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Amended Safety Assessment of Methylisothiazolinone as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) reviewed the safety of methylisothiazolinone (MI), which functions as a preservative. The Panel reviewed relevant animal and human data provided in this safety assessment and in a previously published safety assessment of MI and concluded that MI is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when they are formulated to be nonsensitizing, which may be determined based on a quantitative risk assessment.

Keywords

methylisothiazolinone, cosmetics, safety

Introduction

In 2010, the Panel published a final report of the safety assessment of methylisothiazolinone (MI) with the conclusion that "MI is safe for use in cosmetic formulations at concentrations up to 100 ppm (0.01%)."[1] At the March 2013 Cosmetic Ingredient Review (CIR) Expert Panel meeting, the Panel reviewed newly provided clinical data indicating a higher than expected frequency of individuals who have allergic reactions to the preservative MI. In some cases, comparative data were available indicating a higher frequency of positive reactions than currently seen with the combination preservative, methylchloroisothiazolinone (MCI)/MI. The Panel reopened this safety assessment to gather and evaluate additional data.

In June 2014, the Panel reviewed the results of quantitative risk assessments (QRAs) performed by Cosmetics Europe and the CIR Science and Support Committee (CIR SSC). The results supported the safety of the use of MI in rinse-off product categories at concentrations up to 100 ppm. However, the QRAs indicated that MI use in many leave-on product categories would be safe only at lower concentrations.

The Panel previously reviewed the safety of the mixture MCI/MI (sold at a ratio of 3:1) with the conclusion that the mixture "may be safely used in 'rinse-off' products at a concentration not to exceed 15 ppm and in 'leave-on' products at a concentration not to exceed 7.5 ppm."[2]

Extensive data from the original MI safety assessment report, which was finalized in 2008 and published in 2010, were considered by the Panel during the review of this amended safety assessment. Because those data are included in the report that was published in 2010[1] (and can be found on the CIR website [https://www.cir-safety.org/ingredients]), only new information will be included in this report. However, notes have been added in text, referring to the original safety assessment, to identify the types of data that were available in that original report.

Chemistry

The definition, physical and chemical properties, method of manufacturing, and impurities of MI were described in the original safety assessment (Figure 1).[1]

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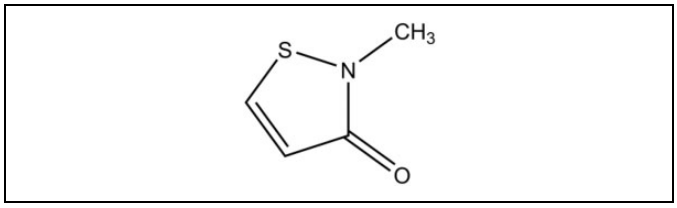

Figure 1. Methylisothiazolinone.

Use

Cosmetic

Table 1 presents the historical and current product formulation data for MI. Methylisothiazolinone functions as a preservative in cosmetic products.[3] According to information from the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database in 2007, MI had 1,125 reported uses, with the majority of the uses reported in noncoloring hair conditioners and shampoos.[1] It should be noted that the information from the VCRP in 2007 did not clearly distinguish cosmetic products in which MI was used in combination with MCI from products in which MI was used without MCI. This safety assessment addresses the use of MI in cosmetic products that do not also contain MCI. In 2008, industry reported the maximum use concentration range to be $4 \times 10^{-6}\%$ to 0.01%, with 0.01% reported in both leave-on and rinse-off baby, noncoloring hair, and dermal contact products.[1] In 2014, the VCRP database indicated that MI is used as an ingredient in 745 cosmetic products that do not also contain MCI, with the majority of the uses reported in leave-on products such as skin moisturizers.[4] A survey of use concentrations conducted by the Personal Care Products Council (Council) in 2014 reported a maximum concentration of use range of $3.5 \times 10^{-8}\%$ to 0.01%, with 0.01% reported in multiple product categories including eye makeup remover, hair shampoos and conditioners, and skin care products (both leave-on and rinse-off).[5]

Methylisothiazolinone was reported to be used in noncoloring hair sprays and hair tonics or dressings that may be aerosolized or become airborne and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[6-9] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[7,8]

The European Union's Scientific Committee on Consumer Safety (SCCS) recently released an updated opinion on the use of MI.[10] It states that, in leave-on cosmetic products (including "wet wipes"), no safe concentration has been adequately demonstrated for induction or elicitation of contact allergy. In rinse-off cosmetic products, the SCCS has recommended that concentrations up to 0.0015% (15 ppm) MI are safe, in terms of the potential for induction of contact allergy, but stated that there is no information available to evaluate the potential for this ingredient to elicit contact allergy. Furthermore, the SCCS opinion states that MI should not be added to cosmetic products that contain MCI/MI. Cosmetics Europe, the personal care products industry trade association in Europe, has recommended the discontinuation of MI specifically in leave-on skin products, including wet wipes.[11]

Noncosmetic

The noncosmetic uses of MI include use in water-based paints, which has been noted in a number of case studies of sensitization reactions (eg, see Table 2). The uses of MI in paints and other noncosmetic products were described in the original safety assessment of MI that was published in 2010.[1]

Toxicokinetics

Absorption, Distribution, Metabolism, and Excretion

Absorption, distribution, metabolism, and excretion studies are summarized in the original safety assessment of MI that was published in 2010.[1]

Toxicological Studies

Acute Toxicity

Acute oral and dermal toxicity studies are summarized in the original safety assessment of MI that was published in 2010.[1]

Repeated Dose Toxicity

Oral repeated dose toxicity studies are summarized in the original safety assessment of MI that was published in 2010.[1]

