

Occupational contact dermatitis caused by D-limonene

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Summary

Background. Limonene is widely used as a fragrance substance and solvent in cleansing products. Oxidized limonene is a frequent contact allergen among consumers of cosmetics, personal care products, and scented household cleaning products. Less is known about the sources of occupational exposure and occupational contact dermatitis caused by limonene.

Objective. To report 14 patients with occupational contact allergy to limonene.

Methods. The patients were examined in 2008–2013. An in-house preparation of oxidized limonene was patch tested as 3% and 5% in petrolatum from 2008 to August 2010, and after this as 3%, 1% and 0.3% pet. From 2012 onwards, a commercial test substance of limonene hydroperoxides was also used. We assessed the patients' occupational and domestic exposure to limonene.

Results. Occupational limonene allergy was observed in workers who used limonene-containing machine-cleaning detergents and hand cleansers, and in workers who used limonene-containing surface cleaners and dishwashing liquids similar to those used by consumers. In 3 cases, the occupational limonene allergy resulted from work-related use of limonene-containing, leave-on cosmetic products.

Conclusions. Limonene is a frequent occupational sensitizer in hand cleansers and cleaning products. Occupational limonene contact allergy may also be caused by exposure to cosmetic products scented with limonene.

Key words: contact allergy; D-limonene; limonene hydroperoxides; occupational contact dermatitis; oxidation of limonene; patch testing.

D-Limonene, one of the most common fragrance terpenes, is frequently used in various scented cosmetic, domestic and industrial products (1–3). It is also used as a solvent and degreasing agent in industrial and household cleaning products (4, 5). Although dipentene, the

racemic mixture of the D-enantiomer and L-enantiomer of limonene, has long been patch tested as a suspected contact allergen, only a few cases of contact allergy to dipentene have been reported (6–9). Pure, that is, unoxidized, limonene is an irritant at high concentrations (10, 11), but a weak sensitizer that seldom causes positive patch test reactions (12). However, unoxidized limonene has been shown to form allergenic oxidation products upon contact with air (13). The primary oxidation products, limonene hydroperoxides, and the secondary oxidation products, carvone and limonene oxide, have been identified as skin sensitizers (13–20). Patch testing with oxidized limonene has shown that contact allergy to limonene is relatively common in dermatological patients,

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with frequencies ranging from 1.1–2.4% to 2.3–12.1% having been reported in Europe (21, 22). Less is known about occupational contact allergy to limonene. At the Finnish Institute of Occupational Health (FIOH), an in-house test preparation of oxidized limonene has been used since 2008. We describe 14 patients diagnosed with occupational contact dermatitis caused by limonene, and their occupational and domestic limonene exposure.

Materials and Methods

At the FIOH, all patients are investigated because of suspicion of occupational skin disease. They come from all over Finland. Occupational and non-occupational (domestic) exposure to the allergens shown by patch testing is examined in detail, on the basis of product information such as safety data sheets and labelling, inquiries to the manufacturers of the products, and, when necessary, analyses of the products' limonene content.

Patch testing

The patch tests were performed with the Finn Chamber® method according to the recommendations of the ICDRG. The tests were read two or three times (on D2, D3 and D4, or on D2, D3 and D6, or on D2 and D5), depending on the day of the week on which the patch tests were applied.

An in-house preparation of oxidized limonene was patch tested as 5% and 3% in petrolatum in 2008–2010, and thereafter as 3%, 1% and 0.3% pet. Since 2009, in-house oxidized limonene has been included in the baseline series; that is, it has been routinely tested in all patients patch tested at our clinic (Table 1).

Since September 2010, unoxidized limonene (10% pet.; Chemotechnique Diagnostics, Vellinge, Sweden) has been included in the fragrance series, which is tested in patients with suspected fragrance allergy. Limonene hydroperoxides (0.3% pet.; Chemotechnique Diagnostics) has been patch tested in all of our patients since August 2012 (Table 1).

Dipentene (1% pet., in-house preparation) and tea tree oil (*Melaleuca alternifolia*) (5% pet.; Chemotechnique Diagnostics), which contains D-limonene (23), were patch tested in selected patients. *Myroxylon pereirae* (25% pet.), fragrance mix (8% pet.), fragrance mix II (14% pet.), colophonium (20% pet.; Trolab Hermal, Reinbeck, Germany) and compositae mix (2.5% pet.; Chemotechnique Diagnostics) were patch tested in all of the patients.

