Amended Safety Assessment of Methylchloroisothiazolinone and Methylisothiazolinone as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reassessed the safety of the mixture Methylchloroisothiazolinone (MCI)/Methylisothiazolinone (MI), which functions as a preservative in cosmetic products. The Panel reviewed relevant animal and human data provided in this safety assessment, and data from the previously published safety assessment of this mixture, and concluded that MCI/MI is safe in cosmetics when formulated to be non-sensitizing, based on the results of a quantitative risk assessment (QRA) or similar methodology; however, at no point should concentrations exceed 7.5 ppm in leave-on products or 15 ppm in rinse-off products.

INTRODUCTION

This safety assessment is on the combination of Methylchloroisothiazolinone (MCI) and Methylisothiazolinone (MI) as used in cosmetics. In 1992, the original report on MCI/MI was published by the Cosmetic Ingredient Review (CIR), and the Expert Panel (Panel) concluded that this mixture 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."[1] The stated safe-for-use concentration refers to a mixture containing 76.7% MCI and 23.3% MI (roughly, 3:1). According to its Procedures, the CIR evaluates the conclusions of previously-issued reports. The Panel determined that this safety assessment should be re-opened to reassess the conclusion based on the numerous sensitization studies and reports that have been published since 1992.

While defined as separate ingredients that function as preservatives in cosmetics in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*),[2] MCI is only known to be used in concert with MI. This safety assessment does not directly address the safety of the cosmetic use of either ingredient alone; however in 2014, the Panel assessed the safety of MI formulated without MCI, and concluded that MI (alone) 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 non-sensitizing, which may be determined based on a QRA.[3]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

CHEMISTRY

Definition

Methylchloroisothiazolinone (CAS No. 26172-55-4) is the heterocyclic organic ingredient that conforms to the following structure:[2]

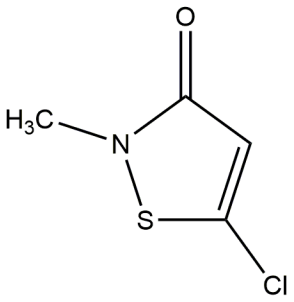

Figure 1. Methylchloroisothiazolinone

Methylisothiazolinone (CAS No. 2682-20-4) is the heterocyclic organic ingredient that conforms to the following structure:[2]

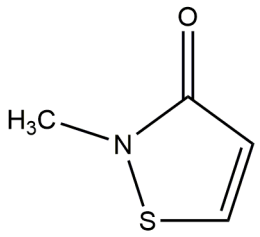

Figure 2. Methylisothiazolinone

Physical Properties

MCI/MI is readily miscible in water, lower alcohols, glycols, and other hydrophilic organic solvents.[1] This mixture is a clear, light amber liquid with a specific gravity of 1.19 (at 20 ºC), a pH of 3.5 (as supplied), and a freezing point of -18 to -21.5 ºC.

Impurities

Dimethylnitrosamine was reported to be formed as a reaction by-product at very low concentrations.[1] To limit the presence of this impurity, methyl-3-mercaptopropionate is added during production.

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

MCI and MI are reported to the VCRP separately, and not as a mixture. According to 2019 VCRP survey data, the total number of uses reported for MCI is 5137; 480 of these are in leave-on products (Table 1).[5] MI has 6037 reported uses; 1042 of these are in leave-on products. The uses have increased significantly since the original report on MCI/MI was published; in 1986, the total number of uses reported for the ingredient mixture was 381.[1] In 2019, the Council reported that MCI/MI (3:1) is used at up to 7.5 ppm in leave-on products and at up to 15 ppm in rinse-off products.[6] In the original report, concentration of use was reported as a range; the concentration of use range for MCI/MI in both leave-on and rinse-off products was reported to be < 0.1 - 1% (< 1000 - 10,000 ppm).[1]

MCI/MI may be used in products that can be incidentally ingested or come into contact with mucous membranes; for example, there are uses reported in lipsticks (reported in the VCRP only; concentration not reported), bath preparations (0.000019 ppm), and bath soaps and detergents (up to 15 ppm).[5] Additionally, this mixture has been reported to be used in products that may come into contact with the eyes; for example, these ingredients are reported to be used in eye makeup preparations (reported in the VCRP only; concentration not reported). Moreover, this mixture has been reported to be used in spray and powder products that could possibly be inhaled; for example, MCI and MI are reported to be used in colognes (0.075 ppm), hair sprays (7.5 ppm), and face powders (reported in the VCRP only; concentration not reported).

In the European Union, MCI/MI is listed under Annex V, the list of preservatives allowed in cosmetic products, with the restriction that the combination may be used at a maximum concentration of 0.0015% (i.e. 15 ppm) in rinse-off products as a 3:1 ratio of MCI:MI.[7] The Scientific Committee on Consumer Safety (SCCS) in 2009 noted that MCI/MI is a well-recognized skin sensitizer at current conditions of use and concentration. The SCCS concluded that MCI/MI in a ratio of 3:1 does not pose a risk to the health of the consumer when used as a preservative at a maximum concentration of 0.0015 % in rinse-off cosmetic products, apart from its sensitizing potential.[8] Induction and elicitation were considered less likely in a rinse-off product than when the same concentration is present in a leave-on product In 2016, however, a proposal to amend Annex V to state that no safe concentrations for MI have been adequately demonstrated for use in leave-on cosmetic products (including 'wet wipes') was announced, which would effectively ban MCI/MI from use in leave-on products.[9]

Non-Cosmetic

MCI/MI (3:1) has been determined to be safe for use in indirect food additives as adhesive, coating, and paper and paperboard components only as an antimicrobial agent or a slimicide (21CFR §175.105, §175.300, §175.320, §176.170, and §176.300).