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies are summarized in the original safety assessment of MI that was published in 2010.[1]

Carcinogenicity

Carcinogenicity studies of the sole ingredient MI were not discovered in the published literature, and unpublished data were not submitted to CIR.[1]

Genotoxicity

In vitro genotoxicity studies are summarized in the original safety assessment of MI that was published in 2010.[1]

Neurotoxicity

Neurotoxicity studies are summarized in the original safety assessment of MI that was published in 2010.[1]

Table 1. Historical and Current Use and Concentration of Use Data for Methylisothiazolinone.[1,4,5]

	# of uses		Max conc of use (%)	
Data year	2007[a]	2014[b]	2007	2014
Totals[c]	1125	745	4×10^{-6}-0.01	3.5×10^{-8}-0.01
Duration of use				
Leave-on	236	478	0.002-0.01	3.5×10^{-8}-0.01
Rinse-off	807	260	4.0×10^{-6}-0.01	2.5×10^{-7}-0.01
Diluted for (bath) use	82	7	NR	0.0002-0.01
Exposure type				
Eye area	6	22	NR	0.00019-0.01
Incidental ingestion	NR	1	NR	0.0048
Incidental inhalation—spray	4; 86[d]; 54[e]	3; 268[d]; 114[e]	0.005; 0.008-0.009[d]	0.0002-0.01[d]; 0.0002-0.01[f]
Incidental inhalation—powder	1; 2[g]	114[e]	NR	NR
Dermal contact	469	544	0.0008-0.01	3.5×10^{-8}-0.01[h,i]
Deodorant (underarm)	2[d]	NR	NR	0.0095[j]
Hair—noncoloring	579	190	4.0×10^{-6}-0.01	4.0×10^{-6}-0.01
Hair—coloring	76	NR	NR	5.6×10^{-5}-0.0095
Nail	1	5	NR	0.0002-0.006
Mucous membrane	241	103	0.0015-0.01	9.0×10^{-7}-0.01
Baby products	14	6	0.002-0.01[k]	0.0002-0.0075

Abbreviations: MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; NR, not reported.
[a] Data provided are not clear as to whether uses are MI alone or include uses of MI/MCI.
[b] Data provided are for uses of MI alone.
[c] Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[d] Includes products that can be sprays, but it is not known whether the reported uses are sprays.
[e] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[f] 0.01% in an aerosol hair spray; 0.0002% to 0.01% in a pump hair spray; 0.006% to 0.0095% in a pump hair tonic or dressing.
[g] Includes products that can be powders, but it is not known whether the reported uses are powders.
[h] 0.00023% to 0.01% in a hand soap; 0.01% in a foot scrub.
[i] The Council survey requested that wipe products be identified. One product containing MI was identified as being used as a skin cleansing wipe at a concentration of 0.005%.
[j] Not a spray deodorant.
[k] 0.01% in baby wipes.

Irritation and Sensitization

Irritation

Nonhuman and human dermal irritation studies, and nonhuman ocular irritation studies, are summarized in the original safety assessment of MI that was published in 2010.[1]

Sensitization

Nonhuman. A letter to the editor reporting the reevaluation of published local lymph node assay (LLNA) data indicated that MI should be categorized as a strong sensitizer and not a moderate sensitizer, in contrast to previous reports.[12] The earlier reports incorrectly reported 1.9% as the EC_3 for MI; the correct value is 0.4%, which is the lowest EC_3 estimated from multiple LLNAs using, for example, an acetone/oil vehicle.

Human. Methylisothiazolinone was named the Allergen of the Year for 2013 by the American Contact Dermatitis Society because of the increasing frequency of use of this preservative in consumer products and the increasing incidences of contact allergy reported to be associated with exposures to MI, especially in the European Union.[13-16] The standard series of patch testing includes exposures to 100 ppm MCI/MI mixture (3:1 ratio). This test may miss up to 40% of subjects with contact allergy to MI, alone, because of the relatively low MI concentration in the MCI/MI mixture tested (approximately 25 ppm MI in a 100 ppm MCI/MI test solution).[17,18] Recommendations have been made to test for contact allergy to MI alone, although there currently is no consensus about the concentration of MI that should be used in such testing.[13,19-24]

The dose–response relationship of contact allergy to MI was investigated in 11 MI-allergic patients.[25] The patients were patch tested with 2 dilution series of 12 doses of MI (Neolone 950 9.7% active ingredient) in 10% ethanol and 90% aqua and 12 doses of MI with 9.26 μg phenoxyethanol/cm^2 in 10% ethanol and 90% aqua. (Phenoxyethanol may increase antimicrobial efficacy of MI and was tested to determine whether it influenced reactivity to MI.) The MI doses with and without phenoxyethanol were 0.0105, 0.105, 0.147, 0.21, 0.441, 1.47, 2.94, 4.41, 8.82, 15, 30, and 60 μg MI/cm^2. Controls ($n = 14$) who were not MI-allergic patients were patch tested with 60 μg MI/cm^2 and 9.26 μg phenoxyethanol/cm^2. Each test site received 15 μL of each dilution applied by filter disc in a Finn Chamber and were occluded for 2 days. Readings were performed on days 2, 3 or 4, and 7. The subjects also underwent a repeated open application test (ROAT) with a cream that contained 0, 0.0105, 0.105, or 0.21 μg MI/cm^2 (0, 5, 50, or

Table 2. Quantitative Risk Assessment of Methylisothiazolinone (MI) at Highest Maximum Use Concentration (100 ppm) in Cosmetic Products.[a,28]

