

Differences in contents of organochlorine impurities do not influence responses to patch testing with Majantol[®]

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Summary

Background. Majantol[®] [2,2-dimethyl-3-(3-methylphenyl)propan-1-ol; CAS no. 103694-68-4] has been identified as a contact allergen in humans, despite the lack of sensitizing properties according to animal tests. The question was raised of whether impurities, specifically organochlorines, in Majantol[®] might have been the reason for positive patch test reactions in the past.

Objectives. To assess the allergenic potential in terms of elicitation via patch testing with a standard market-quality version of Majantol[®] ('normal') with a normal content of organochlorine impurities, as compared with an ultra-purified version of Majantol[®] ('pure'), without detectable organochlorine impurities.

Methods. Between 1 October 2013 and 31 December 2014, two different Majantol[®] patch test preparations of the above-mentioned quality were tested 5% pet. in parallel in the 'monitor series', that is, together with the baseline series, in 8005 consecutive patients from 33 departments of dermatology of the Information Network of Departments of Dermatology (IVDK).

Results. Fifty-three of 7740 [0.69% (95%CI: 0.51–0.87)] patch tested patients reacted to at least one Majantol[®] preparation. The majority (n = 32) (60.4%) reacted to both preparations, 13 (24.5%) reacted to the 'normal' version only, and 8 (15.1%) reacted to the 'pure' version only. There was good concordance between results [Cohen's kappa 0.75 (95%CI: 0.65–0.85)], and there was no significant difference in frequency or intensity between the two preparations. More doubtful or irritant reactions than positive reactions were observed, and > 80% of all positive reactions were weak positive.

Conclusion. Organochlorine impurities are very probably not the cause of allergic reactions to Majantol[®].

Key words: 2,2-dimethyl-3-(3-methylphenyl)propan-1-ol; allergic contact dermatitis; CAS no. 103694-68-4; clinical epidemiology; Majantol[®].

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Majantol[®] is a registered trademark substance from Symrise (Holzminden, Germany) (Fig. 1), and was introduced onto the market as a synthetic fragrance ingredient in the late 1980s. In a worldwide multicentre investigation in highly selected patch test populations, Larsen et al., by patch testing fragrance-sensitive volunteers (n = 167 and n = 217), detected 16 patients who were allergic to Majantol[®] (1, 2). In further clinical studies, Majantol[®] was confirmed to be a contact allergen: In 2007, Schnuch et al. found a prevalence of sensitization of 0.5% (95%CI:

0.3–0.7%) by patch testing with Majantol® 5% pet. in 6573 consecutive patients between July 2003 and June 2005 (3), and, in 2009, Heisterberg and Johansen reported that 6 of 722 [0.83% (95%CI: 0.17–1.49%)] patch tested patients reacted positively to Majantol® 5% pet. (4). Between 2005 and 2008, Majantol® was tested by departments of the Information Network of Departments of Dermatology (IVDK) in the monitor series (i.e. in consecutive patients; $n = 2189$) and in a specific fragrance series ($n = 4974$), and 0.36% (95%CI: 0.12–0.60%) and 0.76% (95%CI: 0.49–1.03%) positive reactions, respectively, were observed (5). In a multicentre study in Sweden ($n = 1075$), Lindberg et al. tested, among others, a study-specific fragrance mix (TF2), which contained Majantol® at 1%, and 1.1% of patients reacted positively (6). Unfortunately, breakdown testing of positive reactions to the mix was not performed. In all, the finding of 0.5–1% positive reactions in patch tested patients supports the notion of standard Majantol® being a skin sensitizer in humans.

In contrast, the results of predictive animal tests and human repeated insult patch testing were predominantly negative, and led to the conclusion at the time that Majantol® is not a skin sensitizer. Specifically, guinea-pig maximization tests did not indicate skin sensitization; however, they were not performed according to current guidelines, as the topical induction and elicitation doses were identical (Table 1). Furthermore, several local lymph node assays (LLNAs) were performed with various samples over the years, and, overall, no skin sensitization potential was identified. In particular, a LLNA with a recent production sample, performed according to the latest guidelines, and with a maximum dosage of 100%, did not show sensitizing effects (Table 1). In 2005, a human repeated insult patch test (HRIPT) with 10% Majantol® in diethyl phthalate (DEP)/ethanol (eth.) (3:1), equating to $\sim 5500 \mu\text{g}/\text{cm}^2$, did not show induction of contact allergy in 28 male and 75 female volunteers. However, 1 individual seems to have had pre-existing hypersensitivity, and for 1 individual inconclusive reactions were observed. Another HRIPT in 2007 with 18% Majantol® in DEP/eth. (3:1), equating to $\sim 9900 \mu\text{g}/\text{cm}^2$, tested on 28 male and 70 female volunteers, showed a similar result, with 1 individual probably having pre-existing hypersensitivity, and 1 individual showing increasing reactions at the site of application. In contrast to the test performed in 2005, a series of rechallenges were performed, and these led to the conclusion at the time that the reactions were 'idiosyncratic' and that no induction of contact allergy had occurred (7).

