Amended Safety Assessment of Methylisothiazolinone as Used in Cosmetics

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All interested persons are provided 60 days from the above release date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian J. Gill.

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Ronald A. Hill, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, DPA. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

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ABSTRACT

The Cosmetic Ingredient Review Expert panel (the 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 concluded that MI is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetics products when they are formulated to be non-sensitizing, which may be determined based on a QRA.

INTRODUCTION

In 2010, the Cosmetic Ingredient Review (CIR) Expert Panel published the 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 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/methylisothiazolinone (MCI/MI). The Panel reopened this safety assessment to gather and evaluate additional data. Interested parties were encouraged to provide all available data relevant to this concern about allergic reactions.

The Panel previously reviewed the safety of the mixture MCI/MI (sold at a ratio of 3:1; trade names include Kathon™ microbiocides) 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]

Excerpts from the 2010 report summary are included in each appropriate report section, and are indicated by *italicized text*. The Discussion section of the original 2010 safety assessment is presented here as a reminder of the Panel deliberations of the original review.

CHEMISTRY

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

USE

Cosmetic

Table 1 presents the historical and current product formulation data for MI. MI functions as a preservative in cosmetic products.[3] According to information supplied to the Food and Drug Administration (FDA)'s Voluntary Cosmetic Registration Program (VCRP) database in 2007, MI had 1125 reported uses, with the majority of the uses reported in non-coloring hair conditioners and shampoos.[1] It should be noted that the information provided under the VCRP in 2007 did not clearly indicate whether MI is used alone in products or is used in combination with MCI. In 2008, industry reported the maximum use concentration range to be 4×10^{-6}% to 0.01%, with 0.01% reported in both leave-on and rinse-off baby, non-coloring hair, and dermal contact products.[1] In 2014, the VCRP database indicated that MI is used as a stand-alone ingredient in 745 cosmetic products, 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 3.5×10^{-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]

MI was reported to be used in non-coloring 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 (i.e., 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 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 the potential for 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.

Non-Cosmetic

The non-cosmetic uses of MI were described in the original safety assessment.[1]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

The percutaneous absorption of radiolabeled MI (99.88% radiochemical purity) was determined using rat skin mounted on diffusion cells. Over a 24-hour period, the rate of absorption was 0.0059, 0.0277, and 0.0841 μg equivalents/cm^2/h for 25, 75, and 150 ppm dose groups, respectively, and the mean amount of total applied radioactivity absorbed was 21.4%, 33.7%, and 51.2% for 25, 75, and 150 ppm dose groups, respectively. The total dose absorbed of aqueous solutions containing radiolabeled MI (96.90% radiochemical purity) in human epidermis was 29.8%, 38.0%, and 54.7% for 52.2, 104.3, and 313 μg MI/ml dose groups. The rate of absorption was 0.037 μg/cm^2/h over a 24-hour exposure. In the same study, the total dose absorbed from shampoo, body lotion, and facial cream formulations containing 100 μg MI/ml was 29.5%, 8.98%, and 19.6%, respectively. The rates for absorption of MI in the formulations over a 24-hour exposure ranged from 0.007 to 0.026 μg/cm^2/h. After oral dosing of 100 mg/kg radiolabeled MI (96.70% radio purity) in mice, total radioactive residues (TRR) were highest in the liver and lowest in the bone 1 h post-dosing. At 24 h post-dosing, TRR declined significantly in all tissues and the tissue-to-plasma ratio showed that the radiolabel partitioned preferentially from plasma to tissues. Blood had the highest tissue-to-plasma ratio at 48 h. TRR was higher in male tissues than female tissues overall. Most radiolabeled metabolites of MI (99.08% radio purity) were excreted in urine and feces by rats within 24 h of oral dosing. Tissue sampling at 96 h post-dosing found 1.9-3.6% of the radiolabel, mainly in blood. Total mean recovery of the radiolabel was 92-96%. Major metabolites in urine were N-methyl malonamic acid (NMMA), 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl-propionamide, and N-methyl-3-hydroxyl-propamide. Another metabolism study of radiolabeled MI (96.90% radio purity) conducted on bile duct-cannulated rats had an 88% recovery of the dose at 24 h post oral dosing. The majority of the radiolabel was found in bile, urine, and feces. No intact MI was recovered and the main metabolites were NMMA and 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl-propionamide.

