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Methylisothiazolinone contact allergy — A review

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What's already known about this topic?

The preservative MI is used in both industrial and consumer products. Recently several studies on allergic contact dermatitis caused by MI have been published.

What does this study add?

This review addresses the recent development in MI contact allergy and the use of MI. Based on the development in MI contact allergy we suggest that MI is monitored closely and that the regulatory community takes action and reassess the legislation concerning use of MI in both industrial and consumer products.

Abstract

In the early 2000s the preservative methylisothiazolinone (MI) was released as an individual preservative for industrial products and in 2005 permitted for use in cosmetic products. Up till then MI had only been used in combination with methylchloroisothiazolinone (MCI). MCI/MI is one of the most frequent causes of preservative contact allergy and early studies showed that both MI and MCI are sensitizers.

The prevalence of MI contact allergy is already around 1.5% and sources of exposure are associated with occupation, cosmetic products or household products. Use of MI in industrial products is not restricted and cases of occupational contact allergy to MI e.g. in painters are reported. The frequency of use of MI in cosmetics is low, around 1%, while up to 16.5% of household products were preserved with MI. We found 19 (1.5%) out of 1272 cosmetic products labelled with MI, primarily rinse-off products and analysed the concentration of MI by UV-HPLC-MS. The use concentration ranged between 2 and 100ppm. Repeated exposure to MI showed that many MI allergic patients reacted to 50ppm which is half the maximum permitted concentration of MI in cosmetics.

The recent cases and prevalence studies on MI contact allergy could be the first sign of an epidemic of MI contact allergy. The development in prevalence of MI contact allergy should be closely monitored by including MI in the European Baseline Series at 2000ppm.

Introduction

Methylisothiazolinone (MI, CAS 2682-20-4) has been used in industrial products since the early 2000s and was in 2005 permitted as a preservative in cosmetic products.¹ After its introduction to industrial products the first cases of contact dermatitis caused by MI alone were published.^{2,3} In August 2010 the first cases of cosmetic related cases of contact allergy were published.⁴ Since then other publications on MI has been published.⁵⁻¹¹ In this review we will present the historical background and early studies on MI combined with the latest studies on contact allergy and consumer exposure. Furthermore we have investigated the use of MI in cosmetic products, both frequency and concentrations.

Material and methods

Review

A literature search on “methylisothiazolinone” and “2-Methyl-4-isothiazolin-3-one” in Pubmed Medline and Web of Knowledge was conducted on March 15 2011, furthermore the reference lists of the relevant articles were studied for further publications not found by the two search engines.

Frequency of use and concentration of MI in cosmetics

In October 2010 eight Danish retail stores and a department store were visited and the label of all cosmetic creams, lotions, shampoos, conditioners, sun creams, liquid soaps, shower gels, and wet wipes were investigated for presence of MCI/MI and MI. The total number of products investigated and the number of products labelled with MCI/MI were registered. All products labelled with only MI were purchased for further analysis of the use concentration with the following methodology. Two gram (± 0.1 g) sample was extracted by 25 mL methanol/0.4% acetic acid (20:80) by means of ultrasound. The suspension was filtered (Phenex-GF/CA) and analysed by HPLC equipped with UV and MS detectors (275 nm, m/z 116 and 138). Analytical conditions: Agilent 1946D MSD with ESI inlet, Agilent 1100 HPLC. Analytical column: Synergi Hydro RP-18 4 μ m, 250 x 2,0 mm. Eluent: A:0.4% acetic acid. B:acetonitril/methanol (50/50). Gradient from 80/20 to 100/0. Eluent rate: 0.2 mL/min.