In addition to the negative *in vivo* preclinical results, *in vitro/in silico* considerations indicate no direct sensitizing properties, as the main chemical structure of an aryl alkyl alcohol does not raise any direct structural concerns [OECD QSAR Toolbox (8)].

In view of the discrepancies between the observations in patients and in animals, a working hypothesis was established that centred around the presence of organochlorine impurities as the possible cause of a sensitizing effect. A base material in the production of Majantol® is a benzyl chloride derivative that yielded an EC3 value of 0.6% in a LLNA (Symrise, 2009) (Fig. 1). In addition, other organohalides, such as 1-chloromethyl-4-nitrobenzene (CAS no. 100-14-1), benzylbromide (CAS no. 100-39-0), and 1-bromomethyl-4-nitrobenzene (CAS no. 100-11-8), had been identified as highly potent sensitizers, with EC3 values between 0.05% and <1% (9, 10).

The organochlorine base material and/or further reaction products thereof were apparently more abundant in the finished marketed material during the early days of production of Majantol®. However, from around 2000, the production process was changed, and the presence of organochlorine impurities was significantly reduced. It was hypothesized that people might have been primarily sensitized by such impurities in the past, and that reactions were now elicited by the lower levels of such impurities within today's Majantol®. However, the possibility cannot entirely be excluded that impurities that are still present even after modifications to the synthesis process are sufficient to sensitize people currently. The discussion around organochlorine impurities in Majantol® had led to a purity standard for CAS no. 10694-68-4, 2,2-dimethyl-3-(3-methylphenyl)propan-1-ol by the International Fragrance Association (IFRA) of 25 ppm (chlorine content) in 2010 (11). In order to elucidate the assumed role of impurities in causing allergies to Majantol®, a standard market-quality Majantol® containing low levels of organochlorine impurities was tested in parallel with an ultra-pure version, which was almost completely free of organochlorine impurities. Our hypothesis was that patients reacting to 'normal' Majantol® preparations would not react to the 'pure' Majantol® preparation, or at least would react to a lower degree.

Materials and Methods

The multicentre project IVDK is an instrument of epidemiological surveillance of contact allergy, and has been described in detail elsewhere (12). Patch tests are performed in accordance with the recommendations of the

Fig. 1. Reaction scheme of Majantol®, showing three molecules within the production process, alongside their respective EC3/stimulation index (SI) values obtained in local lymph node assays.

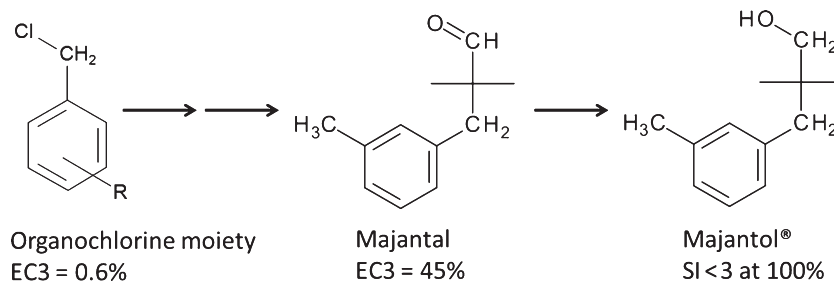


Table 1. Overview of experimental animal test data for various Majantol® samples

Test type	Year	Test sample	Purity (%)	Vehicle	Test concentrations (%)	Results
GPMT	1985	Pilot Manufacturer 1	98	80% ethanol	5–5–5	0/20
GPMT	1987	Production Manufacturer 1	99.2	Peanut oil	5–1–1	0/20
LLNA	2002	Production Manufacturer 1	99.7	AOO (4:1)	3–10–30	1.47–1.30–3.07
LLNA	2002	Pilot Manufacturer 2	98.9	AOO (4:1)	3–10–30	1.29–1.56–2.44
LLNA	2008	Production Manufacturer 2	98.9	AOO (4:1)	25–50–100	1.19–1.38–1.44
LLNA	2008	Purified Sample Manufacturer 2	99.9	AOO (4:1)	25–50–100	1.76–1.47–2.20

Guinea-pig maximization tests (GPMTs) are shown as ratio of animals reacting during the elicitation phase, and local lymph node assays (LLNAs) as stimulation indices for the respective concentrations tested. AOO, acetone–olive oil mixture.