TOXICOLOGICAL STUDIES

Acute Toxicity

In acute oral toxicity studies, MI was slightly toxic in rats in concentrations ranging from 9.69% to 99.7%. At 9.69%, the LD_{50} for male and female rats was 274.6 and 105.7 mg/kg body weight, respectively. Rats that died during these studies had reddened intestines and/or stomach mucosa, clear or red/yellow fluid in the intestines and/or stomach; blackened intestines and distended stomachs. Studies on body lotion, shampoo, and sunscreen formulations in rats containing 100 ppm MI found no treatment related effects and an LD_{50} greater than 2000 mg formulation/kg body weight. Slight toxicity, including gastrointestinal changes, was observed in mice that orally received 97.5% MI. The LD_{50} was 167 mg/kg body weight. An acute oral toxicity study of the metabolite NMMA found the substance slightly toxic. The calculated oral LD_{50} for NMMA in males and females was 3550 and 4100 mg/kg body weight, respectively. MI at 97.5% was slightly toxic in rats in an acute dermal toxicity study. The substance was corrosive to the skin. The LD_{50} was calculated to be 242 mg/kg body weight. In another acute dermal toxicity study, 9.69% MI was corrosive to rat skin, but no deaths occurred during the study. The LD_{50} was greater than 484.5 mg/kg body weight. Acute inhalation toxicity studies in rats found that 53.52% and 97.8% MI were slightly toxic after 4 h exposures. The LC_{50} were 0.35 and 0.11 mg/L. Rats that died during these studies had reddened lungs and distended gastrointestinal tracts. Mice exposed to 10 minutes of atomized 98.6% MI had up to 47% decrease in respiratory rates that equated to moderate responses for sensory irritation.

Repeated Dose Toxicity

No toxic effects were observed when 97.5% MI was administered to rats in drinking water for 13 weeks at concentrations of 0, 75, 250, or 1000 ppm. Dogs that were fed diets prepared with 51.4% MI for 3 months had a NOAEL of 1500 ppm. In a subchronic study, rats fed the metabolites NMMA or malonamic acid for 3 months had no effects observed in body weight, food consumption, hematology, clinical chemistry, urinalysis, ophthalmology, or gross pathologic changes. Beagle dogs that received these metabolites in their diets for 3 months had no systemic toxicity.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In a teratogenicity study, MI was administered by daily single oral doses to pregnant rats at doses of 5, 20, or 60 (reduced to 40) mg/kg body weight/day on gestation days 6-19. Females in the high dose group had clinical signs of rales, gasping, and labored breathing and at necropsy had red areas in the glandular portion of the stomach and lungs. No treatment-related effects were observed in the fetuses. The maternal and developmental NOAEL were 20 mg/kg/day and 40 mg/kg/day, respectively. In a teratogenicity study of MI in rabbits, pregnant females received daily single oral doses of 3, 10, or 30 mg/kg/day MI on gestation days 6-28. Maternal effects in the 30 mg/kg/day group included decreased defecation and dark red areas in the stomach. The maternal NOAEL was 10 mg/kg/day. No treatment-related effects were observed in the fetuses and the developmental NOAEL was determined to be 30 mg/kg/day. A two-generation reproduction toxicity test found that MI in drinking water at concentrations up to 1000 ppm was not a reproductive toxicant.

CARCINOGENICITY

Studies of the carcinogenicity of the sole ingredient MI were not available; however, a 2 year drinking water study in rats concluded that the mixture MCI/MI tested up to 300 ppm was not a carcinogen.