Product category[b]	Product amount applied/day (μg/cm^2)	Consumer exposure level (CEL; μg/cm^2/d)	Sensitization assessment factor (SAF)	Acceptable exposure level (AEL; μg/cm^2/d)[c]	AEL/CEL
Baby shampoo	200	0.02	100	0.15	7.50
Baby lotions, oils, powders, creams	2,200	0.22	300	0.05	0.23
Baby wipes	4,000	0.40	300	0.05	0.13
Other baby products (powders and talc's)	4,200	0.42	100	0.15	0.36
Other baby products (washes)	200	0.02	100	0.15	7.50
Bath oils, tablets, and salts	200	0.02	100	0.15	7.50
Bath soaps and detergents	10	<0.01	100	0.15	150
Bubble baths	200	0.02	100	0.15	7.50
Other bath preparations	200	0.02	100	0.15	7.50
Eyebrow pencil	2,200	0.22	300	0.05	0.23
Eyeliners	2,170	0.22	300	0.05	0.23
Eye shadow	2,170	0.22	300	0.05	0.23
Eye lotion	2,170	0.22	300	0.05	0.23
Eye makeup remover	900	0.09	100	0.15	1.67
Mascara	2,170	0.22	300	0.05	0.23
Other eye makeup	2,170	0.22	300	0.05	0.23
Cologne and toilet waters	1,7700	1.77	100	0.15	0.08
Blushers	1,000	0.10	100	0.15	1.50
Other fragrance products	2,200	0.22	100	0.15	0.68
Hair conditioners	200	0.02	100	0.15	7.50
Hair sprays (aerosol fixatives)	1,390	0.14	100	0.15	1.08
Hair sprays (pump)	2,200	0.22	100	0.15	0.68
Hair straighteners	4,200	0.42	100	0.15	0.36
Permanent waves	4,200	0.42	100	0.15	0.36
Rinses (noncoloring)	170	0.02	100	0.15	8.82
Shampoos (noncoloring)	170	0.02	100	0.15	8.82
Tonics, dressings, and other hair grooming aids	990	0.10	100	0.15	1.52
Wave sets	4,200	0.42	100	0.15	0.36
Other noncoloring hair products	1,000	0.10	100	0.15	1.50
[d]Hair dyes and colors	1,000	0.10	100	0.15	1.50
[d]Hair tints	990	0.10	100	0.15	1.52
Hair rinses (coloring)	200	0.02	100	0.15	7.50
[d]Hair bleaches	1,000	0.10	100	0.15	1.50
Other hair coloring preparations	1,000	0.10	100	0.15	1.50
Face powders	1,000	0.10	100	0.15	1.50
Foundations	3,170	0.32	100	0.15	0.47
Lipsticks	11,460	1.15	300	0.05	0.04
Other makeup preparations	4,200	0.42	100	0.15	0.36
Other manicuring preparations	1,000	0.10	100	0.15	1.50
Other personal cleanliness products	4,400	0.44	300	0.05	0.11
Aftershave lotions	2,210	0.22	100	0.15	0.68
Preshave lotions (all types)	2,200	0.22	100	0.15	0.68
Shaving cream (aerosol, brushless and lather)	70	0.01	300	0.05	7.14
Shaving soaps (cakes, sticks, etc)	70	0.01	300	0.05	7.14
Other shaving preparations	2,200	0.22	100	0.15	0.68
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	900	0.09	100	0.15	1.67
Depilatories	200	0.02	100	0.15	7.50
Face and neck creams, lotions, powders, and sprays	2,700	0.27	100	0.15	0.56
	1,120	0.11	300	0.05	0.45

(continued)

Table 2. (continued)

Product category[b]	Product amount applied/day (μg/cm^2)	Consumer exposure level (CEL; μg/cm^2/d)	Sensitization assessment factor (SAF)	Acceptable exposure level (AEL; μg/cm^2/d)[c]	AEL/CEL
Body and hand creams, lotions, and powders					
Moisturizers	2,700	0.27	100	0.15	0.56
Nail care creams and lotions	970	0.10	100	0.15	1.55
Deodorants (underarm)	8,500	0.85	300	0.05	0.06
Night creams, lotions, powders, and sprays	3,170	0.32	100	0.15	0.47
Paste masks (mud packs)	4,200	0.42	100	0.15	0.36
Skin fresheners	150	0.02	100	0.15	10
Other skin care products	2,200	0.22	100	0.15	0.68
Suntan gels, creams, liquids, and sprays	2,200	0.22	100	0.15	0.68
Indoor tanning preparations	2,200	0.22	100	0.15	0.68
Other tanning preparations	2,200	0.22	100	0.15	0.68
Foot powders and sprays	2,200	0.22	100	0.15	0.68

Abbreviations: AEL, acceptable exposure levels; CEL, consumer exposure level; NESIL, no expected sensitization induction level; QRA, quantitative risk assessment.

[a] Shaded rows indicate the ratio of AEL $\times$ CEL^{-1} is less than 1.

[b] Exposure values assumed for each product category were from the IFRA RIFM QRA Information Booklet (2011)[50] and Api et al. (2008).[51]

[c] Based on NESIL of 15 μg/cm^2/d.

[d] Note that this product category may be diluted prior to application.