ICDRG (13) and the German Contact Dermatitis Research Group (DKG) (14). Patch test material is obtained from Hermal/Trolab (Reinbeck, Germany). Patch test preparations are applied for 24 or 48 h. Readings are performed until at least day (D) 3, according to the following grading based on international standards (15), further refined by the DKG (12): negative, ?, +, ++, +++, irritant, and follicular. The patch test results of every reading, a standardized history [including age, sex, atopic diseases, current and former occupation(s), and presumptive causal exposures] and final diagnoses and site(s) of dermatitis are documented. All data are transferred to the data centre in Göttingen in an anonymized format every 6 months. After a quality check, data from departments fulfilling the quality requirements (16) are pooled and analysed.

Two versions of 2,2-dimethyl-3-(3-methylphenyl)propan-1-ol (CAS no. 103694-68-4, trade name Majantol®, produced by Symrise), were tested. One sample was a standard market-quality version that is used as a fragrance ingredient, with a purity of 99.2% and with a level of organochlorine impurities of 11 ppm, that is, well within the limits set by the IFRA purity standard. The other sample was a specifically prepared ultra-pure version thereof, with a purity of 99.9% and a level of organochlorine impurities of <2 ppm. This value represents the limit of detection of the method used to detect organochlorine moieties. Two patch test preparations with 5% Majantol® of different purity ('normal'

and 'pure') in pet. were manufactured and provided by Almirall/Hermal (Reinbeck, Germany).

For the present analysis, data of all patients who were patch tested between 1 October 2013 and 31 December 2014 with the two patch test preparations of Majantol® of differing purity were initially included (n = 8005, from 33 departments of the IVDK).

For description of the demographic characteristics of the patch tested patients, the MOAHLEA index was used. MOAHLEA is the acronym for male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis, and age ≥40 years (17).

Frequencies of sensitization (as percentage of patients tested) were calculated as crude proportions (%). The concordance of reactions to both Majantol® preparations was calculated, accompanied by a 95% confidence interval (CI). Patients who reacted to at least one Majantol® preparation were analysed for concomitant reactions (crude proportions, and proportions standardized for sex and age). The reaction index (RI) and the positivity ratio (PR) were calculated as summary measures to describe reactivity to the patch test preparations. The RI was calculated on the basis of all allergic reactions versus all non-allergic reactions according to the formula given by Brasch and Hensler (18), and ranges from +1 (all reactions allergic) to –1 (all reactions non-allergic). The PR is the proportion of + reactions among all allergic (+/++/+++ reactions) (19). A very high PR (e.g. >80%) indicates many weak (+) and only a few stronger (++/+++ reactions). Together

with a negative RI (more non-allergic than allergic reactions), this indicates that the patch test preparation may be regarded as 'problematic', with, e.g., the possibility of an unknown number of false-positive reactions. Statistical analysis and data management were performed with SAS software (SAS 9.3; SAS Institute, Cary, NC, USA), following pertinent guidelines (20).

Results

Seventy-two of 8005 (0.9%; 95%CI: 0.69–1.11%) patch tested patients reacted to at least one Majantol® patch test preparation. The majority (n = 42; 58.3%) reacted to both preparations, 17 (23.6%) reacted to the 'normal' preparation only, and 13 (18.1%) reacted to the 'pure' preparation only. There was good concordance between results (Cohen's kappa 0.71; 95%CI: 0.65–0.76). However, the prevalence of sensitization differed considerably between departments, ranging from 0% to nearly 8% (Fig. 2). When the numbers from those two departments (n = 265 patients) with significantly deviating patch test results were excluded (as shown in Fig. 2 and below), the frequency of reactions to at least one preparation decreased slightly, but not significantly, to 53 of 7740, that is, 0.69% (95%CI: 0.51–0.87%) (Tables 2 and 3). Excluding the data from those two departments did not significantly change the frequency of concordant reactions [Cohen's kappa 0.75 (95%CI: 0.65–0.85)].