Oxidation of limonene

For patch testing, we oxidized D-limonene according to the method described by Karlberg (24). D-Limonene of

technical quality (essential oil containing 98% limonene) was purchased from Frey and Lau Henstedt (Ultzburg, Germany). A 50-ml sample of D-limonene was exposed to air at room temperature for 10 weeks, with stirring for 1 hr four times daily. The oxidized D-limonene was then divided into small portions and frozen for storage. A fresh patch test substance was prepared every week by mixing the oxidized limonene with white pet.

Analysis of in-house test substance and products' limonene content

Precisely weighed samples of in-house-oxidized limonene and the products to be analysed for their limonene content were first dissolved in tert-butylmethylether at room temperature, and then analysed by gas chromatography with mass spectrometry (MS) detection. D-Limonene (stabilized, purity 97%; Acros Organics, Geel, Belgium) was used as an external standard for quantification of the limonene content.

In-house preparations of oxidized limonene containing approximately 25–35% pure limonene were accepted as the patch test substance. The presence of oxidation products such as the limonene oxides, carveols, carvones and limonene hydroperoxides was confirmed by MS detection. The commercial test substance hydroperoxides of limonene (Chemotechnique Diagnostics) was not analysed for its content of oxidation products of limonene.

Results

Between January 2008 and May 2013, a total of 511 patients were patch tested with oxidized limonene in our clinic. Of these, 21 reacted to oxidized limonene. Very strong allergic (+++) reactions to oxidized limonene were seen in 9 cases, strong allergic (++) reactions in 6 cases, and weak allergic (+) reactions in 6 cases. Fourteen (61%) of our 21 limonene-allergic patients were diagnosed with occupational contact dermatitis caused by limonene (Table 1). Irritant reactions were seen in 29% of the patients tested with oxidized limonene 5% pet. The highest test concentration of oxidized limonene was then decreased to 3%. After this, irritant reactions to limonene were seen in 8% of the patients tested with oxidized limonene 3% pet. Five (36%) of the 14 patients with occupational limonene contact allergy had a positive or doubtful (+ or ?+) reaction to *M. pereirae*. Of these, 4 had a concomitant positive reaction to fragrance mix, 3 to fragrance mix II, and 2 to colophonium.

Discussion

The most likely sources of limonene sensitization are considered to be scented cleaning products, personal

Table 1. Patch test results and limonene exposure of patients with occupational contact dermatitis caused by limonene

Patient no.	Occupation (year of examination)	Patch tests					Limonene exposure and patch test reactions to own substances/products
		In-house oxidized limonene (pet.)	Tea tree oil 5% pet.	Unoxidized D-limonene 10% pet.	Limmonene hydroperoxides 0.3% pet.	Related allergens in baseline series: <i>Myroxylon pereirae</i> , fragrance mix, fragrance mix II, colophonium, compositae mix	
1	Printer (2008)	5% +++ 3% +++ 1% NT	NT	NT	NT	Negative	At work Detergent for printing machines: S: 3–7% orange-terpene A: 7% D-limonene Patch test: 10% +, 3.2% ++, 1% ?+ Detergents for printing machines: Product 1: A: 0.47% limonene Product 2: A: 0.08% limonene Product 3: A: 0.26% limonene Product 4: A: 0.60% limonene Hand cleansers: Product 1 (Loctite™ 7850): L: dipentene A: 0.006% limonene Product 2: A: 0.24% limonene Hand creams: Product 1: L: limonene Product 2: M: 0.0008% D-limonene Cleansers: Product 1: M: limonene as fragrance Product 2: M: limonene as fragrance Hand cleanser (Loctite™ 7850): S: D-limonene 2.5–7.5% Cutting oil: A: 50 ppm D-limonene Detergents for machines: Product 1: A: 2.3 ppm D-limonene Product 2: S: 0.1% limonene Hand cleansers: Product 1 (Loctite™ 7850): A: 2.5–7.5% D-limonene Patch test: 10% ++, 3.2% + Product 2: M: 5–10% D-limonene Patch test: 10% +, 3.2% negative Product 3: M: <2.5% D-limonene Shower soap: L: limonene None found
2	Printer (2008)	5% ++ 3% ++ 1% NT 0.3% NT	NT	NT	NT	Negative	At home
3	Cleaner (2010)	5% +++ 3% +++ 1% NT 0.3% NT	NT	NT	NT	<i>Myroxylon pereirae</i> +	Dishwashing detergent: L: limonene
4	Maintenance worker on construction machines (2010)	5% +++ 3% +++ 1% NT 0.3% NT	Negative	NT	NT	Negative	Several cosmetic products and household cleaners: L: limonene
5	Assembler of vehicles (2010)	5% +++ 3% +++ 1% NT 0.3% NT	NT	Negative	NT	Negative	None found