MCI/MI is reported to be used in water-based wall paints.[10] Analysis of 60 paint samples found the concentration of MCI to range from 0.5 to 3.5 ppm while the concentration of MI ranged from 1.1 to 142.7 ppm.

TOXICOKINETICS

MCI/MI was absorbed after oral administration and then was excreted in the urine or feces; storage in the tissues was minimal. Up to 62% of a single percutaneous dose was bound to the site of application 24 hours after exposure. The MCI/MI bound to the skin had a 13.1-day half-life.[1]

In an oral metabolism study in humans, four volunteers received 2 mg of labelled 3-[^{13}C]-MI or 3-[^{3}H]-MCI (16.3 and 13 µmol, respectively) in 200 µL of ethanol in a glass of water, separately and at least 2 weeks apart.[11] Over a 48-h period, consecutive and complete urine samples were collected and examined for the content of *N*-methylmalonamic acid (NMMA). NMMA represented 23.7% and 13.3% of the dose excreted in urine after exposure of MI and MCI, respectively, with more than 90% excreted within the first 24 h. Excretion of NMMA was rapid with mean half-lives of 6.1 h and 7.6 h for MI and MCI, respectively.

TOXICOLOGICAL STUDIES

MCI/MI was moderately to highly toxic to rats, and highly toxic to rabbits when administered orally, and moderately toxic when applied dermally.[1] No treatment-related effects were observed in rats which received MCI/MI in oral doses up to 24.4 mg/kg/day for 2 weeks. Doses of MCI/MI up to 2.8 mg/kg/day applied dermally to rabbits, 5 days per week for 3 weeks, produced moderate irritation at the application site but no systemic toxicity. Dermal application of MCI/MI at doses up to 0.4 mg/kg/day for 3 months produced no systemic toxicity in rabbits. No toxicologically significant treatment-related effects were observed in dietary studies of rats or dogs at doses up to 30 and 28 mg/kg/day, respectively.

Short Term Toxicity Studies

Oral

In a 28-day repeated-dose oral study, male and female rats received MCI/MI (1.3%:0.38%) diluted in corn oil via gavage at 0, 0.26, 0.78, 2.3, and 7.0 mg/kg bw/day.[12] Water and feed consumption were monitored during the dosing period. At study end, the rats were killed, organs were weighed, and histological examinations were performed. Hematology, serum clinical chemistry, and biomarkers of inflammation were also assessed. No treatment-related effects on weight gains, organ weight, or hematological parameters were observed. A reduction of serum triglyceride levels in males and induction of hepatic phase 1 xenobiotic metabolizing enzymes in females, with subtle histological changes in the liver, were observed in the 7.0 mg/kg dose group. The authors stated that these changes were likely an adaptive, reversible response. The lowest-observed-effect-level (LOEL) was determined to be 7.0 mg/kg bw/day.

Subchronic Toxicity Studies

Inhalation

In a 13-week repeated-dose inhalation study performed in accordance with Organization for Economic Co-operation and Development (OECD) test guideline (TG) 413, groups of 16 Crl:CD(SD)BR rats per sex were exposed to 14% MCI/MI.[13] The rats were exposed whole body for 6 h per day, 5 days per week, at aerosol concentrations of 0, 0.34, 1.15, or 2.64 mg active ingredient (a.i.)/m^3, with an aerosol particle size of 1.1 to 1.4 µm (mean mass median diameter (MMAD), which is defined as the diameter at which 50% of the particles by mass are larger and 50% are smaller). During the exposure period, the rats were observed for clinical signs of toxicity, and body weight and ophthalmologic evaluations were made. At study termination, hematology, clinical chemistry, gross pathology, and histopathologic evaluations were conducted. No statistically significant effects were observed in the hematology, gross pathology, or ophthalmologic evaluations at any concentration. At 2.64 mg/m^3, rats of both sexes had signs consistent with exposure to a sensory irritant, including chromorhinorrhea, rhinorrhea, eye squint, bradypnea, and dyspnea. Decreased body weight gains, decreased male spleen weights, and decreased serum protein in females were also observed in rats exposed to 2.64 mg/m^3. No treatment-related clinical signs of toxicity, body weight effects, or organ weight effects were observed in the 0.34 or 1.15 mg/m^3 dose groups. Treatment-related histopathologic findings consisting of slight to moderate incidences of eosinophilic droplets in the anterior respiratory mucosa of the nasal turbinates and slight rhinitis in the lining of the anterior portion of the nasal cavity were observed in the 2.64 mg/m^3 dose group. At 1.15 mg/m^3, rhinitis was observed in rats of both sexes. No treatment-related histopathologic effects were observed in the 0.34 mg/m^3 dose group. All histopathologic changes were minor, potentially

reversible, and generally reflective of minimal tissue response to a very mild, low-grade respiratory irritant. Based on the occurrence of rhinitis, the LOEL was 1.15 mg/m^3 a.i. The no-observable-effect-level (NOEL) was 0.34 mg/m^3 a.i.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

MCI/MI administered by gavage to pregnant rabbits (gestation days 6 through 18) at doses up to 13.3 mg/kg/day was toxic to the dam, embryo, and fetus; the compound was not teratogenic.[1] In pregnant rats (gestation days 5 through 15) that received MCI/MI at doses up to 15 mg/kg/day, toxicity was observed in the dams, but no treatment-related effects were noted in any of the reproductive parameters of the surviving dams and fetuses and no teratogenicity was observed.