Review

Historical background

Methylisothiazolinone (MI) in a 1:3 combination with methychloroisothiazolinone (MCI) has been used in industrial and consumer products since the beginning of the 1980s. In 1985 the first cases of MCI/MI contact allergy caused by cosmetics were published.^{12;13} This was followed by both animal and clinical studies, which showed that both MCI and MI could cause contact allergy and that MCI is a more potent allergen than MI.^{14;15} MCI/MI is one of the most frequently used preservatives in cosmetic and industrial products.^{16;17} However, due to its allergenic potency MCI/MI is also one of the most common cause of contact allergy caused by preservatives.^{11;18;19} The maximum permitted concentration of MCI/MI in cosmetics has been regulated since the 1980s, however this has not influenced the prevalence of MCI/MI contact allergy.^{19;20} With the current legislation MCI/MI is permitted in concentrations up to 15ppm in all cosmetics in the EU, and in rinse-off products in the US, while leave-on cosmetics may only be preserved with 7.5ppm in the US.^{1;21} The US legislation is in accordance with the recommendations of the use concentrations from the manufacture of MCI/MI.²²

The maximum permitted concentration of MI in cosmetics is 100ppm, while there are no limitations in industrial products. Both the Cosmetic Ingredient Review in the US and the Scientific Committee for Consumer Safety has evaluated MI and concluded that 100ppm was safe to use in cosmetics.^{23;24} Before 2005 the maximum permitted concentration of MI in cosmetic products was 3.75ppm (1/4 of 15ppm MCI/MI). The introduction of MI alone led to a more than 25-times increase in the permitted concentration of MI in cosmetics.

Sensitization studies

Animal studies

In 1987 Bruze et.al.¹⁵ concluded that MI was a weak sensitizer based on results from the Guinea Pig Maximization Test. MI was tested twice, in the first test four out of 24 (17%) animals reacted and in the second 11 out of 24 animals (46%) reacted to MI.¹⁵ Recently Basketter et.al.²⁵ tested the sensitizing potency of MI in the Local Lymph Node Assay (LLNA) with five different concentrations, two vehicles and four mice in each group. The EC3 value of MI was 0.4 or 2.2 depending on the vehicle. This corresponds to a moderate sensitizer.²⁵ In the same study it was also concluded that MI did not have the capacity to induce respiratory sensitization.²⁵ The producer of MI, Rohm & Hass (now DOW chemicals), has performed a series of both maximization tests and

LLNA, which has been included in safety evaluations in both the EU and the US.^{24;26} The different studies showed that MI only sensitized at high concentrations (>1000ppm) or not at all.²⁴

Studies in humans

Human Repeated Insult Patch Test studies with various concentrations of MI have been conducted by Rohm & Hass. Different MI concentrations (100, 200, 300, 400, 500 and 600ppm) were tested on 98 to 214 healthy test subjects. One subject in both the 400ppm and 500ppm group were sensitized.²⁴ In these studies it was concluded that concentrations up to 600ppm were not a dermal sensitizer.²⁴ Another study showed that the threshold for sensitization was around 1000ppm.²⁶

Prevalence of methylisothiazolinone contact allergy in eczema patients

Three studies have investigated the prevalence of MI contact allergy in patch tested patients.^{5;10;11} At Gentofte Hospital in Denmark 2536 dermatitis patients were patch tested with MI from May 2006 to February 2010. A total of 1.5% (37) were MI allergic.⁵ In the standard patch test series at Gentofte Hospital there are currently 11 different preservatives represented. In the period 2006-2008 the prevalence of MI contact allergy was 1.5% this corresponds to the fourth most common preservative contact allergen in Denmark, despite its limited time on the market.^{5;19} No developing trend in the prevalence was found in the Danish study. In a Finish study 10 821 eczema patients were patch tested from 2006 to 2008 and 1.4% (147) were MI allergic. In this study the prevalence of MI contact allergy increased from 0.9% in 2006 to 1.8% in 2008¹⁰. In a recent article by A. Schnuch et.al.¹¹ on contact allergy to preservatives in the IVDK network 1.6% (215) of 13 433 patch tested patients were allergic to MI.

In the Danish study the patch test concentration was 2000ppm (0.2%).⁵ In the Finish study the patients were patch tested with both 1000ppm (0.1%) and 300ppm (0.03%). Of the 147 patients that reacted to 1000ppm only 69 (47%) reacted to 300ppm.¹⁰ In the IVDK network they test with 500ppm (0.05%).¹¹ In a dose response patch test study 10 of 11 MI allergic patients all reacted to 300, 500, 1000 and 2000ppm MI, while the last patient only had a positive patch test reaction to 2000ppm at day two and no at day four.⁷

Experimental re-exposure to MI

Eleven patients allergic to MI were exposed to MI in a repeated open application test (ROAT) that mimicked the use of a cream preserved with 100, 50 and 5ppm MI (vehicle 10% ethanol, 0.4%

phenoxyethanol and water). In total 64% of MI allergic patients reacted to 100 and 50ppm, while 18% also reacted to 5ppm.⁷ In another study 30 patients performed a ROAT with a cream containing 100ppm MI; 30% of the MI allergic patients reacted to the exposure.¹⁰ The vehicle plays an important role in the reaction pattern in ROATs.²⁷ This could explain the different results in the two studies.