Table 1. Continued

Patient no.	Occupation (year of examination)	Patch tests					Related allergens in baseline series: <i>Myroxylon pereirae</i> , fragrance mix, fragrance mix II, colophonium, compositae mix	Limonene exposure and patch test reactions to own substances/products	
		In-house oxidized limonene (pet.)	Dipentene 1% pet.	Tea tree oil 5% pet.	Unoxidized D-limonene 10% pet.	Limonene hydroperoxides 0.3% pet.		At work	At home
6	Masseur (2012)	5% NT 3% +++ 1% ++ 0.3% +	NT	++	Negative	NT	Negative	Floor cleaner: S: limonene Surface cleaning spray: M: limonene Surface cleaner: M: α -pinene Dishwashing detergent: L: limonene Dishwashing detergent: L: limonene Surface cleaner: M: limonene Hand cleanser: M: limonene	Dishwashing detergent, shampoo, hair conditioner: L: limonene
7	Cook (2012)	5% NT 3% +++ 1% ++ 0.3% ?+	NT	+++	NT	NT	Negative		None found
8	Baker, cook (2012)	5% NT 3% ++ 1% ++ 0.3% negative	NT	NT	Negative	++	Fragrance mix +++ <i>Myroxylon pereirae</i> +	Surface cleaner and dishwashing detergent: M: limonene 667 ppm	Several cosmetic products and household cleaners: L: limonene
9	Cook (2012)	5% NT 3% ?+ 1% ?+	NT	NT	NT	+	Negative	Dishwashing detergent: M: limonene	None found
10	Beautician (2012)	0.3% negative 5% NT 3% + 1% negative 0.3% negative	NT	Negative	Negative	Negative	Negative	Several skin creams, skin cleansers and other products used in beauty salons: L: limonene and linalool, tea tree oil, citrus peel oil, lavender oil, rosewood oil	Several cosmetic products: L: limonene, linalool, tea tree oil, citrus peel oil
11	Construction worker (2012)	5% NT 3% ++ 1% + 0.3% negative	NT	NT	Negative	NT	<i>Myroxylon pereirae</i> + Fragrance mix +++ Fragrance mix II + Colophonium ++ Compositae mix +	Hand cleanser: L: limonene	None found

Table 1. Continued

Patch tests								
Patient no.	Occupation (year of examination)	In-house oxidized limonene (pet.)	Tea tree oil 5% pet.	Unoxidized D-limonene 10% pet.	Limonene hydroperoxides 0.3% pet.	Related allergens in baseline series: <i>Myroxylon perirae</i> , fragrance mix, fragrance mix II, colophonium, compositae mix	Limonene exposure and patch test reactions to own substances/products	
							At work	
							At home	
12	Mechanic (2013)	5% NT 3% +++ 1% ++ 0.3% +	NT	Negative	+++	Negative	Hand cleansers: Product 1 (Loctite™ 7850): S: dipentene Product 2: M: limonene	Shower gel: L: limonene Surface cleaning spray: L: limonene
13	Hairdresser (2013)	5% NT 3% +++ 1% +++ 0.3% +++	+++	Negative	+++	<i>Myroxylon perirae</i> ?+ Fragrance mix ++ Fragrance mix II + Compositae mix ?+ Colophonium ?+	Hair conditioners, hairstyling products, and hand cream: L: limonene Hair dye products: L: limonene	Dishwashing detergent: L: limonene
14	Service technician (2013)	5% NT 3% +++ 1% +++ 0.3% ++	++	++	+++	<i>Myroxylon perirae</i> ?+ Fragrance mix + Fragrance mix II +	Hand cleanser (Loctite™ 7850): S: limonene Detergent for machines: A: 0.006% limonene	Shower gel, shampoo, and deodorant: L: limonene

NT, not tested.