100 ppm MI) with phenoxyethanol in 10% ethanol and 90% water. The patients applied 20 μL of the test solution from 4 different bottles twice a day to four 3 cm^2 areas of the volar forearm. Sites were read on days 2, 3 or 4, 7, 14, and 21, with additional reading if a reaction occurred between visits. In the patch test, results showed that phenoxyethanol had no influence on reactions to MI. The lowest eliciting dose in the patch test was 1.47 μg MI/cm^2 (49 ppm). No reactions were observed at 0.441 μg MI/cm^2 (15 ppm) or lower, nor were there any reactions in the control subjects. In the ROAT, 7 patients (64%) reacted to 0.105 and 0.21 μg MI/cm^2 and 2 patients (18%) reacted to 0.0105 μg MI/cm^2. The authors of this study recommended that the permitted amount of MI in cosmetics be reduced from 100 ppm.

In a human repeated insult patch test (HRIPT) of 226 subjects performed in accordance with the International Contact Dermatitis Research Group criteria for MI, 56 subjects received 100 ppm MI alone and the remaining 170 subjects received 100 ppm MI in combination with various glycols that are used as preservative boosters.[26] No evidence of induced allergic contact dermatitis was observed in any of the subjects, with or without glycols. The study concluded that 100 ppm MI does not cause a risk in cosmetic products when applied on uncompromised skin in the general population. Additional nonhuman and human sensitization studies are summarized in the original safety assessment of MI that was published in 2010.[1]

Quantitative Risk Assessment

Both Cosmetics Europe and the CIR SSC conducted QRAs, assuming 100 ppm (0.01%) MI in many categories of cosmetic products, in response to the increased incidences of contact sensitization to MI in Europe.[27,28] Both of these QRAs were conducted using the same no expected sensitization induction level (NESIL = 15 μg/cm^2/d) and sensitization assessment factors (SAFs).

Table 2 summarizes the QRA conducted by the CIR SSC. A conservative NESIL of 15 μg/cm^2/d was derived for MI based on a weight-of-evidence (WoE) evaluation of data from 5 HRIPTs and 4 LLNAs. The NESIL was then used to calculate acceptable exposure levels (AELs) for the potential for the induction of sensitization from dermal exposure to MI in cosmetic products, assuming the maximal use concentration of 100 ppm MI and product category–specific SAFs. The ratio of the AEL and the consumer exposure level (CEL) was then calculated for each of many cosmetic product categories, ranging from hair conditioners (CEL = 0.02 μg/cm^2/d) to lipsticks (CEL = 1.15 μg/cm^2/d). The concentration of an ingredient is considered to be acceptable in a product when AEL/CEL $\geq$1 (ie, AEL $\geq$ CEL).

According to the Cosmetics Europe calculations, the lowest estimated CEL to MI was 0.0011 μg/cm^2/d for shower gel, and the highest estimated exposure was 2.27 μg/cm^2/d for a nail varnish. The AEL/CEL ratios indicated that concentrations of MI up to 100 ppm (0.01%) would be acceptable for 20 of the 42 categories assessed by Cosmetics Europe and for 27 of the 60 categories assessed by the CIR SSC.

Phototoxicity

Nonhuman and human phototoxicity and photosensitization studies are summarized in the original safety assessment of MI that was published in 2010.[1]

Table 3. Case Studies.

Mode of contact	Patient(s)	Indication	Reference
MI in toilet wipes, carpet glue (100 ppm), and water-based paint (100 ppm and also 100 ppm MCI/MI)	55-year-old nonatopic male employed as a bank clerk	– Eczematous eruptions on the face, neck, retroauricular area, and forearms that appeared after exposure to fresh paint at his place of employment – Earlier in the year, suffered from pruritus ani and occasional eczema in the perineal area after use with a toilet wipe, facial dermatitis following first uses of a perfume after shaving, and dermatitis following use of deodorant – Previous patch tests with a baseline and cosmetic series were negative – Further testing performed with wipes, perfume, the individual ingredients of these products, and fragrance mix II and its components yielded positive reactions to the wipes, perfume, MI, and fragrance mix II on day 2 – Day 2 results from additional testing with repeated baseline series and aqueous dilutions of MI and MCI/MI found +? reaction to 100 ppm MCI/MI, ++ reaction to 1000 ppm MI, and + reaction to a brand of wipes – On day 4, + or +? reactions to 10, 50, and 100 ppm MCI/MI, + reaction to 10 ppm MI, ++ reactions to 100 and 500 ppm MI, +++ reactions to 1000 ppm MI, and ++ reaction to the wipes	[29]
Toilet wipes that contain 90 ppm MI and water-based paint that contained 0.01% MI and 0.01% MCI/MI	62-year-old nonatopic female	– Eczematous eruptions affecting face, trunk, arms, and legs that had started 1 month earlier as acute eczema in the perineal area that the patient attempted to treat with feminine hygiene products – Symptoms occurred 2 months following the initial use of a toilet wipe – Patch testing with European baseline, cosmetic series, the toilet wipe, and a feminine hygiene product yielded positive reactions to the wipe (++ days 2 and 4) and the feminine hygiene product (+ day 4) as well as to 100 ppm MCI/MI (++ days 2 and 4) – Patient returned 4 months later with 1-week history of swollen eyelids and face with severe itching and burning following exposure to water-based wall paint in her home – Patch testing with paint produced a ++ reaction	[29]
Toilet wipes that contain 90 ppm MI	50-year-old nonatopic female	– Patient presented with a 1-year history of perianal dermatitis following the use of moist toilet paper to control anal pruritus – Patch testing with European baseline, 1000 ppm MI, and 200 ppm MCI/MI yielded a + reaction to 200 ppm MCI/MI (day 4) and a + (day 2) and ++ (day 4) reaction to 1000 ppm MI	[29]
Toilet wipes that contain 90 ppm MI	43-year-old nonatopic female	– Patient presented with a 3-month history of eczematous lesions on the genital and perianal area – Patch testing with European baseline, 1000 ppm MI, and toilet wipe yielded a + (day 2) and ++ (day 4) reaction to 1000 ppm MI	[29]
Toilet wipes that contain 90 ppm MI	20-year-old nonatopic female	– Perianal itch and genital lesions that had lasted 4 years that the patient treated under physician's guidance with toilet wipes and then worsened into oozing dermatitis – Patch testing with European baseline and toilet wipe yielded a ++ reaction (day 4) to 100 MCI/MI, a ++ reaction (day 4) to 1000 ppm MI, and ++ reactions (day 2 and 4) to the wipes	[29]