GENOTOXICITY

MI (up to 1000 µg/plate) and the metabolite NMMA (up to 5000 µg/plate) were not mutagenic in the Ames test when tested with and without metabolic activation. In a Chinese hamster ovary cell assay, 97.5% pure MI was non-mutagenic when tested with and without metabolic activation (0.5 - 40.0 µg/ml). However, another CHO assay that studied MI at 97.5% a.i. (0.0785 - 5000 µg/ml) found significant increases in cells with chromosome aberrations, with and without metabolic activation. The aberrations were accompanied by significant cytotoxicity, which may have caused a false positive in this assay. MI was non-mutagenic in an unscheduled DNA synthesis assay and in a micronucleus test.

NEUROTOXICITY

An acute in vitro neurotoxicity study of MI (up to 300 µM) in embryonic rat cortical neurons and glia observed widespread neuronal cell death within 24 h in the cortical cultures. Gliotoxicity was low. A 14-hour in vitro neurotoxicity study of MI (up to 3.0 µM) from the same laboratory concluded that prolonged exposure to MI and related isothiazolones may damage developing nervous systems. However, no evidence of neurotoxicity has been observed in vivo.

IRRITATION AND SENSITIZATION

Irritation

Non-Human

A bovine cornea study classified MI as mildly irritating. Ocular irritation studies in body lotion, shampoo, and sunscreen formulations containing 100 ppm MI found the formulations non-irritating in rabbit eyes. Undiluted 97.8% MI was corrosive to intact rabbit skin after an exposure period of 1 h. Rabbit dermal irritation studies of MI at 9.69% and 10% concluded the chemical was non-irritating. In EpiDerm skin constructs, 1.7% MI applied for 3 or 60 minutes were non-corrosive. In the same study, 51.5% MI was non-corrosive in the 3 minute exposure but corrosive at the 60 minute exposure.

Human

A single 24-hour application of 100 ppm MI in 40 volunteer subjects did not produce skin irritation. Respective skin irritation studies in body lotion, shampoo, and sunscreen formulations containing 100 ppm MI also found MI to be nonirritating.

Sensitization

Non-Human

In a guinea pig maximization test, 0.076% w/v MI was a weak sensitizer and a follow-up study found that 0.015% MI produced no sensitization. An investigation using the Buehler method found that 99.8% MI was a sensitizer at concentrations $\geq$ 1000 ppm. Another maximization test that evaluated the sensitization potential of 99.7% MI concluded that the chemical was not a sensitizer at concentrations up to 800 ppm. MI was a sensitizer at concentrations $\geq$ 1.5% in an open epicutaneous test. Results from one local lymph node assay (LLNA) indicated that 99.8% MI produced sensitization at >10,000 ppm. The SI for30, 000 ppm was 3.2 and the EC_3 value was calculated to be 25,150 ppm. In another LLNA, 10.37% MI produced sensitization at >0.76%. The SI for $\geq$ 1.35%

were ≥ 4.73 and the EC_3 value was calculated to be 0.86%. In a joint study, a LLNA testing MI at concentrations up to 0.85% in acetone/olive oil and up to 9.85% in propylene glycol found MI was a skin allergen with moderate strength, but the cytokine profile of 0.5% MI was not typical of chemical respiratory allergens and concluded that MI was not likely to have a significant potential to cause sensitization of the respiratory tract. The metabolite NMMA did not induce hypersensitivity in a local lymph node assay up to and including 30% concentration.

A letter to the editor reporting the re-evaluation of published 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%.