GENOTOXICITY

The result of genotoxicity testing of MCI/MI varied with the assay used.[1] Mutagenicity was observed in several Ames tests with and without metabolic activation, but no genotoxicity was observed in several in vitro mammalian cell assays. Results were mixed in a mouse lymphoma cell assay, with genotoxicity observed when there was no metabolic activation.

The mutagenicity of a tradename mixture containing MCI/MI (14% a.i.; 10% MCI: 3.4% MI) and five cosmetic products that contained the tradename mixture was studied in an Ames test using *Salmonella typhimurium* strain TA 100, with and without metabolic activation.[14] The cosmetic products were diluted in distilled deionized water and tested at up to 400 µl/plate; MCI/MI was tested at doses ranging from 0.00039 – 0.05 µl/plate. Three of the five products were direct acting mutagens, while the other two were too cytotoxic to determine mutagenicity. Metabolic activation reduced cytotoxicity, but did not eliminate mutagenicity. Mutagenicity was also observed with MCI/MI, with and without metabolic activation, in a dose-dependent manner.

CARCINOGENICITY

Dermal application of 400 ppm of 2.67% MCI/MI in distilled water, 3 times per week for 30 months, had no local or systemic tumorigenic effect in male mice.[1]

DERMAL IRRITATION AND SENSITIZATION

The dermal irritation of MCI/MI was concentration-dependent in rabbits under occlusive patches, with 560 ppm being non-irritating, 2800 ppm being moderately irritating, and 5600 ppm being severely irritating.[1] In humans, MCI/MI was irritating in a dose-dependent manner, with 100 ppm essentially nonirritating, 200 ppm slightly irritating, and 400 - 800 ppm strongly irritating. MCI/MI is a sensitizer: the concentration of MCI/MI in cosmetic products which produced sensitization varies. The available human sensitization test data at concentrations of 50 ppm and above gave mixed results. MCI/MI was not a sensitizer at a concentration of 15 ppm.

Human

In a human repeated insult patch test (HRIPT) of a hand wash containing 12 ppm MCI/MI in 50 volunteers, applications of 0.2 ml were made directly on the back as open patches on an area of approximately 2 cm^2 for a dose of 1.2 µg/cm^2.[15] No adverse effects were observed during the study and no irritation or sensitization was observed during induction or challenge.

PHOTOTOXICITY

MCI/MI was not a photosensitizer at a concentration of 15 ppm in human volunteers. [1]

OCULAR IRRITATION

MCI/MI in an aqueous solution was not a cumulative ocular irritant when tested at 55 ppm in rabbits; it was corrosive when tested at 1.1% (11,000 ppm and higher).[1]

CLINICAL STUDIES

Provocative Studies

A repeated open application test (ROAT) was performed on 15 patients with known contact allergy to 100 ppm MCI/MI and/or MI (6 patients reacted to MCI/MI only, 6 patients reacted to MI only, and 3 patients reacted to both MCI/MI and MI).[16] Each patient was given two sets of aqueous skin creams. One cream contained MI at 100 ppm while the other contained paraben preservatives. The patients applied the creams twice daily for 2 weeks to the outer aspect of the upper arm on an area of 25 cm^2. The sites were evaluated by dermatologists prior to the ROAT commencement; after 1 and 2 weeks, 8

patients had positive allergic responses at the test sites that received the MI-containing creams. Of the patients with the known MI allergy, five had positive responses. Of the patients with the known MCI/MI allergy, six had positive responses.

Baseline series patch tests, photopatch tests, and/or photo-tests were performed on a total of 10 patients with suspected photo-aggravated contact dermatitis to MCI/MI or MI.[17] All 10 patients underwent the baseline patch tests: the test concentrations for MCI/MI were 0.01% or 0.02% aq., and for MI was 0.2% aq. Six patients were photopatch tested with cosmetics containing MCI/MI and/or MI (amount of test substance not reported), with one of the two identical patches being irradiated with 5 J/cm^2 long-wavelength ultraviolet (UVA) light. Photo-tests were performed on two patients with UVA/mid-wave length ultraviolet (UVB) radiation ranging between 290 - 400 nm. Seven patients had positive patch tests to both MCI/MI and MI, and three patients had positive patch tests to only MI. Four patients had transient photosensitivity. Photopatch tests with MCI/MI and/or MI gave stronger reactions than baseline patch tests with these ingredients, indicating photo-aggravation.

Baseline and Retrospective Studies

Dermal

Numerous baseline and retrospective studies which included testing with MCI/MI, have been published since the original report was issued; a sampling of these studies is presented in Table 2. The results of these studies demonstrate that sensitization to MCI/MI is found world-wide, with reported rates as low as 0.7% (out of 703 patients; United States) to as high as 15.4% (out of 635 patients; Thailand).[18-51]

Case Reports

Cases studies include reports of MCI/MI sensitization from a wide range of materials, including personal care products (including wet wipes), ultrasound gels, paints, glues, cleaners, and industrial biocides.[52-69] Dermal sensitization from paint was hypothesized to be from airborne exposure in several patients.[57,59,64,65]

Airway Dysfunction

Peripheral airway dysfunction was observed in a retrospective assessment of 24 children in South Korea, with no underlying disease, who were exposed to MCI/MI as a humidifier disinfectant (HD).[70] The children were exposed to MCI/MI at high density for up to 6 months and were exposed initially as infants. Pulmonary function was assessed with impulse oscillometry. One child died at age 4 months after continuous use of the HD over 3 months.