(continued)

Table 3. (continued)

Mode of contact	Patient(s)	Indication	Reference
Eye cleansing lotion that contained MI	57-year-old atopic female	– Patient presented eczematous lesions to the eyelids, mainly localized in corners of eyes, with 6 months duration – Patch testing with European baseline, cosmetic series, and 1000 ppm MI yielded + reactions (days 2 and 4) to 1000 ppm MI	29
Toilet wipes that contain 90 ppm MI	44-year-old atopic female	– Patient presented pruritus and perianal eczema with 1-year duration following use of toilet wipes that were initially used 2 years prior – Patient also had reactions previously to perfumed bath salts and has experienced severe scalp itch – Patch testing with European baseline, cosmetic series, 10 and 1000 ppm MI, 10 ppm MCI/MI, fragrance mix II ingredients, lavender oil, and the toilet wipe yielded a +++ reactions (days 2 and 4) to 100 ppm MCI/MI, +++ (day 2) and ++ (day 4) reactions to 1000 ppm MI, a + (day 4) reaction to 10 ppm MI, and ++ reactions (days 2 and 4) to the toilet wipes	29
Deodorant containing MI used for 2 weeks	37-year-old atopic woman with past history of jewelry intolerance and no history for previous skin reactions to perfumes and deodorants	– Eczematous lesions affecting both axillae that cleared after treatment with topical corticosteroids – Patch testing with Portuguese baseline series, a fragrance series, and to patient's own product yielded ++ reactions to nickel, 100 ppm MCI/MI, and to the deodorant; – Repeated open allocation test on the volar forearm with the deodorant was strongly positive on day 2 – Patch testing with 200 ppm MI yielded a ++ reaction on day 2	31
Water-based wall paint containing 0.0053% (53 ppm) MI that had been applied to bedroom walls	4-year-old girl with mild atopic dermatitis since birth	– Papular dermatitis affecting face, including nasolabial folds and lower eyelids, followed by generalized skin lesions accentuated at the knee and elbow folds – Rash "waxed and waned" for about 4 weeks with corticosteroid treatment while patient continued to sleep in painted bedroom and then started to clear – Patch testing with adapted European baseline series for children had a + reaction on D4 for MCI/MI at 0.01% or 100 ppm – Child had a history of extensive dermatitis following use of a moist toilet paper that contained MI but not MCI	30
Toilet cleaner containing 10 ppm MI with additional occupational exposures	32-year-old man	– Severe widespread dermatitis caused by heavy exposure to MCI/MI and MI while working at a glue factory – Patch testing revealed + reaction to MCI/MI and ++ reaction to MI – During treatment, patient also developed a 5-cm eczematous reaction on left inner thigh extending to the buttock – Patient had a new toilet cleaner in home toilet that contained both MCI and MI at 11 ppm and 10 ppm, respectively – Eczema improved after removal of toilet cleaner from home	32
Wall paint containing MI	23-year-old nonatopic woman	– Initial symptoms of facial dermatitis including periorbital edema that progressed to vesicular dermatitis began 2 months prior to examination after the patient started working at a restaurant that had just been freshly painted – Patient also experienced burning sensation of the cheeks, malaise, and dizziness that worsened the more	33

(continued)

Table 3. (continued)

Mode of contact	Patient(s)	Indication	Reference
		consecutive days she worked and improved during days off – Patch testing with European baseline series, an extended series with the patient's own cosmetic products, and an extended series with fragrance ingredients yielded ++ reactions to 0.01% MCI/MI and to 0.2% MI – After initial airborne exposure, patch testing and onset of dermatitis, patient was reexposed to MI in a cleansing product to which she had never been exposed and immediately experience marked aggravation of facial dermatitis	
Wall paint containing MI	36-year-old nonatopic male	– Dermatitis on the legs that spread to the face, shoulders, back, abdomen, and arms as well as intense headache that worsened while the patient was at work, but improved on days off – Initial patch testing showed ++ reaction to 2% formaldehyde and +? reactions to fragrance and 0.2% MI – Symptoms disappeared after 2.5 months of sick leave, but reappeared after patient moved to a newly refurbished apartment – Both the apartment and casino (workplace) had been painted with a paint that contained MI	[34]
Wall paints containing 1.2-187 ppm MI, 0.3-10 ppm MCI/MI, and 8.5 -187 ppm benzisothiazolinone (BIT)	57-year-old nonatopic male with a long history of hand eczema and contact allergy	– Patient developed facial erythema, cough, and difficulty breathing a few days after using paint containing isothiazolinones – During the same time period, the patient was participating in a clinical investigation of the dose–response relationship of MI in MI-allergic patients – Patient previously had positive patch tests to formaldehyde, quaternium-15, DMDM hydantoin, *p*-phenylenediamine, melamine formaldehyde, urea formaldehyde, MCI/MI, and MI – Treatment with prednisolone, cetirizine, and corticosteroids helped alleviate the symptoms while at the hospital but all symptoms reoccurred when the patient returned home and even worsened to include dermatitis reactions at the MI test sites from the dose–response study	[34]
Wall paint containing MI	53-year-old nonatopic female	– Patient presented with severe respiratory symptoms, erythema in the face, and edema around the eyes that occurred after the patient moved into a freshly painted apartment – Patch testing with the European baseline series, an extended standard, and a paint series yielded + reactions to 2000 ppm MI and 5% farnesol – Symptoms resolved after the patient moved out of her apartment	[35]
"Waist reduction belt" contact gel containing MI	68-year-old male with longstanding perianal dermatitis and recurrent hand eczema	– Patient presented with pruritic, erythematous patches on abdomen corresponding to contact areas for the gel of a waist reduction belt – Patient used the device 3×/day for 10 minutes each for a few days before developing progressive skin changes – Patch testing with baseline series, preservative series, 5% propylene glycol, and 3 ultrasonic contact gels, including the one used by the patient, yielded doubtful reactions to fragrance mix I and MCI/MI and ++ reaction to 0.05% MI	[36]