Human

In a clinical study of 22 patients tested with fractions isolated from Kathon CG that included MI and MCI, only 2 patients had positive reactions to MI. Sensitization may have been due to cross-reactions to MCI. MI was determined to be a weak sensitizer in a study of 12 patients. In a cumulative irritation/sensitization study of MI in 80 subjects, the sensitization threshold was determined to be at or around 1000 ppm. Eighty-five patients with pre-determined sensitization to MI/MCI were tested epicutaneously to 500 or 1000 ppm MI. The results show that at high concentrations of MI (500 to 1000 ppm), 32% of the subjects with known sensitivity to MCI/MI reacted to MI. A human RIPT in 98 subjects tested with 100 ppm MI concluded that MI did not induce skin sensitization in humans. A series of RIPT evaluating the sensitization of 50% MI at concentrations of 200, 300, 400, 500, or 600 ppm concluded that MI up to 600 ppm was not a dermal sensitizer.

Dermal – Human

MI was named the Contact 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] 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 3.75 ppm in rinse-off products or 1.8 ppm in leave-on products). 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.[13-16]

The dose-response relationship of contact allergy to MI was investigated in 11 MI-allergic patients.[17] 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 if 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 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 HRIPT of 226 subjects performed in accordance with the International Contact Dermatitis Research Group (ICDRG) 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.[18] 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.

QUANTITATIVE RISK ASSESSMENT

Both Cosmetics Europe and the Council's CIR Science and Support Committee (SSC) conducted quantitative risk assessments (QRA) of MI in response to the increased incidences of contact sensitization to MI in Europe.[19,20] Table 4 presents the QRA calculations from the CIR SCC. For the QRA, a conservative weight-of-evidence no expected sensitization induction level (WoE NESIL) of 15 μg/cm^2 was derived based on data from 5 HRIPTs and 4 LLNAs. The NESIL was then used to calculate a margin of safety (MOS) for the potential for sensitization from dermal exposure to this ingredient in cosmetic ingredients, assuming the maximal use level of 100 ppm MI and product specific safety assessment factors (SAFs) (according to the Cosmetics Europe calculations, for example, the lowest estimated consumer exposure to MI was 0.0011μg/cm^2 for shower gel; highest estimated exposure was 2.27 μg/cm^2 for a nail varnish). The MOS calculated was acceptable for 20 of the 42 categories assessed by Cosmetics Europe and for 27 of the 60 categories assessed by the CIR SSC.

PHOTOTOXICITY

MI at 100 ppm was not phototoxic or photosensitizing in guinea pig studies. No phototoxic effects were observed in a study of 200 ppm MI in 12 female subjects. A photosensitization study of 200 ppm MI in 32 subjects did not produce photoallergic reactions.

CLINICAL USE

Case Reports

Three cases of allergic contact dermatitis were reported in patients that had come into contact with coolant solutions containing biocides. Patch testing in 2 of the patients revealed 2+ and 3+ reactions to MI, respectively. An investigator in this study developed eczematous dermatitis while isolating coolant components and had a 2+ reaction to MI during patch testing. Another case study reported hand eczema in a diesel mechanic that was exacerbated with the use of moist toilet paper. The diesel oil and the toilet paper the man came in contact with both contained Kathon biocides. Positive reactions to MI were observed with patch testing. Two cases of occupational contact allergy and dermatitis were reported in patients exposed to compounds containing the biocide MI. Patch testing revealed +++ reactions to MI and Neolone 950. Four out of 14 workers at a Danish paint factory were observed with contact dermatitis after exposure to paint additives containing 7-10% MI. Positive reactions were observed in all 4 patients during patch testing.