In a related study of 530 registered lung disease patients that were exposed to HDs in South Korea, three definite or probable cases of airway dysfunction were reported from use of an HD that contained MCI/MI (127 mg/l MCI:37 mg/l MI).[71] Two of these cases were in infants, and one was in an adult patient who died. Another 33 cases of airway dysfunction were possibly or unlikely/intermittently associated with the HD containing MCI/MI; five deaths were reported in these cases.

Case studies from South Korea related to exposure of an HD containing MCI/MI, resulting in lung injury, included a set of twin girls that were exposed from ages 4 to 6 months, and another girl that was exposed from age 11 to 25 months.[72,73] The twin girls presented with cough, sputum, and respiratory difficulty, and were observed with pneumomediastinum on chest X-ray.[72] In the latter case, the patient presented with coughing, fever, dyspnea, and tachypnea that progressively worsened and she developed acute respiratory distress syndrome: the patient died during hospitalization.[73]

RISK ASSESSMENT

A skin sensitization induction risk assessment of MCI/MI was performed with various personal care products.[74] An estimated daily consumer exposure level (CEL) for rinse-off and leave-on products was calculated using the amount of product applied per application, number of applications per day, a retention factor, the MCI/MI concentration, and body surface area values. The researchers assumed that the products contained the maximum recommended safe concentration of 15 ppm MCI/MI in rinse-off products and 7.5 ppm MCI/MI in leave-on products. The estimated CELs were compared with the no-expected-sensitization-induction-level (NESIL) for MCI/MI of 0.83µg/cm^2, which was based on the value reported by the SCCS from weight-of-evidence (WoE) data from a HRIPT. The sensitization assessment factors (SAFs) were applied to calculate product-specific margins of safety (MOSs). The researchers found that the MOSs for rinse-off products ranged from 5 to 63, whereas the MOSs for leave-on products ranged from 0.03 to 1.49. An MOS of 1 or greater indicates a low likelihood of sensitization induction. The researchers concluded that the results provide evidence that some leave-on products containing the maximum recommended safe concentration of MCI/MI may increase the risk of sensitization induction due to exposure to MCI/MI, while rinse-off products were not associated with a potential increased risk of skin sensitization induction.

In another skin sensitization risk assessment of MCI/MI, the maximum safe concentration of 15 ppm MCI/MI in representative-type cosmetics (which included shampoos, conditioners, soap, lotions, hand and face cream, deodorants, wipes, and eye and face makeup) indicated the possibility of skin sensitization when a NESIL of 1.25 µg/cm^2 was used in the

determination.[75] However, there was no potential for skin sensitization at this concentration for just rinse-off products. In this assessment, the MOS was calculated as the acceptable exposure level (AEL)/CEL, and was considered safe when the AEL/CEL ratio was 1 or more. The AEL is calculated as the NESIL/skin SAF. For the representative type cosmetics, the SAF was 300, while in rinse-off products it was 100. The MOS for representative type cosmetics was determined to be 0.00538 and the MOS for rinse-off products was 2.14.

In a QRA performed by the CIR Science and Support Committee (SSC), a conservative NESIL of 0.83 $\mu g/cm^2$ was derived for MCI/MI based on a WoE evaluation of HRIPT data and data from local lymph node assays (LLNA). [76] The NESIL was then used to calculate AELs for the potential for the induction of sensitization from dermal exposure to MCI/MI in cosmetic products, assuming the maximal use concentration of 15 ppm for rinse-off products and 7.5 ppm for leave-on products and VCRP product category-specific QRA SAFs. The SAFs include 6 component factors (inter-individual, site, skin condition, matrix, occlusion, frequency and duration of exposure). Individual CELs were then calculated for numerous VCRP product categories, ranging from baby shampoo (CEL = 0.0024 $\mu g/cm^2$) to skin cleansing products (CEL = 0.0135 $\mu g/cm^2$). The lowest CEL to MCI/MI was 3.8×10^{-9} $\mu g/cm^2$ for bubble baths, and the highest estimated exposure was 0.0315 $\mu g/cm^2$ for permanent waves. By using the maximum reported MCI/MI concentration of use levels provided by the Council survey (Table 3), an adequate MOS for skin sensitization is provided for all reported uses except for permanent waves (using 7.5 ppm MCI/MI) and for skin cleansing products (i.e., cold creams, cleansing lotions, liquids, and pads; using 15 ppm MCI/MI). The maximum supportable concentration of MCI/MI for permanent waves and skin cleansing products are 2 ppm and 9 ppm, respectively. When using the exposure assumptions in this risk assessment on all reported VCRP product categories of use with the maximum recommended concentrations of use, as set by the original CIR conclusion, of 7.5 ppm in leave-on products and 15 ppm in rinse-off products (Table 4), an adequate MOS could not be assured for baby shampoo (MOS = 0.92), permanent wave (MOS = 0.13), hair tints (MOS = 0.56), skin cleansing products (0.61), or cologne and toilet waters (0.50).

