrated cases of elicitation in patients with known contact allergy to turpentine down to 1 ppm (0.0001%) of Δ^3-carene hydroperoxides (Figure 3) and a clear dose-response curve analogous to that obtained by Bennike et al.[10] when patch testing oxidized limonene (limonene hydroperoxides; Figure 1). Unfortunately, the old Finnish results are only given briefly in a publication honouring the Swedish turpentine researcher Professor Hellerström at his retirement.[42] We were not able to retrieve a subsequent more detailed publication. In the Swedish investigation using microadsorption fractionation, patch tests with the last eluted fraction of oxidized Δ^3-carene gave an initial cutaneous reaction with an amount of approximately 20×10^{-6} g, while a +++ reaction (described as distinct persistent erythema and vesiculation) was produced by approximately 300×10^{-6} g of active constituent.[29] If we postulate that the patches were about the same size as Finn Chambers, it gives 40 and 600 $\mu g/cm^2$ of Δ^3-carene hydroperoxides, respectively. This can be compared with positive reactions to 50 $\mu g/cm^2$ limonene hydroperoxides in 10 of 11 individuals and to 152 $\mu g/cm^2$ limonene hydroperoxides in 11 of 11 in the investigation by Bennike et al.[10] Cases from real life have shown the possibility of

elicitation and ACD from correspondingly low concentrations of terpene hydroperoxides.[53,54] Thus, a limit of 50 ppm for the quantification of hydroperoxides as suggested could not be considered safe from an elicitation point in individuals sensitized.[55] Rather, a method allowing detection of <1 ppm hydroperoxides should be used to exclude contact with hydroperoxide as a cause of ACD.[56]

What about turpentine allergy today? Turpentine (oil of turpentine, steam distilled, CAS number 8006-64-2) is not included in the baseline series recommended by the ESCD, but is still used for patch testing. Cases of contact allergy from turpentine have continuously been recorded. Patch testing with Scandinavian sulfate turpentine in Spain and gum turpentine (Iberian type) in Portugal in the 1980s resulted in many co-reactions to the isolated terpenes.[57,58] The German-Austrian Information Network of Departments of Dermatology (IVDK) has registered and evaluated patch test reactions to turpentine in consecutively tested patients with dermatitis. A significant increase in positive patch tests among patients with dermatitis was observed from 0.5% (1992-1995) up to 4.4% (1998).[59] Since then a decline in positive patch test reactions has been recorded (0.74% during the years 2015 to 2018).[60,61] Oil of turpentine is mainly regarded as a marker for fragrance allergy and patch test reactions are often considered to be caused by contact with terpenes in various consumer products including fragrances (perfumes). A clear age gradient (0.78%-1.77%) in the prevalence of patch test reactions to oil of turpentine was observed in the latest IVDK study, indicating the possibility of historical sensitization among the oldest patients.[61] Turpentine belongs to the natural extracts that are classified as established contact allergens in humans and is only allowed as perfumery material in cosmetics with a restricted peroxide value of <10 mmol.[62,63] It is a most important source for recovery of terpenes including fragrance terpenes such as limonene, caryophyllene, and myrcene. Constituents identified in different types of commercial oils of turpentine are listed in de Groot and Schmidt.[16] The same authors also give an overview of reported cases of ACD to turpentine from 1975 until the first decade of the 21st century.[16] Occupational ACD can still be observed in musicians allergic to turpentine.[64] Outbreaks of occupational ACD have been reported when Δ^3-carene-rich turpentine was introduced in a work place.[65] Once upon a time, ACD from turpentine was used as an example of obvious occupational dermatitis in discussions about compensation for occupational skin diseases.[23] Up to the 1970s occupational dermatitis from turpentine was well-known. At that time, Δ^3-carene hydroperoxides were accepted as the cause of sensitization with no attempts to investigate the impact of other oxidized terpenes.[66] Today we know that detection of occupational exposure to allergenic terpenes is not restricted to patch testing with turpentine. Cases of occupational ACD from terpenes have been identified after testing with oxidized limonene and linalool.[67-69]

The renewed investigations on contact allergy and ACD caused by terpenes have used modern techniques that allowed isolation and structure elucidation of hydroperoxides as well as secondary oxidation products formed at autoxidation during air exposure. The sensitizing potency of pure and autoxidized terpenes and their different oxidation products has been studied experimentally using in vivo and in vitro methods. Several monoterpenes in turpentine, diterpenes in colophonium, and sesquiterpenes were shown to autoxidize and form allergenic oxidation products, especially hydroperoxides.[2,3,48,70] Investigations demonstrated that the hydroperoxides form specific antigens with equal sensitizing potency but without cross-reactions.[71] The reaction mechanisms in the terpene oxidation process were interpreted using computational technique. It was now possible to demonstrate why and how the specific hydroperoxides were formed and which ones were most stable and therefore detected and quantified in the oxidation mixtures. In some cases, the importance of the secondary oxidation products, although less sensitizing compared with the hydroperoxides, was demonstrated to be highly important for the allergenic effect of the oxidized compound.[72] The secondary oxidation products, although less sensitizing compared with the hydroperoxides, are important allergens due to exposure.[73] Determination of the sensitizing potential was performed *in vivo* using the murine local lymph node assay, which allows a quantitative comparison of the sensitizing potency of various compounds. The terpene hydroperoxides were identified as strong sensitizers.[3] The human sensitization potential and potency of several hydroperoxides have been determined in vitro in human cells showing comparable results with the in vivo testing.[74] In-depth studies have shown that the terpene hydroperoxides can form reactive radical intermediates capable of modifying amino acids in epidermal proteins.[75-77]

The experimental investigations were followed by clinical investigations on the eliciting effect in patients who are sensitized.[3] Patch tests studies all over the world demonstrated that monoterpene hydroperoxides, far from being an obsolete source of contact allergy solely related to the use of Scandinavian turpentine, is a common cause of contact allergy in the population.[4-8]

5 | CONCLUSION

About a 100 years of extensive chemical and experimental research as well as repeated clinical studies in dermatology departments around the world should be sufficient to meet the requirement of evidence regarding skin sensitization and ACD caused by terpenes. Autoxidation in contact with air has been shown to be a property inherent in the terpenes. It is difficult to control and eliminate and should therefore be taken into account in all cases of skin contact with these chemicals due to risk of sensitization by the oxidation products formed. The most important information from turpentine history relates to exposure. Historical exposure to terpenes in turpentine showed that at the end of industrial exposure, occupational skin sensitization from these terpenes also ceased at a large. Based on this, the widespread skin sensitization by terpenes in the general population with increasing numbers at patch testing with their oxidation products tells us that the contact is ubiquitous and constant. The requirement of precise quantification of exposure to very unstable compounds such as hydroperoxides in a specific

consumer product with a very heterogeneous composition that may change over time, as evidence of the relevance of ACD observed in a patient, is inappropriate. Moreover, from a preventive point of view, it should not be necessary to demonstrate an allergenic effect for each unsaturated terpene (and terpenoid) but rather to apply a strategy including structure-activity relationship studies in the legislation of these compounds.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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