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.[21-29] Incidences of contact allergy to MI, tested separately from MCI/MI, appear to be increasing in Europe in recent years.[30-41]

SUMMARY

In 2010, the Cosmetic Ingredient Review (CIR) Expert Panel published the 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%)". 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 1125 reported uses, with the majority of the uses reported in non-coloring hair conditioners and shampoos. Industry reported the maximum use concentration range to be 4 x 10^{-6}% to 0.01%, with 0.01% reported in leave-on and rinse-off baby, non-coloring hair, and dermal contact products. In 2014, the VCRP database indicated that reported uses for MI have increased to 3856, with the majority of the uses reported in rinse-off products such as bath soaps and detergents. A survey of use concentrations conducted by the Council reported a maximum concentration of use range of 3.5 x 10^{-8}% to 0.011%, with 0.011% reported in an aerosol hair spray. It should be noted that the information provided under the VCRP in 2007 and in 2014 did not clearly indicate whether MI is used alone in products or is used in combination with MCI. However, a personal communication with FDA's VCRP staff on March 11, 2014 indicated that, of the nearly 3900 ambiguous uses of MI in personal care products reported in 2014, MI alone is used in approximately 800 products. A break-out of the uses was not provided.

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 re-evaluation 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. .

MI was named the Contact 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. Standard series of patch testing includes the mixture MCI/MI, which may miss 40% of contact allergy to MI alone 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.[13-1613-1613-1613-16]

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 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. 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 QRA of MI in response to the increased incidences of contact sensitization to MI in Europe. The QRA, which used a conservative WoE NESIL of 15 µg/cm^2 that was derived from data of 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.

ORIGINAL DISCUSSION

In 1992, the CIR Expert Panel concluded that the mixture MI/MCI (23.3% MI and 76.7% MCI) may be safely used in "rinse-off" products at a concentration not to exceed 15 ppm and in "leave-on" cosmetic products at a concentration not to exceed 7.5 ppm. Currently, MI is used as a stand-alone biocide. Accordingly, it was considered necessary to evaluate the safety of MI alone.

The CIR Expert Panel noted that in vitro studies on MI and related isothiazolinone compounds were positive for neurotoxicity. However, in vivo studies described in this report, including subchronic, chronic, and reproductive and developmental animal studies did not report significant signs of toxicity, including neurotoxicity. The Expert Panel does not consider MI as used in cosmetics to be neurotoxic.

The Expert Panel observed that MI of undetermined particle size had adverse effects in acute inhalation studies in animals. However, the Expert Panel determined that MI can be used safely in hair sprays and other spray products, because cosmetic product sprays contain particles of sizes that are not respirable. The available data demonstrated that the particle size of aerosol hair sprays (~38 µm) and pump hair sprays (>80 µm) is large compared to respirable particulate sizes (≤10 µm).

The Expert Panel noted that MI was a sensitizer in both animal and human studies. A threshold dose response was observed in these studies. Cosmetic products formulated to contain concentrations of MI at 100 ppm (0.01%) or less are not expected to pose a sensitization risk. The Expert Panel also recognizes that cross-sensitization to MCI may occur in individuals sensitized with MI. Most individuals sensitized with MCI, however, do not cross-react with MI. These animal and clinical data support that MCI is a strong sensitizer and MI is a weak sensitizer.

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 the Contact 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 Science and Support Committee using EC_3 values from LLNAs, which have been corrected in the literature since the Panel previously considered this ingredient in 2008, and the results of HRIPTs to conduct the WoE analysis and select an appropriate

NESIL. 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 substantially lower than 100 ppm. 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 be non-sensitizing. The risks of sensitization depend on the exposure concentration and duration and the surface area of the skin exposed. 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 example, 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. The limitations recommended by the Panel are based on anticipated non-inducing exposures to MI and not on concentrations that will preclude elicitation of reactions in previously sensitized individuals. The Panel recommends that sensitized individuals read product labels and avoid products that contain MI.

The Panel discussed the issue of incidental inhalation exposure to MI in in non-coloring hair sprays and hair tonics or dressings. There were no inhalation toxicity data identified or provided. MI reportedly is used at concentrations up to 0.01% in cosmetic products that may be aerosolized. The Panel noted that 95% – 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 http://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 cosmetics products when they are formulated to be non-sensitizing, which may be determined based on a QRA.