Concomitant reactions to other allergens in patients who reacted to at least one Majantol® preparation were analysed. The two departments (n = 197 and n = 68) with extremely high Majantol® figures (7.6% and 5.9%) were also distinguished by a deviating pattern of concomitant reactions. For instance, octyl gallate (48.1%, the most frequent concomitant reaction), Amerchol L101® (16.3%) and propylene glycol (12.4%) belonged to the list of most frequent concomitant allergens in these departments, but were not present in the list of commonly co-reactive allergens in the remaining departments (Table 4). These aforementioned patch test preparations are known to frequently cause irritant reactions, which are easily misinterpreted as allergic. Hence, a deviation of the standards of patch test reading was assumed, and results were further analysed after exclusion of these two departments, regarding the concordance of Majantol® reactions, the frequency of sensitization to Majantol®, and the pattern of concomitant reactions (Table 4). The first six allergens of the list of those co-reacting with Majantol® are related to fragrances. The most frequent associations with Majantol® positivity were seen with *Cananga odorata* (ylang-ylang oil) and fragrance mix I, with 43% and 37.5% positive reactions, respectively.

Table 2. Patch test reactions to two Majantol® preparations of differing purity in patients tested with both preparations in parallel (n = 7740)

'Normal' Majantol®	'Pure' Majantol®		
	Negative/?/irritant	Positive	
Negative/?/irritant	7687	8	7695
Positive	13	32	45
	7700	40	7740

A kappa value of 0.75 (95%CI: 0.65–0.85) indicates good concordance between the preparations despite differing purity. Reactions to both materials, 32/53 (60.4%); reactions to 'normal' only, 13/53 (24.5%); and reactions to 'pure' only, 8/53 (15.1%).

The reaction profiles, namely the number of ?, + to +++ and irritant reactions to both preparations, are shown in Table 3. The PR and the RI of pure Majantol® were calculated as 82.5% (95%CI: 67.2–92.7%) and –0.45 (95%CI: –0.60 to –0.31), respectively. For normal Majantol®, the PR was 82.2% (95%CI: 67.9–92.0%) and the RI was –0.45 (95%CI: –0.59 to –0.31), indicating, in both cases, 'problematic' patch test preparations (17). The number of ? and irritant reactions exceeding the number of allergic reactions (resulting in a negative RI) and a high number of only + reactions as compared with all positive reactions (PR > 80%) may indicate the potential for false-positive reactions. Analysis of the PR and RI separately for the two departments that were excluded from the overall evaluations (clinics 16 and 69) showed a shift to allergic + reactions at the expense of ? and irritant reactions, as compared with the above data ['pure' Majantol®, PR = 93.3% (95%CI: 68.1–99.8%) and RI = –0.17 (95%CI: –0.49 to +0.16); and 'normal' Majantol®, PR = 92.9% (95%CI: 66.1–99.8%) and RI = –0.24 (95%CI: –0.56 to +0.07)]. Considering the strength of the reactions in more detail (Table 3), the majority (n = 25) of concordant reactions to both samples were +. Six patients showed ++ reactions to both samples, and 1 patient showed +++ reactions. The remainder (n = 21) were discordant allergic reactions (n = 20, +; n = 1, ++). Overall, the strength of reactions did not differ between the two samples.

The MOAHLFA index was used to describe the patch test population and the subgroup of patients reacting positively to Majantol® (Table 5). Overall, the populations did not differ with regard to the MOAHLFA index, except for leg dermatitis, which showed a significant difference of 22.6% (95%CI: 11.3–33.9%) versus 10.2% (95%CI: 9.5–10.9%).

Discussion

The present study confirms the sensitizing potential of Majantol®, with a prevalence of positive patch test

Fig. 2. Prevalences of positive reactions to Majantol® in the Information Network of Departments of Dermatology departments taking part in the study.