SUMMARY

This safety assessment is on the combination of MCI and MI as used in cosmetics. Each ingredient is reported to function as a preservative in cosmetic products. In 1992, the original report on MCI/MI was published with the Panel's conclusion that this mixture 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." The stated safe-for-use concentration refers to a mixture containing 76.7% MCI and 23.3% MI.

MCI and MI are surveyed separately in the VCRP, and not as a mixture. According to 2019 VCRP survey data, the total number of uses reported for MCI is 5137; 480 of these are in leave-on products. MI has 6037 reported uses; 1042 of these are in leave-on products. The number of uses has increased significantly since the original report on MCI/MI was published; in 1986, the total number of uses for the ingredient mixture was 381. In 2019, the Council reported that MCI/MI (3:1) is used at up to 7.5 ppm in leave-on products and at up to 15 ppm in rinse-off products. In the original report, concentration of use was reported as a range; the concentration of use range both leave-on and rinse-off products was reported to be < 0.1 – 1%.

In the European Union, MCI/MI is listed as a preservative in Annex V; it is limited to a maximum concentration of 0.0015% (i.e. 15 ppm) in rinse-off products as a 3:1 ratio of MCI:MI. The SCCS concluded in 2009 that MCI/MI in a ratio of 3:1 does not pose a risk to the health of the consumer when used as a preservative at a maximum concentration of 0.0015% in rinse-off cosmetic products, apart from its sensitizing potential. In 2016, however, a proposal to amend Annex V to state that no safe concentrations for MI have been adequately demonstrated for use in leave-on cosmetic products (including 'wet wipes') was announced, which would effectively ban MCI/MI from use in leave-on products. At that time, Annex V was amended to restrict the use of MI in rinse-offs to no more than 100 ppm, though the amendment to ban use in leave-ons was deferred.

MI and MCI were determined to metabolize into NMMA in humans after oral ingestion. Excretion of the metabolite through urine was rapid.

The LOEL for MCI/MI in a 28-day repeated-dose oral study in rats was 7.0 mg/kg bw/day, the highest dose that was tested. At this dose, a reduction of serum triglyceride levels was observed in males and induction of hepatic phase 1 xenobiotic metabolizing enzymes with subtle histological changes in the liver were observed in females. In a 13-week inhalation study of 14% MCI/MI in rats that followed OECD TG 413, MCI/MI was tested at up to 2.64 mg a.i./m^3. Based on the occurrence of rhinitis, the LOEL was 1.15 mg/m^3. The NOEL was 0.34 mg/m^3.

A tradename mixture containing MCI/MI (14% a.i.) and cosmetic products containing this mixture were mutagenic in an Ames test, with and without metabolic activation.

An HRIPT of a hand wash containing 12 ppm MCI/MI was not irritating or sensitizing in 50 volunteers. Provocative baseline patch tests and phototoxicity tests produced positive results in patients with suspected MCI/MI allergy. Numerous baseline and retrospective studies that included MCI/MI indicate that sensitization to this preservative occurs world-wide. Numerous case studies demonstrate sensitization to MCI/MI resulting from exposure to a wide range of materials, including personal care products, paints, glues, and cleaners. Peripheral airway dysfunction has been observed in patients in South Korea that were exposed to MCI/MI as a humidifier disinfectant.

Skin sensitization induction risk assessments of MCI/MI in multiple personal care and cosmetic products using a NESIL of 0.83 $\mu g/cm^2$ found that some leave-on products (e.g., colognes and toilet waters) with MCI/MI at the recommended safe concentration of 7.5 ppm may increase the risk of sensitization induction. In most rinse-off products, 15 ppm MCI/MI was not associated with a potential increase risk of skin sensitization induction.

DISCUSSION

This safety assessment is on the combination of Methylchloroisothiazolinone (MCI) and Methylisothiazolinone (MI) as used in cosmetics. Based on the numerous sensitization studies and reports that became available since the original report was issued, this safety assessment was re-opened to reassess the conclusion published in 1992.

The Panel noted the results of a QRA for skin sensitization performed by the CIR Science and Support Committee. The results indicated that some leave-on products comprising MCI/MI at the recommended maximum safe concentration of 7.5 ppm may yet increase the risk of inducing dermal sensitization. In most rinse-off products, 15 ppm MCI/MI was not associated with a potential increased risk of skin sensitization induction. Individuals previously sensitized to MCI/MI should avoid products that contain this ingredient mixture.

MCI/MI is a useful and necessary preservative system in cosmetic products. The Panel is aware that the conclusion herein differs from that reached by counterparts in the European Union. In part, the differing conclusions are based on interpretation of earlier LLNA data on which the hazard assessments were determined. However, the Panel supports managing sensitization risks by the use of valid assessment tools and strategies, such as a QRA system (or similar methodology). Instead of banning ingredients that may pose a risk under certain conditions (e.g., formulation, body-part exposure), the Panel has proposed that such risk-mitigating tools and strategies can be applied by formulators, and thus avoid exhausting available preservative systems. Such systems are necessary to protect consumers from microbial contaminations that would otherwise occur in cosmetic products.

In response to concerns of reports of adverse events observed in infants following inhalation exposure to humidifier disinfectants that contained the MCI/MI preservative mixture, the Panel requested, and received, an inhalation study of at least 3 months in duration that is in accordance with the OECD TG 413. The Panel determined that the data mitigated concern for the use of this ingredient mixture at the reported concentrations in cosmetic products that could be incidentally inhaled following use. The concentrations used in the humidifier disinfectant were orders of magnitude greater than those found in cosmetics.