TABLES

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***	**2014****	**2007**	**2014**
Totals†	**1125**	**745**	**4 x 10^{-6}-0.01**	**3.5 x 10^{-8}-0.01**
Duration of Use				
Leave-On	236	478	0.002-0.01	3.5 x 10^{-8}-0.01
Rinse-Off	807	260	4.0 x 10^{-6}-0.01	2.5 x 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[a]; 54[b]	3; 268[a]; 114[b]	0.005; 0.008-0.009[a]	0.0002-0.01[a]; 0.0002-0.01[c]
Incidental Inhalation-Powder	1; 2[d]	114[b]	NR	NR
Dermal Contact	469	544	0.0008-0.01	3.5 x 10^{-8}-0.01[e,f]
Deodorant (underarm)	2[a]	NR	NR	0.0095[g]
Hair - Non-Coloring	579	190	4.0 x 10^{-6}-0.01	4.0 x 10^{-6}-0.01
Hair-Coloring	76	NR	NR	5.6 x 10^{-5}-0.0095
Nail	1	5	NR	0.0002-0.006
Mucous Membrane	241	103	0.0015-0.01	9.0 x 10^{-7}-0.01
Baby Products	14	6	0.002-0.01[h]	0.0002-0.0075

* Data provided are not clear as to whether uses are MI alone or include uses of MI/MCI.
** Data provided are for uses of MI alone.
NR = Not reported
†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.
a. Includes products that can be sprays, but it is not known whether the reported uses are sprays.
b. Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
c. 0.01% in an aerosol hair spray; 0.0002-0.01% in a pump hair spray; 0.006-0.0095% in a pump hair tonic or dressing.
d. Includes products that can be powders, but it is not known whether the reported uses are powders.
e. 0.00023-0.01% in a hand soap; 0.01% in a foot scrub.
f. 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%.
g. Not a spray deodorant.
h. 0.01% in baby wipes.

Table 2. Quantitative risk assessment of methylisothiazolinone in cosmetic products.[20]

Product Category	Max Use Concentration (%)	Product Exposure (μg/cm^2)	CEL (μg/cm^2)	NESIL (μg/cm^2)	SAF	AEL	AEL/CEL
Baby shampoo	0.01	200	0.02	15.00	100.00	0.15	7.50
Baby lotions, oils, powders, creams	0.01	2200	0.22	15.00	300.00	0.05	0.23
Baby wipes	0.01	4000	0.40	15.00	300	0.05	0.13
Other baby products (powders and talcs)	0.01	4200	0.42	15.00	100.00	0.15	0.36
Other baby products (washes)	0.01	200	0.02	15.00	100.00	0.15	7.50
Bath oils, tablets and salts	0.01	200	0.02	15.00	100.00	0.15	7.50
Bath soaps and detergents	0.01	10	0.00	15.00	100.00	0.15	150.00
Bubble baths	0.01	200	0.02	15.00	100.00	0.15	7.50
Other bath preparations	0.01	200	0.02	15.00	100.00	0.15	7.50
Eyebrow pencil	0.01	2200	0.22	15.00	300.00	0.05	0.23
Eyeliners	0.01	2170	0.22	15.00	300.00	0.05	0.23
Eye shadow	0.01	2170	0.22	15.00	300.00	0.05	0.23
Eye lotion	0.01	2170	0.22	15.00	300.00	0.05	0.23
Eye makeup remover	0.01	900	0.09	15.00	100.00	0.15	1.67
Mascara	0.01	2170	0.22	15.00	300.00	0.05	0.23
Other eye makeup	0.01	2170	0.22	15.00	300.00	0.05	0.23
Cologne and toilet waters	0.01	17700	1.77	15.00	100.00	0.15	0.08
Blushers	0.01	1000	0.10	15.00	100.00	0.15	1.50
Other fragrance products	0.01	2200	0.22	15.00	100.00	0.15	0.68