(continued)

Table 3. (continued)

Mode of contact	Patient(s)	Indication	Reference
Household wipes and skin cleansing products containing MI	39-year-old nonatopic female employed as a neonate nurse	– Labeling of the contact gel used by patient indicated the presence of both MCI and MI – Patient presented with eczematous skin lesions on the arms, neck, and trunk of 7 months duration – Patient also developed palmar hand dermatitis 2 months later, after receiving treatment for the initial symptoms – Patient had previously developed a severe eczematous reaction on the hands to water-soluble paint and eyelid dermatitis while her house was being painted – Patient had daily contact to nitrile gloves, hospital soap, skin cleansing products, baby wipes, household wipes, and rubber – Patch testing with the European baseline series, cosmetic and rubber series, and patient's products and the known allergens in them yielded + reactions to 500 ppm MI, 5% Compositae mix, a cosmetic body milk tested "as is," and a household wipe tested "as is" – Household wipes were analyzed by a lab that determined they contained 60 ppm MCI/MI; however, the patient tested negative to 100 ppm MCI/MI.	[37]

Abbreviations: BIT, benzisothiazolinone; DMDM, 1,3-Dimethylol-5,5-dimethyl; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

Clinical Use

Case Reports

A sampling of case reports and retrospective and multicenter studies reporting MI allergy are summarized in Tables 3 and 4, respectively. Numerous reports of contact allergy, particularly to toilet wipes and water-based wall paint containing MI, have been reported.[29-37] Incidences of contact allergy to MI, tested separately from MCI/MI, appear to be increasing in Europe in recent years.[38-49] Additional case reports are summarized in the original safety assessment of MI that was published in 2010.[1]

Summary

In 2010, the Panel published the final report of the safety assessment of MI with the conclusion that "MI is safe for use in cosmetic formulations at concentrations up to 100 ppm (0.01%)." At the March 2013 CIR Expert Panel meeting, the Panel reopened this safety assessment to gather and evaluate newly provided clinical data indicating a higher than expected frequency of individuals who have allergic reactions to the preservative MI. This summary only contains newly identified information on the MI. The original report should be consulted for the information that was previously reviewed by the Panel.

According to the FDA's VCRP database in 2007, MI had 1,125 reported uses, with the majority of the uses reported in noncoloring hair conditioners and shampoos. Industry reported the maximum use concentration range to be $4 \times 10^{-6}\%$ to 0.01%, with 0.01% reported in leave-on and rinse-off baby, noncoloring hair, and dermal contact products. The information obtained from the VCRP in 2007 did not clearly distinguish cosmetic products in which MI was used in combination with MCI from cosmetic products in which MI was used without MCI. This safety assessment addresses the use of MI in cosmetic products that do not also contain MCI. In 2014, the VCRP database indicated that MI was used as an ingredient in 745 cosmetic products that do not also contain MCI, with the majority of the uses reported in leave-on products such as skin moisturizers. A survey of use concentrations conducted by the Council in 2014 reported a maximum concentration of use range of $3.5 \times 10^{-8}\%$ to 0.01%, with 0.01% reported in multiple product categories including eye makeup remover, hair shampoos and conditioners, and skin care products (both leave-on and rinse-off).

The European Union's SCCS has a recently updated opinion on the use of MI and has found that in leave-on cosmetic products (including "wet wipes") no safe concentration has been adequately demonstrated for induction or elicitation of contact allergy. In rinse-off cosmetic products, the SCCS has concluded that concentrations up to 0.0015% (15 ppm) MI are safe, in terms of induction of contact allergy, but recognized that there is no information available to evaluate the potential for this ingredient to elicit contact allergy. Furthermore, the SCCS states that MI should not be added to cosmetic products that contain MCI/MI. A reevaluation of the LLNA results reported in the published literature in an editorial article indicates that MI should be categorized as a strong sensitizer, and not a moderate sensitizer as previously reported.

Methylisothiazolinone was named Allergen of the Year for 2013 by the American Contact Dermatitis Society due to the rise of use of the preservative and the increased incidences of contact allergy being reported, especially in the European Union. A standard series of patch testing includes the mixture MCI/MI, which may miss 40% of contact allergy to MI alone

Table 4. Retrospective and Multicenter Studies.