CONCLUSION

The Panel concluded that the ingredient mixture MCI/MI is safe in cosmetics when formulated to be non-sensitizing, based on the results of a QRA or similar methodology; however, at no point should concentrations exceed 7.5 ppm in leave-on products or 15 ppm in rinse-off products.

TABLES

Table 1. Current (2019) and historical (1986) frequency and concentration of use according to duration and type of exposure for Methylisothiazolinone and Methylchloroisothiazolinone[1,5,6]

	# of Uses (2019)	*# of Uses (2019)*	*Max Conc of Use (2019) (ppm)*	*# of Uses (1986)*	*Max Conc of Use (1986) (%)*
	Methylchloroisothiazolinone*	**Methylisothiazolinone***	**MCI/MI¥**	**MCI/MI**	**MCI/MI‡**
Totals†	**5137**	**6037**	**0.000019-15**	**381**	**≤0.1-1**
Duration of Use					
Leave-On	480	1042	0.021-7.5	137	≤0.1-1
Rinse Off	4521	4849	0.15-15	244	≤0.1-1
Diluted for (Bath) Use	136	146	0.000019	NR	NR
Exposure Type					
Eye Area	32	60	NR	8[d]	≤0.1-1[d]
Incidental Ingestion	NR	1	NR	NR	NR
Incidental Inhalation-Spray	11; 192[a]; 112[b]	14; 470[a]; 286[b]	0.075-7.5; 7.4-7.5[a]	5[a]; 95[b]	≤0.1-1[a,b]
Incidental Inhalation-Powder	1; 112[b]; 2[c]	1; 286[b]; 2[c]	NR	95[b]	≤0.1-1[b]
Dermal Contact	3486	4163	0.000019-15	178[d]	≤0.1-1[d]
Deodorant (underarm)	NR	NR	NR	NR	NR
Hair - Non-Coloring	1567	1780	0.5-15	203[e]	≤0.1-1[e]
Hair-Coloring	68	68	0.15-11	[e]	[e]
Nail	1	4	NR	NR	NR
Mucous Membrane	2981	3099	0.000019-15	8	≤0.1-1
Baby Products	11	16	12	NR	NR

NR = Not reported.

* MCI and MI are reported separately in the VCRP database. While it is likely that all MCI totals are for MCI/MI, there is no way to verify this information.

† 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.

¥ No wipe products were reported.

‡ Concentrations were reported as general ranges in 1986.

[a.] It is possible these products may be sprays, but it is not specified 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.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

[d.] Eye and facial makeup preparations were reported together in the original safety assessment. The reported number was only accounted for in the eye area exposure

[e.] Non-coloring and coloring hair preparations, except for non-coloring shampoos, were reported together in the original safety assessment. The reported number was only accounted for in the non-coloring hair products.

Table 2. Baseline and retrospective studies

Number of Patients	Clinical Testing Type	Country and Time Span	Results	Reference
5899 patients	Swedish baseline patch test series using Finn Chambers secured with Scanpor tape; 15 µl o f 0.02% aq. MCI/MI (200 ppm; 3:1) and serial dilutions of MI alone	Southern Sweden; March 2003-December 2012	184 patients (3.1%) reacted to MCI/MI, with a notable increase in frequency from 4.3% in 2010 to 7.6% in 2012	[18]
141 recently diagnosed with sensitivity to 0.02% aq. MCI/MI	Tested MCI (0.015%) and MI (0.005%) separately with simultaneous application of haptens (0.2 ml); patches were Haye's test chambers with Soffix tape; occluded for 2 days	8 clinics in Italy; January 2016-December 2016	110 patients (78.1%) reacted to MCI, of which 60 (42.6%) reacted only to MCI and 50 (35.5%) reacted to both MCI and MI	[19]
229 children (96 were 7 years old and 133 were 16 years old) identified as having eczema through an allergy screening survey	Patch testing with 10 most common contact sensitizers in children in Europe; MCI/MI tested at 0.01% aq. with Chemotechnique™ IQ Ultra Chambers for 2 days	Poland; 2007	6.3% of 7-year olds and 0.8% of 16-year olds had a positive reaction to MCI/MI	[20]
14,274 work-related contact dermatitis cases	Baseline series of the British Society of Cutaneous Allergy; MCI/MI tested a 0.01% aq. until 2008, then changed to 0.02% aq.	United Kingdom; 1996-2012	4.1% (358) patients per annum had dermatitis attributed to MCI/MI; occupations of affected workers included beauty workers, hairdressers, healthcare workers, cleaners exposed to detergents, painters, manufacturing, and other industrial work.	[21]
3201 with either widespread or localized dermatitis	European baseline series and international standard series along with patients' products; MCI/MI was tested at 0.02% aq.; patches were Finn chambers applied for 2 days	Thailand; January 2005-December 2016	15.4% (98/635) patients with widespread dermatitis and 9.1% (204/2244) patients with localized dermatitis reacted to MCI/MI	[22]
4860 patients	Patch tested with screening series of 70 allergens, including 0.01% MCI/MI aq. and 0.2% MI aq.; patches were Finn chambers on Scanpor tape	13 centers from the North American Contact Dermatitis Group (NACDG); January 2013 to December 2014	6.3% (305) patients had positive reaction to MCI/MI, a significant increase from the previous testing cycle (5.0%; 2011-2012); 10.9% (527) patients had positive reaction to MI	[23,24]
124 patients with long-lasting perianal dermatitis	Patch tests with Spanish research group standard series, and depending on patient clinical history, more specific test series and suspected personal products; patch test were occluded for 2 days; additional diagnostic protocols including biopsies and cultures were performed	Spain; April 2004 to August 2016	13.7% (17/124) of patients reacted to MCI/MI	[25]
2315 patients	Baseline patch tests series with 0.02% MCI/MI aq.	2 centers in the United Kingdom; August 2011 to June 2013	9.4% (217/2315) of patients reacted to MCI/MI	[26]
997 patients	British baseline patch tests series with 0.02% MCI/MI aq.	United Kingdom; January to December 2015	3.9% of patients reacted to MCI/MI, this was a decrease from 7.9% in 2014	[27]
44 patients identified through a survey as having airborne allergic contact dermatitis caused by paint	Tested with 0.02% and /or 0.01% MCI/MI aq. and 0.02%, 0.05%, and 0.2% MI aq.	17 dermatology departments and 2 private offices in France and Belgium; survey occurred May 2015 to May 2016 with patients diagnosed from January 2012 to January 2016	36/44 (82%) patients had positive reactions to MCI/MI and 43/44 had positive reactions to MI	[28]
206 patients	Standard series patch tests (39 allergens); patches were 8 mm Finn chambers on Scanpor tape; results read at 48 and 72 h	Thailand; 2012 to 2015	13.6% (28/206) of patients tested positive to 0.01% MCI/MI	[29]
324 patients	European baseline series with 0.02% MCI/MI aq. and 0.2% MI aq.; patches were IQ Ultra chambers and readings were day 2 and day 4	Turkey; January 2016 to June 2018	6.17% (20/324) of patients tested positive to MCI/MI; 8.02% of patients tested positive to MI	[30]