Consumer exposure and MI contact allergy

Two studies have published cases on cosmetic related MI contact allergy.^{4;5} One study describes six patients with anal lesions caused by wet wipes used for intimate hygiene, and one patient with facial dermatitis caused by a makeup remover.⁴ In the other study 13 out of 37 MI allergic patients were exposed to MI, MCI/MI or both from consumer products. One patient was exposed to MI from a household product (washing-up liquid) and the remaining 12 were exposed to MI through cosmetic products. The majority (64%) of the products were rinse-off products (shampoo, conditioner and liquid soap).⁵

Airborne allergic contact dermatitis

Airborne contact dermatitis most likely caused by MI in carpet glue or wall paint was mentioned in the study by García-Gavín.⁴ At Gentofte Hospital we have had two patients who developed airborne contact dermatitis after exposure to MI from wall paint used in their home. One of the patients had to be hospitalized with severe respiratory problems due to the exposure, and were unable to stay in his house three weeks after it was painted.⁸

Market surveys

We investigated cosmetics in 9 different stores in Denmark for products preserved with MI and MCI/MI. We checked the label of 1272 cosmetic products, some might have been identical since some of the retail stores are owned by the same company and the same products are sold in different stores. We found 19 (1.5%) individual products preserved with MI and 132 (10.4%) products preserved with MCI/MI. Of the 19 cosmetic products labelled with MI 15 were rinse-off products, three were leave-on and four were wet wipes. The concentrations of MI were measured by HPLC-UV-MS and the results are shown in table 1. Two of the products were labelled with MI but MI was not detected in the products (limit of detection = 1ppm). The concentration of MI in the different

products ranged from 2ppm to 100ppm, however 14 (74%) of the 19 products contained more than 50ppm MI and 5 (26%) contained more than 95ppm (table 1).

A recent survey from Sweden on preservatives in 204 cosmetic products (rinse-off and wet wipes) showed that only one product were preserved with MI, while 16 (16.5%) out of 97 detergents (multipurpose cleaners and washing-up liquids) were preserved with MI.⁹ In Italy 30 (10.3%) out of 291 household cleaning products were preserved with MI.²⁸

Occupational exposure and MI contact allergy

The first cases of occupational contact dermatitis caused by exposure to MI were published in 2004 and 2006.^{2;3} Both studies describes cases of MI contact allergy associated with paint. A study showed that MI contact allergy was statistically significantly associated with occupational dermatitis ($p=0.03$) when compared to other patch tested patients.⁵ Eleven out of 37 MI allergic patients were exposed to MI through their occupation; five of them were painters.⁵ Based on information from a few large manufactures of paint the use concentrations of MI ranges from 100ppm to 270ppm MI, and MI is now preferred instead of MCI/MI which previously was frequently used in paint.¹⁶

Cross reactivity between isothiazolinones

Besides MCI and MI there are also other isothiazolinones available for industrial products.²⁹ Especially benzisothiazolinone is frequently used in paint. A few studies have investigated cross reactivity in patients allergic to MCI/MI and MI.^{2;29;30} Besides infrequent reactions to other isothiazolinones patients sensitized with high doses of MCI reacted to low doses of MCI in the patch test and high doses of MI. In patients sensitized to MI the patient reacts to low doses of MI and high doses of MCI.^{29;30} Patients with a positive patch test to MI has frequently concomitant reactions to MCI/MI as well.^{5;10;11} This gives several different possibilities. Is MCI or MI the primary sensitizer? Is it a cross reaction between MI and MCI? Is it a reaction to the two different concentration of MI? As long as MCI and MI is tested together and we rarely know what the primary sensitizer is we can not answer these questions, however MI alone can undoubtedly induce and elicit contact allergic reactions as recently documented from their use in paint.^{2;3;8} Another problem concerning patch test reactions to MI and MCI and cross reactivity is the use of different concentrations of MCI/MI and MI in the different studies. In the European Standard Series it is recommended to test with 100ppm MCI/MI (0.01%). However, some uses 200ppm MCI/MI

(0.02%) instead. In the three different epidemiological MI studies four different concentrations of MI has been used.^{5;10;11} These differences makes it difficult to compare results from different countries.

