

Photoaggravated allergic contact dermatitis and transient photosensitivity caused by methylisothiazolinone

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Summary

Background. Photoaggravated allergic contact dermatitis caused by methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) and MI has been reported.

Objectives. To describe the clinical characteristics and results of (photo)patch tests and photo-tests of 10 patients in Belgium and France suffering from photoaggravated contact dermatitis caused by MI.

Patients and Methods. Five men and five women, with a median age of 49.5 years, were investigated between January 2012 and February 2017 because of suspected photoaggravated contact dermatitis. Patch tests, photopatch tests and/or photo-tests were performed.

Results. Seven patients had positive patch test reactions to both MCI/MI and MI, whereas 3 patients had positive patch test reactions only to MI. In most cases, MI was the (strong) primary sensitizer. Photopatch tests with MCI/MI and/or MI gave stronger reactions than patch tests with these derivatives, indicating photoaggravation. Sensitization probably took place from cosmetics and work-related biocides, whereas elicitation of dermatitis was remarkably often related to airborne exposure to MI present in paints or industrial biocides. Four patients suffered from transient photosensitivity.

Conclusion. Photoaggravated allergic contact dermatitis and transient photosensitivity caused by MI is a peculiar clinical presentation of allergic contact dermatitis caused by this preservative, and should be considered in daily clinical practice.

Key words: airborne allergic contact dermatitis; cosmetics; dilution series; methylchloroisothiazolinone; methylisothiazolinone; occupational; paints; photoaggravation; photosensitivity; photo-tests; sunscreens.

Photoaggravation in cases of sensitization to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI)

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has been reported previously (1, 2). Here, we describe 10 patients, 7 from Belgium and 3 from France, suffering from photoaggravated dermatitis, in some cases followed by transient photosensitivity, after sensitization to these biocides.

Patients and Methods

Ten patients, 5 men and 5 women, with a median age of 49.5 years, were investigated in Bordeaux, Marseille, and Toulouse (1 patient each; patients 1–3), in

Antwerp ($n = 4$; patients 4–6 and patient 10) and in Leuven ($n = 3$; patients 7–9) between January 2012 and February 2017. All had presented with skin lesions in a photodistributed pattern, or showed more pronounced lesions on ultraviolet (UV)-exposed skin regions, often involving the face and/or the back of the hands. Seven of them, upon referral to the patch test clinic, gave a clear history of consistent photoaggravation whenever their dermatitis was exposed to sunlight. In others (e.g. patient 2) the relative photodistribution of the skin lesions became apparent only during further follow-up, when UV-exposed skin became more prominently affected. For patients 7 and 9, no information had been documented regarding subjective symptoms upon sun exposure. However, also in these 2 patients, UV-exposed skin areas were more strongly affected. Occasionally (patients 1 and 5), generalization of the dermatitis occurred, and was sometimes (patient 5) considered to be potential systemic allergic dermatitis resulting from the inhalation of isothiazolinone derivatives present in water-based paint. In these cases, the dermatitis had also worsened upon exposure to sunlight.

All patients were patch tested with a baseline series (containing MCI/MI 0.01% or 0.02% aq., and MI 0.2% aq.), and sometimes with additional series, depending on their history. All commercial allergens were from Chemotechnique® (Vellinge, Sweden). Six of 10 patients were photopatch tested with cosmetics containing MCI/MI and/or MI. Patient 6 was also patch tested and photopatch tested with a dilution series of MI (0.05%, 0.025%, 0.0125% and 0.00625% aq.), whereas patient 10 was additionally patch tested and photopatch tested with a lower concentration of MI (i.e. 0.01% aq.). In Antwerp, patch test chambers from Allergeaze® (SmartPractice, Calgary, Canada) were used, in Leuven, Bordeaux and Toulouse, IQ Ultra™ units (Chemotechnique®) were used, and in Marseille, Finn Chambers® on Scanpor® tape (SmartPractice) were used. All patch tests were occluded for 2 days with Fixomull® stretch (BSN Medical, Hamburg, Germany) in Antwerp, or with Mefix® (Mölnlycke, Göteborg, Sweden) in Leuven; in France, Micropore™ (3M, Saint Paul, MN, USA) or Urgoderm® (URGO, Chenove, France) were used in Marseille, and in Toulouse and Bordeaux, respectively. All (non-irradiated) patch tests were read, according to ESCD guidelines (3), on day (D) 2, D3/4, and sometimes also on D7.