Table 2. Baseline and retrospective studies

Number of Patients	Clinical Testing Type	Country and Time Span	Results	Reference
1287 patients	Baseline series with 0.02% MCI/MI aq., 0.2% MI aq., 0.1% benzisothiazolinone pet., and 0.1% octylisothiazolinone pet.; the occluded patches were IQ Ultra chambers and readings were on day 2 and day 4	United Kingdom; September 2014 to December 2015	9.2% (118) of patients had positive reactions to any isothiazolinone; cross-sensitization thought to occur between MCI/MI, MI, and octylisothiazolinone	[31]
703 patients	Retrospective review of patients tested with the North American Contact Dermatitis Group standard series; MCI/MI tested at 100 ppm and MI tested at 200 to 2000 ppm	United States; January 1, 2012 to December 30, 2014	0.7% (5) reactions to MCI/MI and 2.4% (17) reactions to both MCI/MI and MI	[32]
2703 patients	Testing in consecutive patients with 0.01% and 0.02% MCI/MI aq.; patches were 8 mm Finn chambers on Scanpor tape	8 centers in 8 countries that included Japan, Germany, Belgium, Sweden, Uruguay, India, Denmark, and Singapore; January 1, 2014 to December 31, 2014	3.7% and 5.6% of patients had reactions to 0.01% and 0.02% MCI/MI, respectively	[33]
2576 patients to MCI/MI and 964 to MI	Patients tested with Mayo Clinic Institution's standard series that included 0.2% MI aq. and 100 ppm MCI/MI aq.; patches were Finn chambers on Scanpor tape	Mayo Clinic; January 1, 2011 to December 31, 2015	5.9% and 13.6% of patients had allergic reactions to MCI/MI and MI, respectively	[34]
1745 patients	Retrospective study of patients tested with a modified Finnish baseline or antimicrobial series; 0.01% and 0.02% aq. MCI/MI, 0.1% and 0.03% aq. MI, 0.05% pet. benzisothiazolinone, and 0.1% pet. octylisothiazolinone; patches were Finn chambers occluded for 48 h	Finland; January 2002 to February 2013	2.6% and 0.2% of patients had allergic reactions to MCI/MI and MI, respectively	[35]
490 patients	Prospective study using the Spanish baseline series; 100 and 200 ppm aq. MCI/MI and 2000 ppm aq. MI; Finn chambers on Scanpor tape and occluded for 2 days	Spain; October 2011 to June 2013	10% and 4.5% of patients had reactions to MCI/MI and MI during the 2-year study; prevalence to MCI/MI allergy increased from 7.8% in 2011 to 14.3% in 2013 while prevalence to MI allergy increased from 1% to 7.7%	[36]
79 patients out of 9037 that had allergic reactions to a wipe	Retrospective analysis of patients patch tested to a screening series of 70 allergens; MCI/MI tested at 0.01% aq. and MI tested at 0.2% aq.	13 centers from NACDG; January 1, 2011 to December 31, 2014	59% of the patients that had reactions to wipes had a reaction to MI while 35.6% had reaction to MCI/MI	[37]
2165 patients	Patients tested with Swedish baseline series; 200 ppm aq. MCI/MI and 2000 ppm aq. MI; 8 mm diameter Finn chambers on Scanpor tape	Sweden; 2012 to 2014	8.1% (175) and 7.1% (153) of patients had reactions to MCI/MI and MI, respectively; 9.5% (206) of patients were found to have allergy to MCI/MI and/or MI	[38]
2028 patients	Patch testing in accordance with European Society of Contact Dermatitis guidelines; 0.2% aq MI and 0.01% aq. MCI/MI	Italy; January 2012 to December 2014	7.5% (152) and 5.2% (106) of patients had reactions to MCI/MI and MI, respectively	[39]
3253 patients	Patients tested with 100 ppm aq. MCI/MI and 2000 ppm aq. MI (only tested in 2014); Finn chambers under occlusive for 2 days	Thailand; January 2009 to June 2014	9.8% of patients had positive patch tests to MCI/MI; 40.7% (22/54) of patients had positive patch test to MI	[40]
80 patients with facial dermatitis	Patients tested with British Society for Cutaneous Allergy (BSCA) standard series and their own cosmetic products; 0.02% MCI/MI and 0.2% MI	Ireland; January 2012 to March 2014	6.3% (5) and 5% (4) of patients tested positive to MCI/MI and MI, respectively	[41]
4094 patients	Patients tested with baseline patch test series; Finn chambers on Scanpor tape; test concentrations not reported	Switzerland; 2000 to 2004	2.1% (88) of patients tested positive to MCI/MI	[42]
964 patients	Retrospective review of patients tested with BSCA standard series and individualized additional test series; IQ ultra chambers for 48 h; 0.01% aq. or 0.02% aq. MCI/MI	Ireland; 2007 to 2010	2.2% (21/964) of patients tested positive to MCI/MI; of these, 1.6% (11/697) were positive to 0.01% and 3.8% (10/267) were positive to 0.02%	[43]

