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ORIGINAL ARTICLE

The epidemic of methylisothiazolinone contact allergy in Europe: follow-up on changing exposures

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Abstract

Background Methylisothiazolinone (MI) has caused an unprecedented epidemic of contact allergy in Europe and elsewhere. Subsequently, regulatory action has been taken, at least in Europe, aiming at reducing risk of MI sensitization.

Objective To follow-up on the prevalence of contact allergy to MI in consecutively patch tested patients and assess the spectrum of products containing MI or methylchloroisothiazolinone (MCI)/MI in patients positive to MI which elicited current allergic contact dermatitis.

Methods A cross-sectional survey was performed in 2016 and 2017, including all adult patients patch tested with the baseline series (including MI 0.2% aq.) between 1 May and 31 October at 14 centres in 11 European countries. Patients with positive reactions (+ to +++) to MI were further examined regarding history, clinical characteristics and eliciting products, which were categorized into 34 types and 4 classes (leave-on, rinse-off, household, occupational). The results were compared with the reference year 2015.

Results A total of 317 patients, $n = 202$ of 4278 tested in 2016 (4.72%) and $n = 115$ of 3879 tested in 2017 (2.96%), had positive reactions to MI; the previous result from 2015 was 5.97% ($P < 0.0001$). The share of currently relevant contact allergy among all positive reactions declined significantly as well ($P = 0.0032$). Concerning product classes, a relative decline of leave-on and a relative increase of rinse-off and household products was noted.

Conclusion The prevalence of MI contact allergy decreased by 50% from 2015 to 2017. As a consequence of regulation, the share of cosmetics products (leave-on in particular) eliciting allergic contact dermatitis is decreasing. The chosen method of analysing causative products in sensitized patients has proven useful to monitor effects of intervention.

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Conflicts of interest

W.U. has accepted honoraria for presentations on contact dermatitis from mixed dermatopharmaceutical sponsors and the Paul Ehrlich Institute and travel reimbursement for workshop attendance from cosmetic industry associations. KEA is medical advisor for SmartPractice, Hillerød, Denmark. CF has accepted honoraria

for participation in advisory boards from Abbvie and Sanofi and travel reimbursement from Novartis. AGA is medical advisor for Uriach Pharma, Genentech, Novartis, FAES, GSK, Sanofi, and received research grants supported by Uriach Pharma, Novartis, Grants from Instituto Carlos III-FEDER and for educational activities for Uriach Pharma, Novartis, Genentech, Menarini, LEO PHARMA, GSK, MSD, Almirall, Sanofi. MG participated in advisory boards and received lecture fees by Novartis, Sanofi-Genzyme and Abbvie. TR has accepted honoraria for presentations on contact dermatitis and immunology from Hollister, Leo Pharma, ALK Abello, Novartis and Sanofi-Genzyme and has received research grants from SmartPractice, Cosmetic Europe, DermaSun and Sanofi-Genzyme.

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Introduction

The use of preservatives is essential to render cosmetic and other water-based products resistant to microbial growth, avoiding subsequent health risks and enabling prolonged shelf life. However, as by definition, preservatives are biologically active, they are usually also contact allergens (haptens). This has been proven by repeated epidemics following introduction and subsequent broad use of a given preservative, first index cases of allergic contact dermatitis (ACD) and then a veritable epidemic of various sizes, before withdrawal or ban eventually resulted in a decline.[1] The most recent example of such an epidemic – to methylisothiazolinone (MI) – was unprecedented in terms of the incidence of ACD in those having been exposed to cosmetic, but also household and some other types of products containing MI.[2] As a consequence, after acknowledging the problem, industry (Cosmetics Europe) recommended not using MI in leave-on cosmetics in late 2013. At the same time, risk was reassessed by the Scientific Committee on Consumer Safety (SCCS), resulting in the recommendation to ban the use of MI in leave-on cosmetics and restrict the maximum permissible level to 15 ppm in rinse-off cosmetics.[3,4] While this recommendation took time to translate into actual regulation, and regulation again allowed for transition periods, it can be assumed that regulations will change exposure even before being fully effective. Hence, besides following up the prevalence (as a proxy of incidence) of MI contact allergy, the present audit assessed the pattern of exposure in consecutively patch tested patients found sensitized to MI. Results of a 'reference' year, 2015, have been published;[5] using an identical method, patients tested in the years 2016 and 2017, respectively, were assessed, the results being reported here, and, where appropriate, compared with 2015.