Concerning the photopatch tests, in the Belgian patients the occlusion time of the allergens was 2 days, whereas in France it was 1 day; one of two identical patch test series was always irradiated with 5 J/cm² UVA. Readings of these tests were performed on D2, D4 and D7 in

Belgium, and on D2 and D3 in France, application of the tests considered as D0. Although the methodology of the photopatch tests was different in Belgium and France, the patch and photopatch tests were always compared with each other at the same time point (i.e. on D4 in Belgium and on D3 in France). In Toulouse, patient 2 was additionally tested with a third series of patch tests irradiated with UVB [three-quarters of the minimal erythema dose (MED) of UVB].

In 2 French patients, photo-tests were also performed: in patient 1 (Bordeaux) with the use of a Multiport UV Solar Simulator Model 601 (Solar Light, Philadelphia, PA, USA), emitting UV radiation in a region of 290–400 nm, and in patient 2 (Toulouse) with the use of a solar simulator (Dermolum UM-Müller; Müller Elektronik®, Moosinning, Germany), providing polychromatic irradiation (UVB, UVA, and visible light) with dosimetry, performed with a thermopile and with a UVA lamp (UVA 700 lamp; Waldmann, Villingen-Schwenningen, Germany), emitting UVA1 radiation (340–400 nm), with an incorporated dosimeter.

None of the patients was taking any photosensitizing drugs. Additionally, control tests were performed: 10 MI-negative patients were patch and photopatch tested with MI 0.2% aq., and 5 other randomly selected patients were patch and photopatch tested with nickel 5% pet.

Results

The demographic and clinical characteristics of the patients, and the results of patch tests, photopatch tests, and photo-tests, are summarized in Tables S1 and S2, respectively. Seven patients had positive patch test reactions to both MCI/MI and MI, whereas 3 patients had positive patch test reactions only to MI. In 7 of 10 patients, the primary sensitizer was considered to be MI (strength of reaction to MI greater than strength of reaction to MCI/MI), whereas in 3 patients the primary sensitizer could not be determined (equal strengths of reaction to MI and MCI/MI; MCI was not tested separately). The patch test reaction to MI 0.2% aq. was usually very strong (++ in 6 patients, +++ in 2 patients, and + in 2 patients) (Table S2).

Of the 6 patients in whom photopatch tests with MCI/MI and/or MI were performed, 4 showed stronger reactions to MI 0.2% aq. on the irradiated side than on the non-irradiated side, supporting a diagnosis of photoaggravated contact dermatitis. In patient 6, a dilution series of MI showed reactions to lower concentrations of MI (down to 0.00625% aq.) upon photopatch testing than upon patch testing (reactivity down to 0.0125% aq.). In patient 10, patch tests with a sunscreen (bought

in the United States and normally containing a maximum of 0.01% MI) and MI at a lower concentration of 0.01% gave negative results, whereas photopatch tests with both of these gave positive reactions (Table S2).

Possible sensitization to MCI/MI and/or MI occurred from cosmetics (including sunscreens and wet wipes) in 7 patients (5 women and 2 men), and from work-related industrial biocides and paint in 2 patients and 1 patient (all males), respectively. Besides cosmetics, subsequent elicitation took place through airborne contact with allergens in 8 of 10 patients, that is, from vapours in industrial biocides in 2 patients, and from water-based paints in 6 patients, resulting in airborne allergic contact dermatitis, which subsequently became photoaggravated. Figures 1 and 2 show examples of such airborne allergic contact dermatitis, caused by paints and industrial biocides, respectively, followed by subjective intolerance to sunlight with aggravation of dermatitis on sun-exposed skin areas. Occupational sensitization occurred in 4 of 10 patients (2 labourers, 1 painter, and 1 bus driver); interestingly, in patient 7, a painter, sensitization was considered to have occurred from cosmetics, whereas elicitation occurred from water-based paints.