Table 2. Quantitative risk assessment of methylisothiazolinone in cosmetic products.[20]

Product Category	Max Use Concentration (%)	Product Exposure (μg/cm^2)	CEL (μg/cm^2)	NESIL (μg/cm^2)	SAF	AEL	AEL/CEL
Hair conditioners	0.01	200	0.02	15.00	100.00	0.15	7.50
Hair sprays (aerosol fixatives)	0.01	1390	0.14	15.00	100.00	0.15	1.08
Hair sprays (pump)	0.01	2200	0.22	15.00	100.00	0.15	0.68
Hair straighteners	0.01	4200	0.42	15.00	100.00	0.15	0.36
Permanent waves	0.01	4200	0.42	15.00	100.00	0.15	0.36
Rinses (noncoloring)	0.01	170	0.02	15.00	100.00	0.15	8.82
Shampoos (noncoloring)	0.01	170	0.02	15.00	100.00	0.15	8.82
Tonics, dressings and other hair grooming aids	0.01	990	0.10	15.00	100.00	0.15	1.52
Wave sets	0.01	4200	0.42	15.00	100.00	0.15	0.36
Other noncoloring hair products	0.01	1000	0.10	15.00	100.00	0.15	1.50
*Hair dyes and colors	0.01	1000	0.10	15.00	100.00	0.15	1.50
*Hair tints	0.01	990	0.10	15.00	100.00	0.15	1.52
Hair rinses (coloring)	0.01	200	0.02	15.00	100.00	0.15	7.50
*Hair bleaches	0.01	1000	0.10	15.00	100.00	0.15	1.50
Other hair coloring preparations	0.01	1000	0.10	15.00	100.00	0.15	1.50
Face powders	0.01	1000	0.10	15.00	100.00	0.15	1.50
Foundations	0.01	3170	0.32	15.00	100.00	0.15	0.47
Lipsticks	0.01	11460	1.15	15.00	300.00	0.05	0.04
Other makeup preparations	0.01	4200	0.42	15.00	100.00	0.15	0.36

Table 2. Quantitative risk assessment of methylisothiazolinone in cosmetic products.[20]

Product Category	Max Use Concentration (%)	Product Exposure (μg/cm^2)	CEL (μg/cm^2)	NESIL (μg/cm^2)	SAF	AEL	AEL/CEL
Other manicuring preparations	0.01	1000	0.10	15.00	100.00	0.15	1.50
Other personal cleanliness products	0.01	4400	0.44	15.00	300.00	0.05	0.11
Aftershave lotions	0.01	2210	0.22	15.00	100.00	0.15	0.68
Preshave lotions (all types)	0.01	2200	0.22	15.00	100.00	0.15	0.68
Shaving cream (aerosol, brushless and lather)	0.01	70	0.01	15.00	300.00	0.05	7.14
Shaving soaps (cakes, sticks, etc.)	0.01	70	0.01	15.00	300.00	0.05	7.14
Other shaving preparations	0.01	2200	0.22	15.00	100.00	0.15	0.68
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01	900	0.09	15.00	100.00	0.15	1.67
Depilatories	0.01	200	0.02	15.00	100.00	0.15	7.50
Face and neck creams, lotions, powders and sprays	0.01	2700	0.27	15.00	100.00	0.15	0.56
Body and hand creams, lotions and powders	0.01	1120	0.11	15.00	300.00	0.05	0.45
Moisturizers	0.01	2700	0.27	15.00	100.00	0.15	0.56
Nail care creams and lotions	0.01	970	0.10	15.00	100.00	0.15	1.55
Deodorants (underarm)	0.01	8500	0.85	15.00	300.00	0.05	0.06
Night creams, lotions, powders, and sprays	0.01	3170	0.32	15.00	100.00	0.15	0.47
Paste masks (mud packs)	0.01	4200	0.42	15.00	100.00	0.15	0.36
Skin fresheners	0.01	150	0.02	15.00	100.00	0.15	10.00
Other skin care products	0.01	2200	0.22	15.00	100.00	0.15	0.68
Suntan gels, creams, liquids and sprays	0.01	2200	0.22	15.00	100.00	0.15	0.68