Number of dermatitis patients tested; location	Concentration of MI tested	Years analyzed	Results	Reference
2,536; Gentofte, Denmark	2000 ppm in supplemented European baseline series	May 2006 to February 2010	– 1.5% (37/2536) of the patients patch tested with MI had contact allergy – MI contact allergy more often associated with occupational exposure, hand eczema, and age above 40 years – 12/37 cases (32%) were cosmetics exposure and 11/37 cases (30%) were occupational exposure, with half of these occurring in painters	[38]
10,821; Finland	0.1% (1000 ppm) and 0.03% (300 ppm) in addition to being tested with MCI/MI	2006-2008	– 1.4% and 0.6% had positive patch test reactions to 0.1% and 0.03% MI, respectively – 66% of those who were MI-positive were also positive to 100 ppm MCI/MI – Of 33 patients who submitted to a use test, 10 had positive results	[39]
653; Australia	200 ppm in the Australian baseline series; testing with100 and 200 ppm MCI/MI also performed	January 1, 2011 to June 30, 2012	– 43 (7%) reactions were observed, 23 (4%) of which were deemed relevant – 7 of the patients were parents of young children with hand dermatitis caused by allergic contact dermatitis to MI in baby wipes – Remaining patients reacted to MI in shampoos, conditioners, deodorants, moisturizers, a skin cleanser, and a facial wipe – 3 patients had occupational exposure to hand cleansers – 34/43 patients (79%) had concomitant reactions with MCI/MI	[40]
2,766 to MI, 2,802 to MCI/MI, and 2,413 to BIT; Gentofte, Denmark	2000 ppm MI, 100 ppm MCI/MI, and 1000 ppm BIT	2010-2012	– Contact allergy to MI increased from 2.0% in 2010% to 3.7% in 2012 – Contact allergy to MCI/MI increased from 1.0% in 2010% to 2.4% in 2012 – MI-allergic patients tended to have occupational exposure, hand and face dermatitis, and were $>$ 40-years-old – Cosmetic products were the most common substances causing relevant exposure in both MCI/MI- and MI-allergic patients	[41]
1,289; London	500 ppm MI in a cosmetics/face patch test series	July 2010 to September 2012	– In 2010, 1/85 patients (0.5%) had a positive reaction to MI – In 2011, 18/521 patients (3.5%) had a positive reaction to MI – In 2012, 33/584 patients (5.7% had a positive reaction to MI) – Reactions appeared to be more prevalent in patients $\geq$40 years old	[42]

(continued)

Table 4. (continued)

Number of dermatitis patients tested; location	Concentration of MI tested	Years analyzed	Results	Reference
219 painters and 1,095 controls; Gentofte, Denmark	0.01% MCI/MI in European baseline series with testing with MI and other isothiazolinones of unreported concentrations performed as dictated by patient's exposure history	2001 to 2010	– 22/219 (10%) of painters had positive reactions to MCI/MI ($P < 0.0001$) – 11/41 (27%) of painters had positive reactions to MI – 5/21 (25%) of painters had positive reactions to octylisothiazolinone – 7/37 (19%) of painters had positive reactions to benzisothiazolinone (BIT)	43
~120,000 with baseline series and ~13,000 with preservative series; Germany, Switzerland, Austria (IVDK network)	0.05% MI in pet and 0.01% MCI/MI in pet	January 1996 to December 2009	– 2.22% of patients had positive reactions to MCI/MI in baseline series – 1.54% of patients had positive reactions to MI in preservative series – 67% (134/199) of MI-positive patients also reacted to MCI/MI – MI sensitization observed more often with occupational dermatitis	44
563 and 2,056 for 2 different concentrations of MI, 2,489 for MCI/MI; Leeds, United Kingdom	0.002% MI (2009-2012); 0.2% (2011-2012); and 0.02% MCI/MI (2008-2012)	January 2008 to June 2012	– 3.8% and 4.6% of patients had positive reactions to 0.2% MI in 2011 and 2012, respectively – Percentage of patients positive to 0.02% MI increased from 0.6% in 2009 to 2.5% in 2012 – percentage of patients positive to 0.02% MCI/MI increased from 0.9% in 2008 to 4.9% in 2012	45
245 for MI and ~25,000 for MCI/MI; European Surveillance System on Contact Allergy Network	0.05% MI and 0.01% for MCI/MI	2007 to 2008	– 2.6% of patients (n = 245 in the Netherlands) had positive reactions to MI – Additional results reported were 1.1% and 1.7% positive reactions in 281 Finnish patients to 0.03% MI and 0.1% MI, respectively, and 1.4% positive reactions in 1280 Danish patients to 0.2% MI – For MCI/MI, an average of 2.5% of the patients across 11 countries had positive reactions	46
28,922; IVDK network	0.05% MI (500 ppm) in water	2009 to 2012	– An average of 3.83% of patients tested had positive reactions to MI – Prevalence of MI sensitization reported to have increased from 1.94% in 2009 to 6.02% in 2012 – Increases observed in female patients ≥40 years old, patients with face dermatitis, and use of cosmetics	47
477; France	0.02% and 0.05% (200 and 500 ppm) MI	2 year period, years not reported	– Out of 477 patients tested with European baseline and 2 concentrations of MI, 10 patients had relevant reactions – All 10 patients reacted to 0.05% MI, while only 5 reacted to 0.02% MI	48

(continued)

Table 4. (continued)

Number of dermatitis patients tested; location	Concentration of MI tested	Years analyzed	Results	Reference
12,427 in 2009, 12,802 in 2010, and 12,575 in 2011; IVDK network	500 ppm MI and 100 ppm MCI/MI	2009-2011	– Only 1 patient of the 10 reacted to 100 ppm MCI/MI – All 5 patients who had been tested with personal care products containing MI reacted – 1.9%, 3.4%, and 4.4% positive reactions in 2009, 2010, and 2011, respectively – Proportion of MI-positive patients in those reacting to MCI/MI increased from 43% to 59% between 2009 and 2011	[49]

Abbreviations: MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

due to the relatively low concentration of MI in the mixture. Recommendations have been made to test for MI contact allergy separate from the MCI/MI, although there currently is no consensus of about the concentration of MI that should be tested.