During follow-up, 4 patients, all with proven photoaggravated contact dermatitis, reported photosensitivity, despite avoidance of their contact allergens. In 3 of these (patients 1, 2, and 4), a relapse of dermatitis occurred whenever they were exposed to sunlight, with 2 of them (patients 1 and 2) showing a lower MED upon photo-testing with UVB. Furthermore, in patient 2, a repeated polychromatic (UVB) photo-test (three times the MED value on 3 consecutive days), and a repeated UVA photo-test (60 J/cm^2 on 3 consecutive days), both resulted in positive skin reactions, a skin biopsy of which, in conjunction with the clinical picture, showed histological signs 'compatible' with photoallergic dermatitis. Following avoidance of all contact allergens, the dermatitis in patient 2 eventually cleared 2 months later, and his photosensitivity disappeared. This was confirmed by a normalization of the MED UVB (450 mJ/cm^2 , as compared with 303 mJ/cm^2 previously). Unfortunately, detailed information on the extent and duration of the (transient) photosensitivity in the other 3 patients (patients 1, 3, and 4) could not be retrieved.

Of the 10 MI-negative control patients, none showed any skin reactions to the patch test of MI 0.2% aq. irradiated with UVA. Two nickel-allergic patients had equally strong reactions to a patch test and a photopatch test with nickel 5% pet., whereas 1 nickel-allergic patient had a weaker reaction to the photopatch test with nickel (+) than to the patch test (++) ('photo-amelioration'). Two

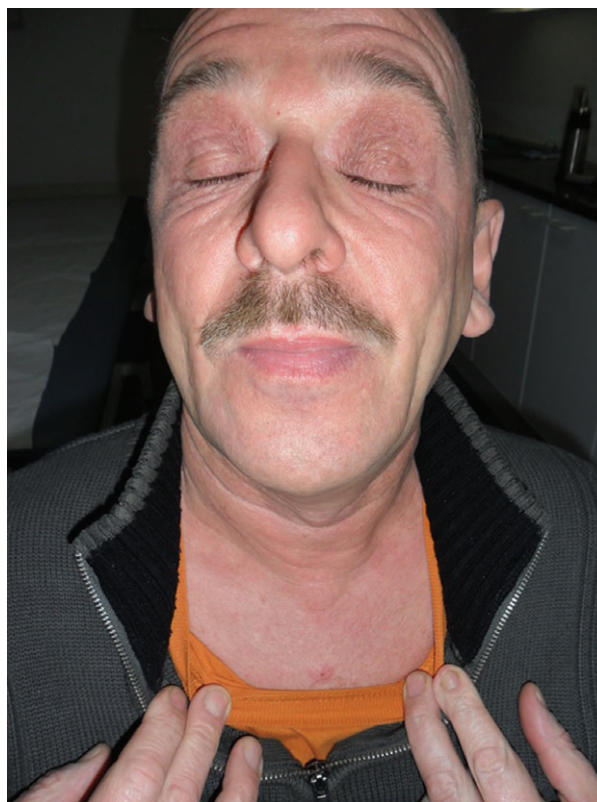


Fig. 1. Photoaggravated airborne allergic contact dermatitis caused by a methylisothiazolinone-containing paint in patient 4.

nickel-negative patients still had negative test results after UVA irradiation.

Discussion

Atypical clinical presentations caused by sensitization to MCI/MI and MI have been reported (4), and potential photoaggravation was first reported in 2014 (1). Pirmez et al. recently confirmed the latter observation, and reported 30 patients, the majority being females, who experienced photoaggravated contact dermatitis caused by MCI/MI: 27 'possible' cases, based on a review of medical files and clinical images, and also 3 'certain' cases, in whom photopatch tests showed higher reactivity to MCI/MI following exposure to UVA (2). Mainly, the component MI has been considered to be responsible for photoaggravation, and such cases are now being diagnosed more frequently in our daily clinical practice (data on file). Similar cases have also been reported in Portugal (5), Germany (6), the United Kingdom (7), and recently also in Australia (8).

A diagnosis of photoaggravated contact dermatitis may be suspected from the relative photodistribution of the



Fig. 2. Photoaggravated airborne and generalized dermatitis caused by vapours from a methylisothiazolinone-containing chemical (industrial) biocide in patient 1.

skin lesions, or from the history, although not all of our patients were initially aware of such photoaggravation. The dermatitis can be rather exclusively localized on sun-exposed skin, although UV-exposed skin can also become more intensely affected than non-UV-exposed skin [as was also reported by Pirmez et al. (2)]. Moreover, spread to covered body regions, and even generalization, may occur.

As the majority of our patients were strongly sensitized (++ to +++) to MI, it may be interesting to patch test and photopatch test with lower concentrations of MI (e.g. 0.01%, as performed in patient 10), or to use a dilution series with MI starting from 0.05% aq. (as in patient 6), or even lower concentrations, in order to differentiate the skin reactivity when photopatch tests are compared with patch tests, and hence to better prove the photoaggravated character of the dermatitis. No exclusive photocontact allergy to MI was observed in the present series.