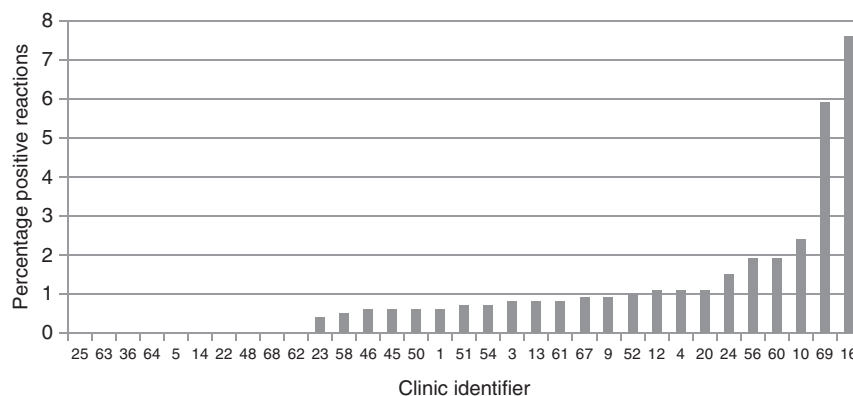


Table 3. Reaction profile of two patch test preparations of different Majantol® samples, excluding data from two departments with exceptionally high prevalences (see text)

'Normal' Majantol®	'Pure' Majantol®						Total
	Negative	?	+	++	+++	Irritant	
Negative	7544	22	5	0	0	6	7577
?	30	49	2	0	0	0	81
+	9	2	25	0	0	1	37
++	0	1	0	6	0	0	7
+++	0	0	0	0	1	0	1
Irritant	11	0	1	0	0	25	37
Total	7594	74	33	6	1	32	7740

The positivity ratio (PR) and the reaction index (RI) were calculated as PR = 82.5% [95%CI: 67.2–92.7%] and RI = –0.45 [95%CI: –0.60 to –0.31] for 'pure' Majantol®, and as PR = 82.2% [95%CI: 67.9–92.0%] and RI = –0.45 [95%CI: –0.59 to –0.31] for 'normal' Majantol®.

reactions in the range of 0.5–1% (1–5). However, the main question of this study was whether different contents of potent sensitizing organohalides regarded as impurities in Majantol® would result in different reaction frequencies when Majantol® preparations were patch tested. The high concordance of reactions to the two preparations indicates that impurities, and specifically organochlorine ones, are very unlikely to be the reason for allergic reactions to Majantol®, at least at the low levels present in the two preparations tested. Thus, the purity required by the IFRA Standard apparently ensures that organochlorine moieties are not of concern with regard to skin sensitization.

Another possible explanation for the allergenicity would be the conversion of Majantol® to its respective aldehyde, Majantal (CAS 107737-97-3 alpha, alpha,3-trimethyl-Benzenepropanal) in the skin (21). In this case, Majantol® would be considered as a prohaptent, and Majantal as the actual haptent. Majantal itself is a weak sensitizer, according to its EC3 value of 45% determined with the LLNA (Symrise, 2008, unpublished data; see also Fig. 1). However, a prerequisite for the validity of this theory would be substantially different metabolic conversion and reactions

between mice and humans, given that Majantol® itself proved to be negative in the LLNA. There are some rare examples where similarly predictive animal testing (such as the LLNA) gave negative results but clinical observations identified cases of skin sensitization, such as to propylene glycol (22), monoethanolamine (23), benzyl alcohol (24, 25), kanamycin (26–28), or hydrocortisone (26–28).

Patients sensitized to Majantol® were frequently characterized by concomitant leg dermatitis. Leg dermatitis is a risk factor for acquiring contact allergy, and a typical characteristic in patients who are sensitized to weak allergens such as lanolin or parabens (29). At a molecular–mechanistic level, pre-existing dermal inflammation is thought to deliver 'danger signals' enhancing the process of sensitization (30). All of the other parameters of the MOAHLFA index were inconspicuous when patients who reacted to Majantol® were compared with those who did not react.

Patch test reactions to both Majantol® preparations showed the pattern of a 'problematic' patch test preparation: the negative RI indicated more questionable/irritant than allergic reactions, and a PR of >80% indicated that the number of stronger allergic reactions was limited.