In sensitization studies conducted in 11 MI-allergic patients, the lowest eliciting dose in a patch test was 1.47 μg MI/cm^2 (49 ppm). No reactions were observed at 0.441 μg MI/cm^2 (15 ppm) or lower, nor were there any reactions in the controls. In a ROAT, 7 (64%) patients reacted to 0.105 and 0.21 μg MI/cm^2 and 2 (18%) patients reacted to 0.0105 μg MI/cm^2. In a HRIPT of 100 ppm MI, with or without various glycols, no evidence of induced allergic contact dermatitis was observed in any of the subjects.

Numerous reports of contact allergy, particularly to toilet wipes and water-based wall paint containing MI, have been reported. Incidences of contact allergy to MI, tested separately from MCI/MI, appear to be increasing in Europe in recent years.

Cosmetics Europe and the CIR SCC conducted QRAs of MI in response to the increased incidences of contact sensitization to MI in Europe. The QRA, which used a conservative NESIL of 15 μg/cm^2/d that was derived based on a WoE evaluation of data from 5 HRIPTs and 4 LLNAs, predicted that consumer exposures to 100 ppm MI in skin leave-on products and cosmetic wet wipes could induce skin sensitization, while exposures to the same concentration in rinse-off products and hair care leave-on products would not induce skin sensitization.

Discussion

The Panel noted the numerous reports of contact allergy to MI in Europe and the increased incidences of contact allergy to MI observed in their own clinical experience. The Panel also noted that MI was named Allergen of the Year for 2013 by the American Contact Dermatitis Society because of the increasing incidence of contact allergy associated with the increasing use of this ingredient as a preservative in cosmetics. The Panel reviewed the results of QRAs performed by Cosmetics Europe and the CIR SSC using an appropriate NESIL (ie, 15 μg/cm^2/d) selected based on a WoE evaluation of EC_3 values from LLNAs and the results of HRIPTs. The results supported the safety of the use of MI in rinse-off product categories at concentrations up to 100 ppm. However, the QRA indicated that MI use in many leave-on product categories would be safe only at concentrations lower than 100 ppm. As shown in Table 3, for example, the AEL/CEL calculated for 100 ppm (0.01%) MI in baby wipes was 0.13, which the Panel recognizes to be consistent with the reports of increasing incidence of contact allergy associated with the use of MI in wet wipes.

Based on the QRA results, the Panel felt that the current limitation of 100 ppm supported the safety of MI in rinse-off products. Nonetheless, they felt that leave-on products should be formulated to contain MI concentrations below 100 ppm and to be nonsensitizing, as demonstrated, for example, by QRA estimates of safe exposures (typically expressed in μg/cm^2/d) for the relevant cosmetic product category.

The risk of inducing sensitization depends on the dose of MI per unit area of the skin exposed (eg, expressed in units of μg/cm^2/d). One type of cosmetic product will differ from another in the potential to cause sensitization at a given MI concentration if they differ substantially in application rate, which depends on the amount of product applied per day and the total surface area of the skin to which the product is applied. This helps to explain why the risks associated with MI in rinse-off products are less than those associated with leave-on products and, for instance, why the risks associated with exposures to MI in leave-on hair conditioners would likely be substantially lower than those associated with MI in wipes.

It is important to note that appropriate exposure assumptions used in a QRA can vary depending on factors such as differences in regional habits and practices, properties of the formulation, and degree to which conservative default assumptions and exposure scenarios may be refined based on specific exposure data. The Panel stressed the importance of clearly

identifying and justifying the exposure assumptions, and the sources of the assumptions, used in any QRA that might be conducted to predict concentrations of MI unlikely to induce sensitization from the use by consumers of a specific cosmetic product or product category.

The Panel determined that the maximum MI concentration should never exceed 100 ppm (0.01%) in any hair product, leave-on product, or rinse-off product, based on the potential for inducing sensitization and concentrations greater than 100 ppm.

The Panel's recommendations for MI in rinse-off and leave-on cosmetic products are intended to prevent the induction of sensitization to MI. The Panel cautioned that following these recommendations may not necessarily prevent the elicitation of allergic reactions in individuals who are already allergic to MI. Individuals sensitized to MI should avoid products that contain MI.

The Panel discussed the issue of incidental inhalation exposure to MI in noncoloring hair sprays and hair tonics or dressings. There were no chronic inhalation toxicity data identified or provided. Methylisothiazolinone reportedly is used at concentrations up to 0.01% in cosmetic products that may be aerosolized. The Panel noted that 95% to 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposures expected in the breathing zone and the absence of significant signs of toxicity in subchronic, chronic, and reproductive and developmental animal studies reviewed previously by the Panel, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

Conclusion

The CIR Expert Panel concluded that MI is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when they are formulated to be nonsensitizing, which may be determined based on a QRA.

Authors' Note

Unpublished sources cited in this report are available from the Executive Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

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C. L. Burnett contributed to conception, design, acquisition, analysis, and interpretation, drafted the manuscript, and critically revised the manuscript. I. Boyer contributed to analysis and interpretation. W. F. Bergfeld, D. V. Belsito, R. A. Hill, C. D. Klaassen, D. C. Liebler, J.G. Marks, R. C. Shank, T. J. Slaga, P. W. Snyder, and L. J. Gill contributed to conception, design, analysis, and interpretation, critically revised the manuscript, and gave final approval. B. Heldreth contributed to analysis and interpretation, critically revised the manuscript, and gave final approval. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

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