Notwithstanding the fact that, in the majority of our cases, MI was considered to be the most likely primary sensitizer (on the basis of reactions to MI being stronger than those to MCI/MI), it may also be interesting to (photo)patch test with MCI separately (although this

is not commercially available), to verify whether the chlorinated component may also be involved in photoaggravated skin reactions. Although we cannot fully exclude a secondary phototoxic effect, or non-specific UV absorbance by MI when this molecule is exposed to UVA, we believe that photoaggravated contact allergy is a reasonable hypothesis: (i) the patch test and photopatch test responses in our patients were considered to be entirely of an 'allergic' morphology, without an additional irritant component; (ii) photopatch testing of MI in 10 MI-negative control patients did not result in any (irritant) skin reaction; and (iii) 3 nickel-allergic control patients did not show any signs of photoaggravation of their nickel-positive patch tests upon exposure to UVA.

As the majority of patients reported here did not undergo photo-testing, an alternative explanation may still be that primary photosensitivity, induced by MI, produces the 'photoaggravated' patch test result. However, a contact allergen, depending on its chemical structure, may sometimes behave as a photocontact allergen, resulting in photoaggravated or true photocontact allergy, and may at the same time give rise to (transient) photosensitivity (see, for example, the experience with ketoprofen).

In previous animal experiments on guinea-pigs treated with MI 200 ppm and irradiated with UVA at $\sim 10 \text{ J/cm}^2$, MI was not considered to be a phototoxic substance or a photosensitizer (9). However, it has a heterocyclic unsaturated structure of five atoms, and the presence of a double bond might predispose it to absorb UV irradiation, and thus to become a potential photosensitizer. Indeed, MI has been shown to have optimal UV absorption at a wavelength of 274 nm (9), which would fall within the UVB spectrum. It might be argued that it is more interesting to perform photopatch tests with UVB, although, in our series, UVA proved to be sufficient, and in 1 of our patients (patient 2) it could be shown that the photoaggravated response was equally strongly elicited by UVA as by UVB.

Overall, the clinical experience summarized in this article and in similar reports (7) indicates that UV may be an important cofactor in facilitating the contact-allergic response (induction and/or elicitation) to MI. Furthermore, differentiating photoaggravated contact dermatitis from airborne allergic contact dermatitis can be challenging, but both can coexist, as also highlighted by Pirmez et al. in their series (2). Important features that may point towards photoaggravated dermatitis are: (i) subjective and consistent aggravation of the dermatitis upon sun exposure (although this is sometimes not initially noted by the patient); and (ii) more pronounced dermatitis on UV-exposed skin than on non-UV-exposed skin.

Although most patients became symptom-free following avoidance of their allergens, minor relapses sometimes still occurred. Such relapses might be explained by ongoing exposure to low (volatile) amounts of MI (e.g. from detergents or paints by proxy), which may not even be noticed by the patient; certainly, the fact that most patients were strongly sensitized (++ or +++) to MI would support this. Nevertheless, in patients 1–4, re-exposure to sunlight was repeatedly recognized as an additional trigger causing a relapse of skin symptoms and/or visible dermatitis, and this was confirmed by photo-tests in 2 of them (patients 1 and 2). Patient 2, when photo-tested again after 2 months, showed normalization of his MED UVB, confirming the transient character of photosensitivity. Unfortunately, no information could be retrieved on the extent or duration of the (transient) photosensitivity in the other 3 patients (patients 1, 3, and 4). For the remaining 6 patients (patients 5–10), its existence could not be established. Performing photopatch tests with MCI/MI and MI, and additional photo-tests, may thus be interesting: not only do they explain what is clinically happening with the patient (more pronounced skin lesions on UV-exposed skin parts, and subjective intolerance to sunlight), but they also offer a rationale to discuss photoprotection with patients sensitized to MCI/MI and/or MI.