Discussion

Experiments in animals and humans showed in 1987 that both MCI and MI were potent allergens.^{14;15} Through the 1980s, 1990s and 2000s MCI/MI has remained one of the most predominant preservative contact allergens with a constant prevalence around 2%.^{11;18;19;31} In the early 2000s MI alone were introduced to industrial products, shortly after the first cases of occupational MI contact allergy were published.^{2;3} Many of the specific cases of MI contact allergy published are related to MI exposure through paint, either from a paint factory,³ occupational cases^{2;5} or allergic airborne contact allergy to MI from paints in consumers.^{4;8} Currently there are no restrictions on the use of MI in industrial products, and the use concentrations are higher than what is permitted in cosmetic products. In the EU the REACH programme is currently assessing the safety of chemicals used in the EU. It is important that the development in occupational MI contact allergy, and the fact that many cases of MI contact allergy is caused by exposure to high concentrations of MI in industrial products is considered in the REACH evaluation of MI.

In 2005 MI was permitted in cosmetic products with a maximum concentration of 100ppm. In 2010 two studies were published with the first cases of cosmetic related MI contact allergy.^{4;5} These studies reported MI contact allergy caused by rinse-off and leave-on products as well as wet wipes. Market surveys have shown that only a few products are preserved with MI and that MI is mainly used in rinse-off products (table 1 and⁹). 3/4 of the cosmetic products were preserved with more than 50ppm MI and 1/4 contained more than 95ppm. In a ROAT 64% of the participants reacted to 50ppm MI and 18% reacted to 5ppm.⁷ In detergents the frequency of use are higher, 10% and 17% respectively.^{9;28}

Three studies on the overall prevalence of MI contact allergy in dermatologic patients have been published. Despite a four fold factor difference in patch test concentration, all studies report a prevalence of around 1.5%.^{5;10;11} None of the studies reports of any time trend development, however, in the Finish study the prevalence doubled from 0.9% in 2006 to 1.8% in 2008.¹⁰ These results suggest that MI should be included in the European patch test standard series in order to monitor the development of MI contact allergy and identify cases of MI allergy, which otherwise would be undetected. In a dose response study one out of 11 MI allergic patients reacted only to

2000ppm, while the remaining 10 patients all reacted to 300, 500, 1000 and 2000ppm, furthermore none of 14 healthy controls who also participated in the study had any irritant reactions to 2000ppm MI.⁷ In another study more than twice the number of patch tested patients reacted to 1000ppm than to 300ppm.¹⁰ More studies are needed to establish the optimal patch test concentration, but the preliminary results suggest that 2000ppm is an appropriate patch test concentration.

A review by Thyssen et.al.³² showed that epidemics of contact allergy often began with cases of occupational contact allergy, followed by consumer cases and first when an epidemic is consolidated the authorities takes action and regulates the use of the allergen. With MI we may see the early signs of an epidemic and it is crucial that the prevalence is monitored closely in both the EU and the US.

Furthermore we need more studies in order to establish a possible safe use concentration for both industrial and consumer products. This could potentially stop another costly contact allergy epidemic and ensure that MI could still be used as a preservative in lower safe concentrations.

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Table 1: Type of product and concentration of MI in 19 different cosmetic products

Product	Type	MI (ppm)
1	RO [*]	53
2	RO	58
3	RO	54
4	RO	53
5	RO	100
6	RO	100
7	RO	99
8	RO	100
9	RO	53
10	RO	52
11	RO	<LOD
12	RO	<LOD
13	LO [†]	96
14	LO	87
15	LO	2
16	WW [‡]	87
17	WW	17
18	WW	39
19	WW	72

RO, Rinse-off; LO, leave-on; WW, wet wipes, LOD, limit of detection; 1 ppm.