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Contact sensitization to thymol: IVDK-data of the years 1990 – 2021 and review of the literature

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Background

Thymol (CAS 89-83-8) is a fragrance material with preservative and disinfectant properties, used by consumers and professional workers (1). It originates from essential oils or is synthetically produced from *m*-cresol and isopropyl chloride. It is mainly used to synthesize menthol and is also found in fragrances or fragranced products, food, washing and cleaning products, air care products, polishes and waxes, mouthwashes, toothpastes and other dental products. Decades ago, it was also used for treating hook worm infections and as intestinal antiseptic agent (2).

Thymol is present in several essential oils, e.g., in Spanish thyme oil (39.2 – 56.2%) and thyme oil ex *Thymus vulgaris* (0.2 – 47.8%), and maybe also in propolis (1). However, as essential oils are mixtures of numerous (sensitizing) compounds, patch test results obtained with thyme oil and other essential oils will not be considered in our following analysis.

With one exception, numerous animal tests on sensitization potential of thymol were negative (3). In the single guinea pig maximization test with a positive test outcome, 20 female guinea pigs were pre-treated with the skin irritant sodium lauryl sulfate (SLS), and 10% thymol was used for induction, which is a very high concentration. Weak sensitization effects were observed with 20% thymol at challenge only, while the challenge with 10% remained negative.

In the Combined Draft Assessment Report to (EC) No 1107/2009 (renewal) and the CLH report, Proposal for Harmonised Classification and Labelling Based on Regulation (EC) No 1272/2008 (CLP Regulation) for Thymol, 5-methyl-2-(propan-2-yl) phenol, Volume 1 of February 2023, it is being proposed to categorize thymol as skin sensitizer category 1. Our objective is to analyse epidemiological data on thymol in order to review the proposed categorization of thymol as skin sensitizer category 1 from the allergological point of view.

Methods

The IVDK is a network of currently 58 departments of dermatology in Germany, Switzerland, and Austria, dedicated to clinical epidemiology of contact allergy. Patients' medical histories, clinical data, and patch test results are recorded in local databases in the participating centres and, after pseudonymization, transmitted to the IVDK central office at the University Medical Centre of Göttingen twice a year. Data are subjected to standardized quality control, added to the central IVDK database, and analysed according to international standards (4).

All IVDK members are also members of the German Contact Dermatitis Research Group (DKG). Patch testing and evaluation of reactions is performed according to DKG guidelines (5, 6). For the present data analysis, patch test reactions at day 3 (D3) were considered. In a few exceptional cases, when a patch test reading was performed on day 4 instead of D3, this reading was selected. Readings coded as +, ++ or +++, i.e., positive reactions with erythema, infiltration, papules and/or (coalescing) vesicles, were rated as positive.

Data was managed and analysed using the statistical analysis software SAS©, version 9.4 (SAS Institute, Cary, NC, USA). Literature was found in the library of the IVDK or by using Pubmed and Google.

Results

Patch test results in consecutive patients

IVDK data

Thymol was never part of a DKG test series and was therefore tested in individually selected patients only.

Literature review

Menighini et al. reported patch testing of consecutive patients visiting a dermatological department in Bari, Italy in 1971 (7). In this publication, the maximum non-irritating dose for thymol was 5% in petrolatum as ascertained in 50 healthy individuals. Patch tests were finally performed with thymol 1% in petrolatum in 290 patients with contact, stasis, atopic, seborrheic, nummular and other forms of dermatitis. All patients had a negative test outcome. In another publication of the same group in 1970, 100 consecutive patients were patch tested with 1% in petrolatum; all tests were negative (8). However, it is unclear whether these patients were also contained in the beforementioned publication (7) and data will therefore not be considered.

Patch testing of 1200 Italian contact dermatitis patients with 1% thymol in petrolatum as part of a multicentre study on fragrance allergy in 1983/1984 did not elicited any (0%) positive reaction (9).

Patch test results in selected patients

IVDK data

Test results are summarized in table 1.

Table 1. Patch test results with thymol in selected patients.

Years	test preparation	tested (n)	+	++	+++	?	ir	neg	% pos
1990-1999	1% pet.	416	1	0	0	1	0	414	0.2%
1990-1999	1% alc.	240	16	1	0	6	5	212	7.1%
2000-2021	1% pet.	231	0	1	0	0	0	230	0.4%

pet, petrolatum; alc, alcohol; reaction scores: +, weak positive; ++, strong positive; +++, extreme positive; ?, questionable; ir, irritant; neg, negative; % pos, percent positive.

From 1990 to 1999, thymol was patch tested 1% in petrolatum in 416 patients, and one patient had a weak positive reaction (1/416 = 0.2%). In the same period of time, another test preparation (1% in alcohol) was tested in 240 different patients and showed 17 positive reactions (17/240 = 7.1%) in addition to 6 questionable and 5 irritant reactions. In the years 2000 – 2021, thymol 1% in petrolatum was tested in 231 patients, which led to a strong positive reaction in 1 patient (1/231 = 0.4%).

Literature review

In a German article published by Dohn in 1980, 1 of 221 (0.45%) patients of a dermatologist's practice with suspected contact dermatitis and who were not employed in handicraft or factories showed a positive reaction to thymol 1% in petrolatum (10).

In a Japanese single centre study, of 365 patients patch tested with a cosmetics series from 1978 to 1986, 2 (0.5%) had a positive reaction to 1% thymol (11).