In Europe, the authorities have banned the use of MI in leave-on cosmetics, including suncreams, effective from 22 February 2017 (EU 2016/1198), and have limited the use of MI to 15 ppm in rinse-off products from 27 April 2018 (EU 2017/1224). However, a 6-month transition period was foreseen, during which the cosmetic industry could still produce leave-on cosmetic products containing MI (10). Also, the EU regulation does not apply

to leave-on cosmetics bought in non-European countries (e.g. the United States and Canada), which may still contain MI (e.g. the sunscreen from patient 10). Furthermore, paints and detergents may still contain high amounts of MI, and thus remain problematic sources of this allergen. Indeed, also in the present series, the importance of non-cosmetic sources of MI is evident: in 4 of 10 patients, the dermatitis, in either the sensitization or the elicitation phase, was considered to be occupational, and in 2 cases it could be related to paints – in 1 case to cooling fluids, and in another case to silicone emulsions, all containing MI. Of the remaining 6 patients, all presenting with non-occupational dermatitis, in 3 the dermatitis was attributed to paints, and in 1 to paints and detergents, whereas in only 2 patients were cosmetics considered to be the only relevant MI source.

In conclusion, in patients with a history of photoaggravated dermatitis, or when patients present with photodistributed skin lesions, sensitization to MCI/MI, and to MI in particular, should be suspected, and transient photosensitivity can be expected. Photopatch tests (possibly with lower MI concentrations and/or dilution series) and/or photo-tests may be valuable diagnostic tools to investigate these patients.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Demographic and clinical characteristics of the patients (n = 9).

Table S2. Results of patch tests, photopatch tests, and photo-tests (n = 9).

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Probable source and route of sensitization	Industrial (non-cosmetic) biocides (cooling fluids); also airborne.	Cosmetics , (including wet wipes)	Cosmetics	Paints; also airborne .	Cosmetics	Industrial (non-cosmetic) biocides (silicone emulsions)	Cosmetics (including wet wipes)	Cosmetics	Cosmetics	Cosmetics (sunscreen)
Source and route of elicitation	Industrial (non-cosmetic) biocides (cooling fluids); also ACD.	Cosmetics	Paints; also ACD.	Paints; also ACD.	Paints; also ACD and possibly SCD***	Industrial (non-cosmetic) biocides (silicone emulsions) ; also ACD.	Cosmetics , paints (also ACD)	Cosmetics , including an MI-containing sunscreen, paints (also ACD)	Cosmetics and various household detergents and paints (also ACD)	Cosmetics (sunscreen)
Occupational dermatitis	Y (laborer)	Y (bus driver)	N	Y (painter)	N	Y (laborer)	N (painter)	N	N	N

Transient photosensitivity* *	Y	Y	Y	Y	U	U	U	U	U	U

M = male

F : female

ND = not done

NEG = negative

Y: yes

N: no

U: unknown

ACD: airborne contact dermatitis

SCD: systemic contact dermatitis

*exclusively photo-distributed skin lesions, or more intensely affected UV-exposed skin as compared to non-UV exposed skin.

**with a relapse of dermatitis and/or with subjective intolerance to sunlight

*** possibly systemic contact dermatitis through inhalation, although secondary spread from cutaneous exposure may have occurred as well.

Table S2: Results of patch, photo-patch and photo-tests (n=9).

Patients	1°	2°°	3	4	5	6	7	8	9	10
Patch test to MCI/MI*	+	+	+	++	+	++	-	++	-	-
Patch test to MI*	+	+	++	+++	++	+++ Dilution series of MI + (0.0125%)	++	++	++	0.2% aq: ++ 0.01% aq: - Sunscreen 'as is' (containing max. 0.01% MI): -
Photo-patch test to MCI/MI*	++	++ (UVA) + (UVB)	ND	+++	ND	ND	ND	++	ND	ND

Photo-patch test to MI*	++	++ (UVA) ++ (UVB)	ND	+++	ND	+++ Dilution series of MI + (0.00625%)	ND	++	ND	0.2% aq: ND 0.01% aq: + Sunscreen 'as is' (containing max. 0.01% MI): +
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MI = methylisothiazolinone
 MCI = methylchloroisothiazolinone
 NEG = negative
 ND = not done
 UVA = ultraviolet A
 UVB = ultraviolet B

*to one given concentration of MCI/MI or MI, read on D4 after application of the patch tests, and on D3/4 after application of the photo-patch tests.

°Photo-tests: UVB minimal erythema dose [MED] lowered to 250 J/cm² (nl. ≥ 400 J/cm²); UVA MED: not done.

°°Photo-tests: UVB: MED lowered to 303 mJ/cm² (nl. ≥ 400 mJ/cm²); UVA MED: normal. Following 2 months of avoidance of the allergens, the dermatitis disappeared and the MED UVB normalized (450 mJ/cm²).