Methods

This prospective multicentre audit was conducted at 14 centres in 11 European countries following the design of the initial cross-sectional audit.[5] Moreover, a similar design had been used by a audit from Zagreb, Croatia, focusing also on follow-up after MI avoidance.[6] The two periods reported on now were from 1 May 2016 to 31 October 2016 and 1 May 2017 to 31 October 2017, respectively. Only patients with positive patch test reactions (reactions designated as +, ++ or +++) to 2000 ppm (0.2%) MI aq. were included (Table 1). Patch testing was performed according to guidelines of the European Society of Contact Dermatitis (ESCD).[7] The patch tests were applied to the upper back and occluded for 2 days. In most departments, readings were performed on day (D) 2, D3/D4 and D7. All patients were patch tested with the European baseline series. All centres used their usual routines and thereby different patch test systems (see Table 1 in[5]). Patch test results to MI (strength of positive reaction), to MCI/MI, selected relevant demographic and clinical characteristics and, foremost, types of cosmetic and other products containing MI or MCI/MI were documented. For this purpose, the MI-positive patients were asked to bring in all their cosmetic products, toiletries, cleaning products and products for occupational use that they had used to be screened for mentioning of MI or MCI/MI on the product label or safety data sheets, respectively. If a product was relevant for the present contact dermatitis, additional information, such as manufacturer and specific product name, was registered.

All data were anonymously recorded using an online documentation system implemented using a SoSci server (https://www.soscisurvey.de/en/index). At the end of the data acquisition period, data were extracted in a csv format and subsequently managed and analysed using the R statistical software package (version 3.3, https://www.r-project.org/, RRID:SCR_001905) according to pertinent guidelines.[8]

Results

A total of 317 patients, $n = 202$ of 4278 tested in 2016 (4.72%) and $n = 115$ of 3879 tested in 2017 (2.96%), had positive reactions to MI. The distribution across the departments and the (half) years, including the reference year, is shown in Table 1. Considering the prevalence of positive reactions in 2015, i.e. 5.97%, a significant downward trend of MI contact allergy was observed ($P < 0.0001$). Overall, the strongest reaction,

Table 1 Characteristics of contributing EECDRG departments. 2015 was the reference year; detailed results have already been reported[5]

Country	Department	2015			2016			2017		
		Tested	Pos.	(% pos.)	Tested	Pos.	(% pos.)	Tested	Pos.	(% pos.)
BE	Leuven	302	22	(7.3)	260	16	(6.2)	286	7	(2.4)
DK	Bispebjerg	241	12	(5)	260	3	(1.2)	230	2	(0.9)
DK	Gentofte	519	27	(5.2)	447	11	(2.5)	513	18	(3.5)
DK	Odense	257	15	(5.8)	297	18	(6.1)	259	9	(3.5)
FI	Helsinki	54	7	(13)	64	7	(10.9)	51	2	(3.9)
DE	Heidelberg	–	–	–	36	2	(5.6)	30	1	(3.3)
DE	Osnabrueck	–	–	–	161	7	(4.3)	172	4	(2.3)
IT	Bari	313	8	(2.6)	449	7	(1.6)	377	8	(2.1)
PT	Coimbra	177	15	(8.5)	168	19	(11.3)	182	24	(13.2)
ES	Barcelona	255	17	(6.7)	196	15	(7.7)	215	8	(3.7)
SE	Malmö	386	34	(8.8)	429	25	(5.8)	404	8	(2)
CH	Basel	–	–	–	79	5	(6.3)	–	–	–
NL	Amsterdam	–	–	–	964	43	(4.5)	658	8	(1.2)
UK	Leeds	404	21	(5.2)	468	24	(5.1)	502	16	(3.2)
UK	London	526	27	(5.1)	–	–	–	–	–	–
	Total	**3434**	**205**	**(6)**	**4278**	**202**	**(4.7)**	**3879**	**115**	**(3)**

Instead of MI 2000 ppm aq., exceptionally 500 ppm aq. was used in Osnabrück, as this was the only licensed test preparation in Germany.

considering D4 and D7, had been + in 39.1%, ++ in 45.1% and +++ in 15.8%.