Table 4. Concomitant reactions in Majantol®-positive patients (after exclusion of the results of two departments; see text)

Allergen	n tested	n positive	Crude % positivity (95%CI)	Standard % positivity (95%CI)
Ylang-ylang (I + II) oil	51	20	39.2 (25.8–53.9)	43.0 (26.5–59.5)
Fragrance mix I	49	17	34.7 (21.7–49.6)	37.5 (21.1–53.9)
<i>Myroxylon pereirae</i>	50	17	34.0 (21.2–48.8)	33.0 (17.7–48.2)
Colophony	51	16	31.4 (19.1–45.9)	31.0 (15.5–46.6)
Sandalwood oil	51	14	27.5 (15.9–41.7)	32.9 (16.7–49.1)
Fragrance mix II	51	13	25.5 (14.3–39.6)	28.1 (12.7–43.5)
Propolis	51	8	15.7 (7.0–28.6)	15.5 (4.2–26.8)
Oil of turpentine	51	7	13.7 (5.7–26.3)	15.8 (3.4–28.2)
Compositae mix II	51	7	13.7 (5.7–26.3)	15.7 (2.7–28.6)
Nickel(II) sulfate 6H ₂ O	50	6	12.0 (4.5–24.3)	15.3 (2.2–28.3)
Thiuram mix	51	4	7.8 (2.2–18.9)	11.9 (0 to 24.2)
Paraben mix	51	5	9.8 (3.3–21.4)	11.3 (0 to 22.7)
Jasmin absolute	51	6	11.8 (4.4–23.9)	9.3 (1.8–16.9)
Cocamidopropyl betaine	38	5	13.2 (4.4–28.1)	9.2 (1.8–16.7)
Woolwax alcohols	51	5	9.8 (3.3–21.4)	8.2 (0.9–15.5)
Cetylstearyl alcohol	51	4	7.8 (2.2–18.9)	5.7 (0.3–11.2)

Frequency of sensitization (%) is given as crude proportions, standardized for sex and age, and accompanied by a 95% confidence interval (CI).

Table 5. MOAHLFA index of patients with allergic patch test reactions to at least one of the Majantol® preparations (n = 53) and of patients with negative reactions (n = 7544), out of a total of 7740 patients tested, the remainder showing non-allergic reactions

	Positive (%) n = 53	Negative (%) n = 7544
M Men	45.3	37.6
O Occupational	13.2	18.0
A Atopic dermatitis	22.6	23.6
H Hand dermatitis	26.4	32.1
L Leg dermatitis	22.6	10.2
F Face dermatitis	18.9	17.0
A Age ≥ 40 years	71.7	71.9

Significant difference in bold type.

Therefore, an unknown number of e.g. false-positive reactions may be expected, putting into perspective the frequency of sensitization to Majantol®. Sensitization risk is probably comparable to that of eugenol (25). An analysis of the reaction profiles from the two departments excluded from the overall assessment showed a shift to allergic + reactions at the expense of ?+ and irritant reactions, as compared with the data from the remaining departments. This very probably indicates a larger proportion of false-positive reactions being documented in these two departments. Together with higher frequencies of sensitization and an implausible pattern of concomitant reactions, deviations in patch test reading practice in these two departments can be assumed. Therefore, these departments were excluded from further analyses of IVDK data for this study.

Concomitant reactions to other allergens in Majantol®-positive individuals were most often related to other fragrance ingredients. Contact allergy to Majantol®

was most often associated with positive reactions to *C. odorata* (ylang-ylang oil) (43%) and fragrance mix I (38.5%). Generally, concomitant reactions can occur as cross-reactions between structurally related molecules. In the case of Majantol®, however, no striking structural similarities to the known single compounds of *C. odorata* extract, especially those known to be skin sensitizers, are discernible. Likewise, no such similarities to the components of fragrance mix I exist. An alternative explanation for concomitant reactions is co-exposure (simultaneous or successive). Uter et al. analysed the co-occurrence of 26 fragrance allergens (to be labelled according to the EU Cosmetics Regulation), and found that, for example, fine fragrances (such as Eau de Toilettes) contained up to nine different fragrance allergens among those 26 that had to be labelled (31). Hence, it is no surprise that, in former studies, a high degree of co-reactivity between different fragrance patch test preparations was a common finding (32–34), and Majantol® is most probably no exception.

Conclusions

1. There was no detectable difference between a standard market-quality Majantol® preparation with ~11 ppm organochlorine impurities and an ultra-pure preparation that had no detectable organochlorine impurities (limit of detection of 2 ppm) with regard to the frequency and intensity of reactions in Majantol®-allergic patients. Hence, allergic reactions to Majantol® are probably caused by the molecule itself (or a presumptive metabolite),

but not by impurities, at least not at the low levels present in the standard market-quality preparation tested in this study.

2. The importance of clinical surveillance for risk identification and the support of risk management is again highlighted, as preclinical hazard identification by animal testing failed in this instance.
3. The reasons for non-responses in mice (as shown in the LLNA) and observed human sensitization to Majantol® still need to be elucidated.

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