Table 2. Quantitative risk assessment of methylisothiazolinone in cosmetic products.[20]

Product Category	Max Use Concentration (%)	Product Exposure (μg/cm^2)	CEL (μg/cm^2)	NESIL (μg/cm^2)	SAF	AEL	AEL/CEL
Indoor tanning preparations	0.01	2200	0.22	15.00	100.00	0.15	0.68
Other tanning preparations	0.01	2200	0.22	15.00	100.00	0.15	0.68
Foot powders and sprays	0.01	2200	0.22	15	100	0.15	0.68

Shaded rows indicate the ratio of AEL x CEL^{-1} is less than 1.
*Note that this product category may be diluted prior to application

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 non-atopic 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.	[21]
toilet wipes that contain 90 ppm MI and water-based paint that contained 0.01% MI and 0.01% MCI/MI	62-year-old non-atopic 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.	[21]
toilet wipes that contain 90 ppm MI	50-year-old non-atopic 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.	[21]
toilet wipes that contain 90 ppm MI	43-year-old non-atopic 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.	[21]
toilet wipes that contain 90 ppm MI	20-year-old non-atopic 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.	[21]
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.	[21]

Table 3. Case studies

Mode of Contact	Patient(s)	Indication	Reference
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.	[21]
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 at ++ reaction on day 2.	[23]
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 history of extensive dermatitis following use of a moist toilet paper that contained MI but not MCI.	[22]
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.	[24]
wall paint containing MI	23-year-old non-atopic 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 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 re-exposed to MI in a cleansing product to which she had never been exposed and immediately experience marked aggravation of facial dermatitis.	[25]

Table 3. Case studies

Mode of Contact	Patient(s)	Indication	Reference
wall paint containing MI	36-year-old non-atopic 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 had been painted with a paint that contained MI.	[26]
wall paints containing 1.2-187 ppm MI, 0.3-10 ppm MCI/MI, and 8.5 - 187ppm benzisothiazolinone (BIT)	57-year-old non-atopic 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.	[26]
wall paint containing MI	53-year-old non-atopic 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.	[27]
"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 3x/day for 10 min 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; -labeling of the contact gel used by patient indicated the presence of both MCI and MI.	[28]
household wipes and skin cleansing products containing MI	39-year-old non-atopic female employed as a neonate nurse	-patient presented with eczematous skin lesions on the arms, neck and trunk of 7-month 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.	[29]

Table 4. Retrospective and multicenter studies

Number of dermatitis patients tested, location	Concentration of MI tested	Years analyzed	Results	Reference
2536; Gentofte, Denmark	2000 ppm in supplemented European baseline series	May 2006 – Feb 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	[30]
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 that submitted to a use test, 10 had positive results	[31]
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.	[32]
2766 to MI, 2802 to MCI/MI, and 2413 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.	[33]
1289; 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 ≥ 40-years-old.	[34]
219 painters and 1095 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.	[35]

Table 4. Retrospective and multicenter studies

Number of dermatitis patients tested, location	Concentration of MI tested	Years analyzed	Results	Reference
~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.	[36]
563 and 2056 for 2 different concentrations of MI, 2489 for MCI/MI; Leeds, UK	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.	[37]
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.	[38]
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 $\geq$ 40 years-old, patients with face dermatitis, and use of cosmetics.	[39]
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 two concentrations of MI, 10 patients had relevant reactions; -all 10 patients reaction to 0.05% MI, while only 5 reacted to 0.02% MI; -only 1 patient of the 10 reacted to 100 ppm MCI/MI -all 5 patients that had been tested with personal care products containing MI reacted.	[40]
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	-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.	[41]

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