Demographic characteristics, along the lines of the initial presentation,[5] are shown in Table 2. Overall 14.7% had widespread contact dermatitis, defined as involvement of more than three anatomical sites. Positive patch test reactions to MCI/MI 0.02% aq., tested in 246 patients, were seen in 176 (71.5%) of the MI-positive patients, with little difference between 2016 and 2017 results (71.7 vs. 71.3%). Onset of dermatitis (Fig. 1) was recent in the majority of cases, either in the same year the patch test was performed or the year before. This was particularly pronounced in the 2015 reference period. While positive reactions to other baseline series allergens were documented, there was no particular pattern discernible (data not shown).

The proportion of patients in whom current clinical relevance could be identified was 72.7% in 2015,[5] while in 2016, it was 57.4% and in 2017 58.3%. In absolute terms, the number of positive reactions and of relevant positive reactions, respectively, decreased significantly (Fig. 2). Relevance was mainly found concerning rinse-off and household products, and, to a lesser extent, leave-on cosmetics and occupational exposures (Table 3). Similar to the 2015 results, many patients were exposed not only to one product considered as cause of current allergic contact dermatitis (n = 85; 46.4%), but to two (n = 48; 26.2%), three (n = 20; 10.9%), four (n = 16; 8.7%) or more (n = 14; 7.7%) products.

Of the 183 patients in whom MI contact allergy was currently clinically relevant, and related to one or more products (see above), MI was identified on the product(s) label in 161 (88%) of the patients. In comparison, MCI/MI-containing products were (also) found in 75 (41%) of the patients positive to MI. In 55 patients (30.1%), both MI and MCI/MI-containing products

Table 2 Demographic and clinical characteristics of patients positive to MI (N = 317), stratified for years (for 2015 results see[5])

	2016	2017
Age (years), mean	44.1	47.6
1–30, *n* (%)	59 (29.2)	18 (15.7)
31–50, *n* (%)	61 (30.2)	49 (42.6)
>50, *n* (%)	82 (40.6)	48 (41.7)
Female sex, *n* (%)	151 (74.8)	80 (69.6)
Previous AD, *n* (%)	42 (20.8)	16 (13.9)
Current AD, *n* (%)	38 (18.8)	23 (20)
No present CD, *n* (%)	32 (15.8)	26 (22.6)
Anatomical site of CD, *n* (%)		
Widespread, *n* (%)	24 (13.1)	19 (17.4)
Hands, *n* (%)	103 (56.3)	58 (53.2)
Face (NEC), *n* (%)	61 (33.3)	36 (33)
Arms, *n* (%)	48 (26.2)	29 (26.6)
Trunk, *n* (%)	40 (21.9)	22 (20.2)
Axilla, *n* (%)	10 (5.5)	9 (8.3)
Eyelids, *n* (%)	31 (16.9)	16 (14.7)
Neck, *n* (%)	23 (12.6)	16 (14.7)
Legs, *n* (%)	30 (16.4)	24 (22)
Anogenital, *n* (%)	8 (4.4)	5 (4.6)
Feet, *n* (%)	16 (8.7)	12 (11)
Scalp, *n* (%)	8 (4.4)	4 (3.7)

AD, atopic dermatitis; CD, contact dermatitis; NEC, not elsewhere classified.