Sources of information on the products' limonene content: L, product labelling; S, safety data sheet; M, information from the manufacturer; A, chemical analysis.

care products, and cosmetics (25). Previously, cases of occupational contact dermatitis caused by limonene have been reported in a worker involved in picking and handling citrus fruits (26), from laboratory work in which a limonene-based solvent was used in preparing histopathological specimens (27), and from the use of hand cleansers (28) and a degreasing product (29). In addition, occupational allergic contact dermatitis caused by dipentene, the racemic mixture of D-limonene and L-limonene, has been reported from handling honing oil (6) and wax polish (7). Limonene also occurs naturally in plant oils, including essential oils from, for example, lemon, orange, bitter orange (*Citrus aurantium*), lemongrass, peppermint, laurel, and eucalyptus (30, 31), which may be used as ingredients in massage oils and aromatherapy products.

We observed several cases of occupational contact allergy to limonene in mechanics, maintenance workers and assemblers of vehicles who were involved in dirty work and used limonene-containing cleansers for construction machines and hand cleansers that contained limonene. Notably, 5 of the 14 patients with occupational limonene allergy had used the same hand-cleansing product, that is, Loctite™ 7850, which is an abrasive lotion containing limonene as the cleansing solvent (Henkel, technical data sheet, September 2013). Two cases of occupational limonene allergy were seen in printers who handled limonene-containing detergents for printing machines. In addition, we observed several cases of occupational limonene allergy in workers who used limonene-containing surface cleansers and dishwashing liquids similar to those used by consumers. These included 3 cooks and a masseur. In 3 of our patients, the occupational sources of limonene exposure were cosmetic products in which limonene was used as a fragrance. One of these cases was a cleaner who used limonene-containing hand creams several times a day and wore watertight gloves, which may have increased the penetration of limonene into the skin.

When it is oxidized upon contact with air, limonene forms strong contact allergens such as limonene hydroperoxides (13). The analogous formation of allergenic oxidation products has been shown to occur for several other fragrance terpenes, such as linalool, linalyl acetate, and geraniol (22, 32, 33), as well as for the major component of colophonium, abietic acid (34). Unoxidized limonene has been shown to rarely cause positive patch

test reactions in dermatitis patients (35, 36). In our patients, the unoxidized limonene was patch tested in 8 patients with positive reactions to oxidized limonene, and was positive in only 1 of them. On the basis of our experience, we see little benefit of patch testing with unoxidized limonene.

Tea tree oil, the essential oil from the *Melaleuca alternifolia*, is marketed and used as a topical antimicrobial and anti-inflammatory substance as such and as an ingredient in cosmetic products (37). It has been shown to contain several terpenes, including D-limonene, which form contact allergens upon oxidation (23, 38). Of our limonene-allergic patients, 5 were patch tested with tea tree oil (5% pet.), and strongly positive reactions were seen in 4 of them.

Concomitant reactions to fragrance mix, *M. pereirae* and colophonium are known to be frequent among patients with contact allergy to oxidized limonene (21, 24). Accordingly, 5 (36%) of our patients with occupational limonene allergy had positive patch test reactions to *M. pereirae*, and 4 also to fragrance mix.

Most of our patients with occupational limonene contact allergy had strong patch test reactions to limonene (++ or +++). Limonene is a common irritant in the patch test. Owing to the frequently seen irritant reactions (29% of the tested patients), the highest patch test concentration of oxidized limonene was decreased from 5% to 3% in our clinic in 2010. In order to distinguish allergic and irritant reactions, we patch test oxidized limonene as a dilution series, currently as 3%, 1% and 0.3% pet.

A commercial patch test product of oxidized limonene (limonene hydroperoxides) has been available since 2012. Six of our patients with occupational contact allergy to limonene were patch tested with the commercial test substance hydroperoxides of limonene, and all of them tested positive, except for 1 patient, who showed a mild allergic reaction (+) to 3% in-house-oxidized limonene.

In conclusion, oxidized limonene is a frequent skin sensitizer that may also cause occupational contact dermatitis. In our patients, occupational contact allergy to limonene was most often caused by limonene in detergents used for cleaning machines and in hand cleansers. Occupational limonene contact allergy may also be caused by work-related exposure to surface cleansers and dishwashing liquids, or to cosmetic products scented with limonene.

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