In 1966, Djerassi and Berowa published patch test results of 300 workers in a stomatology office in Sofia, Bulgaria (12). They found 39 patients (13 %) with positive reactions to thymol 5% in glycerol. Patch test reading criteria were different from the today's largely standardized patch test method. Positive patch test reactions were defined as 'hyperaemia, blistering, possibly necrosis' (translated from German language). Hence, questionable (erythema) reactions as well as clear-cut irritant or even toxic reactions were judged as "positive", which leads to an overestimation of positive reactions. Unfortunately, more detailed information on the reaction strength was not given by the authors.

In another Bulgarian study from 1990, of 84 contact dermatitis patients employed as dentist personnel, a dental nurse of (1.2%) was patch test positive to 1% thymol in petrolatum (13).

In a single centre study from the Netherlands published in 1987, over a 10-year period, 16 patients with an allergic contact dermatitis reaction to Hirudoid® cream, which contained 0.1% thymol, were investigated (14). Most patients used Hirudoid® on inflamed skin to treat chronic venous insufficiency of their legs. In seven patients, 3-(hydroxy-ethyl)-5-methyl-8-(2-methyl-ethyl)3,4-dihydro-2H-1,3-benzoaxine, which is a reaction product of thymol and 2 degradation products of 1,3,5-trihydroxyethylhexahydrotriazine, was identified as the culprit allergen. Thymol 1% in petrolatum was patch tested in 7 patients and all showed negative reactions. In one Japanese case of allergic contact dermatitis to Hirudoid® cream, thymol was patch test positive (15).

Thymol was identified as culprit allergen in one American patient with contact dermatitis to Listerine® (16). Sensitization was acquired by prolonged and occlusive skin contact when treating a paronychia and the patch test reaction to thymol 1% in petrolatum was strong (++). However, short-term oral contact to Listerine® was still tolerated by the patient.

In a case of an Italian woman with chronic paronychia, 4% thymol in chloroform was used as treatment (17). She subsequently developed an eczema reaction. The patch test to chloroform was negative, whereas thymol 1% in petrolatum provoked a strong (++) reaction.

In a study from Belgium, of 127 patients who reacted to pharmaceutical preparations between 1978 and 2008, thymol was identified as clinically relevant allergen in 1 patient (0.8%) (18).

In several other small case series, i.e.with 79 Canadian patients with eyelid dermatitis (19), 54 Italian patients with suspected contact dermatitis to toothpastes (20) and 20 patients with perfume dermatitis (21) as well as in a case report of a sawmill worker with occupational dermatitis to cedar wood (22), no positive reactions to thymol were noticed.

Discussion

Thymol appears to be a weak sensitizer which needs prolonged (occlusive) application on pre-damaged skin to be a sensitizer, as already concluded from leg dermatitis patients investigated by Fisher in 1989 (16). The same impression arose from the above-mentioned Italian case of the patient who had used a thymol-containing topical medicament on pre-damaged skin (17). This is in line with animal data, which generally showed no sensitizing effects of thymol. The one exception was a study, in which the skin irritant SLS was used as adjuvant for induction of sensitization in a guinea pig maximization test (3). However, high – almost irritant – concentrations of thymol were still required for both, induction and elicitation.

Ideally, a diagnostic patch test should be either positive (indicating contact sensitization in allergic patients) or negative. However, in real life, it also elicits unwanted reactions. These are clear-cut irritant reactions as well as doubtful reactions with erythema only (coded as "?"). The latter may indicate skin irritation or a weak sensitization.

The patch test concentration of thymol 1% in petrolatum seems to be adequate for diagnostic purposes. Concerning IVDK data from 1990 to 2021, positive reactions outnumbered questionable and irritant reactions. Irritant reactions were not seen in over 600 patients tested with this test preparation (table 1). In two rare cases of plausible sensitization to thymol, clear-cut positive (++) reactions were observed (16, 17).

In contrast, the preparation thymol 1% in alcohol lacks discriminatory power (table 1). It produced many irritant and questionable responses and a high share of weak (+) positive reactions. This barrage of reactions should be interpreted as rather non-specific. Therefore, thymol 1% in alcohol seems to be an inadequate diagnostic agent and was omitted from our analysis.

Similarly, data obtained with thymol 5% in glycerol should also not be considered (12). The concentration of 5% was shown to be the maximum non-irritation dose in another study (7). The occlusive use of glycerol as vehicle may be additionally irritating. Furthermore, as already addressed above, the applied reading criteria introduced another bias towards false-positive reactions. Hence, only patch test results obtained with thymol 1 % in petrolatum were used for our consolidating analysis in the following paragraph.

No positive patch test reaction to thymol 1% in petrolatum was documented in 1490 consecutive patients [95%-confidence interval, 0.0 - 0.3] (7, 9). As expected, reaction frequencies to thymol in selected patients were slightly higher and ranged from 0.0% to 0.8% in several case series (10, 11, 18-21). These studies sum up to a reaction frequency of 4/866 = 0.5% [95%-confidence interval, 0.2 – 1.2]. In addition, a few (n < 100) single cases with clinically relevant allergic reactions to thymol were reported in the literature (14-17).

Conclusion

In our opinion, the available clinical-epidemiological data on skin sensitization to thymol, based on several hundred patients, are sufficient for sub-categorization. According to the guidance of the application of the CLP criteria (Version 5.0 – July 2017), the frequencies of sensitization to thymol in all sub-categories considered (i.e., consecutive and selected patients, case reports) were found to be very low by analysis of IVDK data and the scientific literature, even if 95% confidence intervals are

considered. Therefore, from the clinical-epidemiological point of view, it is not adequate to just allocate category 1 to thymol. We suggest to assign the lowest category for skin sensitizers available to thymol, which is category 1B.

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