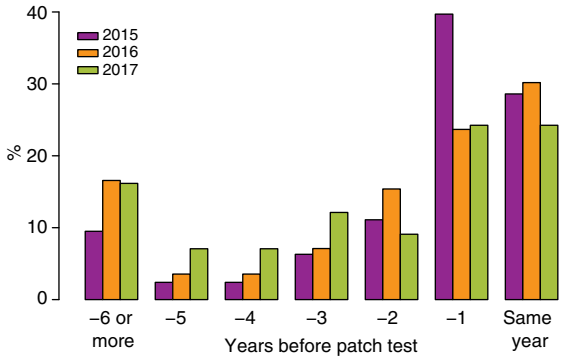

Figure 1 The year of onset of contact dermatitis in 332 patients with clinically relevant contact allergy to methylisothiazolinone. (missing data: $n = 44$). Year 2015 results have been published.[5]

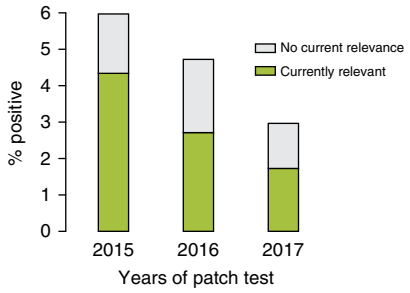

Figure 2 Prevalence of positive patch test reactions to methylisothiazolinone in the 3 audit years (light grey) and, among the positive reactions, share of currently clinically relevant reactions (green). The decline of currently relevant positive patch test reactions among all positive reactions was significant (Cochran–Armitage trend test: $P = 0.0032$), as was the decline in positive reactions (see text).

Table 3 Exposures to products – aggregated to four categories – containing methylisothiazolinone (MI) or methylchloroisothiazolinone/MI in 183 patients with currently relevant MI contact allergy

Product category	2016: *n* (%)	2017: *n* (%)
Number of patients with currently relevant MI contact allergy	116	67
Both leave-on and rinse-off cosmetic products	41 (35.3)	12 (17.9)
Rinse-off cosmetic products	38 (32.8)	34 (50.7)
Leave-on cosmetic products	15 (12.9)	6 (9)
Irrespective of cosmetics exposure:		
Household products	58 (50)	28 (41.8)
Paints or chemical products for occupational use	14 (12.1)	6 (9)

For better comparability with Table 4 in the reference audit:[5] in 2016, 16 (13.8%) and in 2017, 11 (16.4%) were exposed to household products, but not to cosmetic products.

were identified. In two additional patients, 'other' products, i.e. not included in above categories, were a source of MI exposure; in one, printing ink, in the other, a leather sofa. Among the 20 patients with relevant exposure to occupationally used products, there were 6 painters, 4 metal workers, 2 woodworkers and a variety of other single occupations ($n = 8$). Household products are an important source of MI or MCI/MI exposure (Table 3). Their relative importance increased from 28.2 in the 2015 reference year to 50% in 2016 and slightly decreased again to 41.8% in 2017. Table 4 shows a detailed breakdown of the product types identified to elicit allergic contact dermatitis in MI-allergic patients.

Altogether 38 of the 317 patients (12%) sensitized to MI reported symptoms after having been in freshly painted rooms: $n = 31$ developed dermatitis, $n = 6$ rhinitis, $n = 5$ conjunctivitis and $n = 4$ asthma-like symptoms. Beyond painted rooms, 16 patients reported airborne reactions to exposures other than paint, with a similar distribution of complaints to above; due to

Table 4 Exposures to domestic and occupational product types containing methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI)/MI in 317 European patients sensitized to MI

Product type	MI, *n* (%)	MCI/MI, *n* (%)
Shampoo	68 (21.5)	39 (12.3)
Dishwashing liquid	72 (22.7)	12 (3.8)
Liquid soap	33 (10.4)	16 (5)
Shower gel	34 (10.7)	12 (3.8)
Cleansing agent	28 (8.8)	13 (4.1)
Hair conditioner	17 (5.4)	12 (3.8)
Body cream/lotion	21 (6.6)	6 (1.9)
Paint	10 (3.2)	8 (2.5)
Hairstyling gel	10 (3.2)	6 (1.9)
Household cleansing spray	11 (3.5)	5 (1.6)
Face cream/lotion	13 (4.1)	1 (0.3)
Cream/lotion (unspecified)	7 (2.2)	3 (0.9)
Hand cream/lotion	7 (2.2)	3 (0.9)
Wet wipes	8 (2.5)	2 (0.6)
Sunscreen	7 (2.2)	1 (0.3)
Rinse-off (unspecified)	5 (1.6)	2 (0.6)
Glue	3 (0.9)	2 (0.6)
Hairstyling spray	4 (1.3)	0 (0)
Cutting fluid	4 (1.3)	0 (0)
Cream/lotion for feet	2 (0.6)	1 (0.3)
Make-up remover	1 (0.3)	2 (0.6)
Deodorant (unspecified)	1 (0.3)	1 (0.3)
Deodorant roll-on	1 (0.3)	1 (0.3)
Hairstyling product (unspecified)	1 (0.3)	1 (0.3)
Tinted make-up	1 (0.3)	0 (0)
Mouth wash	1 (0.3)	0 (0)
Shaving product	1 (0.3)	0 (0)

The following product types were additionally considered, but no such products containing MI or MCI/MI were presented: eye cream, self-tanning, deodorant spray, face mask, eye make-up, nail products.

the structure of the audit data, it is not possible to relate these reactions to certain products.

Discussion

The present audit has monitored, over 3 years, including the initial reference year 2015,[5] both the prevalence of contact allergy to MI in consecutively patch tested patients and, moreover, the types of MI- or MCI/MI-containing products to which the patients had been exposed, and which were relevant for current dermatitis. While a few reports already demonstrate that the epidemic of MI contact allergy is starting to decline, surveillance of currently eliciting product types is a unique approach, as discussed later.

Declining incidence of methylisothiazolinone contact allergy

Initial steps were taken to limit the use of MI in cosmetics in late 2013, followed by a process of re-evaluation in the European Commission.[3,4] This finally resulted in a ban of MI in leave-on cosmetics and a restriction of the use concentration in rinse-off cosmetics to 15 ppm, the latter becoming effective only in 2018. Following this regulatory action, a decline of the incidence of MI contact allergy was expected. Indeed, some single-centre data[9] or national contact allergy network data[10] indicated that 2013/14 was probably the peak in the MI contact allergy epidemic, and a more or less marked decline was seen thereafter. For instance, in Australia MI had been banned from leave-on cosmetic products, and a decline of MI sensitization frequency in consecutive patients was noted in 2017,[11] which suggests some pre-emptive measures, reducing exposure already before the regulatory deadline. The present data support the observation of a clear downward trend, based on several European countries. Thereby, the protective or preventive effect of MI regulation, leading to a significant decline of positive and especially of currently relevant positive reactions, can clearly be demonstrated. However, evidently the prevalence of MI contact allergy, after leaving a level which could be termed 'historical' without exaggeration, did not plummet to zero. This not only concerns overall per cent positive reactions, but also currently relevant positive reactions and indicated that sensitization to MI via other sources than the leave-on cosmetics which had been a driving force of the previous epidemic is ongoing.

In line with decreasing dynamics of the MI contact allergy epidemic, a 50% reduction of the major share of incident cases with onset in the same year or the year preceding the patch test was seen in the later 2 years as compared to 2015 (Fig. 1). However, despite measures taken to eliminate or reduce exposure conveyed by products put on the market, transition periods – as granted in recent MI regulation – during which products containing preregulation levels of MI could still be sold have been in effect. In addition, shelf life in the consumer's hands may lead to sporadic exposure to preservatives or preservative levels which had been phased out – but not in every home. This had nicely been illustrated by two belated cases of allergic contact dermatitis from the Apobase preservative in Finland.[12] Evidently, products imported from outside the EU or areas of the world adopting EU regulation will contribute to ongoing MI exposure by cosmetics to a presumably limited extent.

Shift in types of products eliciting allergic contact dermatitis

The other main objective of the present project had been to monitor product types eliciting allergic contact dermatitis in patients sensitized to MI. This analysis reflects the effects of above-mentioned regulation and probably also self-regulation installed already since end of 2013: basically, the relative importance, and also the importance in absolute terms of leave-on cosmetics has massively declined since the 2015 reference year. Conversely, the relative importance of rinse-off cosmetics has increased. The question whether it has also decreased in absolute terms can be addressed by examining the share of elicitation to rinse-off products, either alone or together with leave-on products, weighted with the prevalence of currently relevant MI contact allergy during the 3 year period: in 2015, 58.4% of 4.34% relevant positive reactions were observed; i.e., 2.53% of positive reactions were (partially) explained by skin contact to rinse-off products. In 2017, for comparison, the prevalence of currently relevant MI allergy was 1.73% overall and, weighed by 68.6% with rinse-off products considered relevant, this amounts to a prevalence of contact allergy (partially) explained by rinse-off products of 1.18%. Hence, despite the relative increase, elicitation by rinse-off products has quite proportionally decreased in absolute terms, too. Regarding household products, a similar calculation as above reveals that in 2015 1.22% of patients had currently relevant MI allergy to these, whereas in 2017, this percentage was 0.81%, all irrespective of other causative exposures, e.g. to cosmetics.

It may thus be assumed that lowering the maximum permitted concentration of MI in rinse-off cosmetics has likely resulted in more than halving elicitation of MI-sensitized patients by such products within just 3 years. Moreover, as it has been stated that 15 ppm MI may not be suitable for preservation, at least if used alone, MI may actually have been replaced by other preservatives in rinse-off cosmetic products. If this holds true, the preventive effect concerning just the concentration reduction would be overestimated by above observations. In fact, it is not known presently whether 15 ppm when used in rinse-off products, often with repeated and daily exposure, will sufficiently protect from elicitation (and sensitization) – the recommendation had been a read-across from evidence of limited, 'tolerable' levels of sensitization after many years of use of MCI/MI at this concentration. A previous ROAT study simulating use of MI in

a liquid soap at different, defined concentration levels has found that 50 ppm MI still elicited 7 out of 9 of patients sensitized to MI during the epidemic.[13]

The fields of exposure beyond cosmetics need to be addressed also, in terms of lowering MI use concentration levels, comprising household/cleaning, technical and, in fact, all products. These include for instance water-based paints[14] which are capable of eliciting severe airborne allergic contact dermatitis.[15] Also spray products can lead to airborne exposure in addition to direct exposure, e.g., by a cleaning spray.[16] Therefore, it has been stressed that the presence of MI should be declared in all products.[17]

Perspectives on methylisothiazolinone and beyond

Regarding MI, progress has been made, as MI is categorized not only as allergen (H 317), but as strong sensitizer (Skin sens. Ia). A respective warning is mandatory on products containing more than 15 ppm, and the presence of MI needs to be indicated in concentrations of 1.5 ppm and above, based on the overarching REACH regulation. However, attention should be paid to the fact that the epidemic of the last few years has sensitized a large part of the population, probably between 1% and 5%, and that this part needs to be protected from MI for several decades to come. This evidently concerns also sources of exposure beyond cosmetics and moreover emphasizes the need for full ingredient labelling of all types of products to enable fully effective secondary prevention for those already sensitized. Evidently, full, global ingredient labelling would also support the planning of patch tests (beyond what is included already in the baseline series) and assessment of clinical relevance, respectively. At present, large gaps in the available information on product composition have very likely resulted in an underestimation of the share of currently (or previously) relevant reactions in the present audit, as in any study, and in clinical routine.

In addition to sensitization to MI itself, cross-elicitation by other isothiazolinones needs to be considered in those sensitized to MI. Generally, cross-reactivity is difficult to assess in humans, as concomitant exposure to several agents, and, with it, independent sensitization, can usually not be excluded. Nevertheless, experimental testing in animals sensitized to MI clearly indicates that positive results can be elicited by benzisothiazolinone (BIT) as well as octylisothiazolinone (OIT).[18] Hence, besides evidently avoiding MCI/MI, MI-sensitized patients are additionally advised to avoid skin contact both with BIT and OIT.[19]

In conclusion, although with a considerable delay, the MI problem seems to have been adequately addressed following reappraisal of risk – at least in Europe, and those areas of the world which (mostly) adopt EU regulations, such as Thailand.[20] However, in reality, problems such as hidden, unexpected sources of exposure,[21,22] mislabelling or lack of labelling[23] will presumably still trouble MI-sensitized patients and their doctors. The years to come will reveal whether further action is needed. Moreover, the problem of replacement of MI by other preservatives, or generally preservation of water-based products will remain a challenge. Introduction of new preservatives requires valid premarketing risk assessment, early detection of the beginning of an epidemic in case of risk assessment failure and rapid action for its containment.

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