Table 2. Baseline and retrospective studies

Number of Patients	Clinical Testing Type	Country and Time Span	Results	Reference
4227 patients	Patients patch tested with a screening series of 70 allergens; MCI/MI tested at 0.01% aq.; Finn chambers on Scanpor tape	12 centers from NACDG: January 1, 2011 to December 31, 2012	5.0% (213) of patients tested positive to MCI/MI; prevalence of allergy had increased since the previous years (2001-2010)	[44]
219 painters with contact dermatitis	Retrospective study of European baseline series patch test results of all painters registered in the Danish National Database for Contact Allergy; MCI/MI tested at 0.01% aq.; MI, octylisothiazolinone, and benzisothiazolinone were also tested (concentrations not reported); patches occluded for 48 h	Denmark; 2001 to 2010	10% (22/219) of the painters tested positive to MCI/MI; 27% (11/41) tested positive to MI; 25% (5/21) tested positive to octylisothiazolinone; and 19% (7/37) tested positive to benzisothiazolinone	[45]
359 patients	Retrospective study of Brazilian standard series results; MCI/MI tested at 0.5% pet.	Brazil; November 2009 to October 2012	11.1% (40/359) of patients tested positive to MCI/MI; increase from previous study period (3.4% from 2006-2009)	[46]
14,693 patients	Retrospective study of European baseline series patch test results; test concentrations not reported	Hungary; 1993 to 2014	Prevalence of MCI/MI hypersensitivity increased from 0.5% (5/1011) of patients in 1993 to 6.0% (23/383) of patients in 2014	[47]
314 patients	Patients prospectively patch tested with 0.01% aq. MCI/MI and 0.2% aq. MI with parallel testing to the European baseline series with 0.01% aq. MCI/MI; IQ chambers and Curatest patches, respectively, and occluded for 48 h	Hungary: February 1, 2014 to January 30, 2015	5.1% (16/314) of patients were positive to MCI/MI and 4.8% (15/314) of patients were positive to MI; no differences between the patch series types	[47]
Up to 6722 patients	Retrospective study of patients consecutively patch tested with 100 ppm aq. or 4 $\mu g/cm^2$ (TRUE test) MCI/MI, 200 or 2000 ppm aq. MI, and 500 or 1000 ppm aq. benzisothiazolinone; occluded 48 h	3 centers in Denmark; 2009 to 2012	3.2% (213/6722) of patients tested positive to MCI/MI, 3.2% (170/5290) tested positive to MI, and 0.9% (34/3636) tested positive to benzisothiazolinone	[48]
Up to 48,720 patients	Retrospective study of data collected by the European Surveillance System on Contact Allergies (ESSCA) from European baseline series and other allergen testing; MCI/MI was tested at 0.01% and 0.02% aq. and MI was tested at 0.05%, 0.1%, and 0.2% aq.	54 centers in 12 European countries; January 2009 to December 2012	4.1% of patients were positive to 0.02% MCI/MI and 3.3% were positive to 0.01% MCI/MI; 4.5% of patients were positive to 0.05% MI, 0.21% were positive to 0.1% MI, and 4.9% were positive to 0.2% MI	[49]
45 children with atopic dermatitis (ages 2 months to 17 years)	Patients tested with the TRUE patch test system; patch test plasters applied to upper back for 2 days; concentrations not reported	Turkey; September 2011 to March 2012	20% (9/45) of the patients had a positive reaction to MCI	[50]
7533 out of 20,107 patients	Meta-analysis of 28 studies of the general population from studies written in English available on PubMed; patch tests were conducted with the European baseline series or something similar; concentrations of MCI/MI tested not reported	Various centers from Asia, Europe, North America, and Australia; 2007 to 2017	Prevalence of allergy is 1.5% (95% CI 0.8-2.5) in the general population based on 6 studies	[51]

Table 3. Quantitative risk assessment of MCI/MI at the highest reported maximum use concentrations in cosmetic products[76]

Product Category	Reported Maximum Concentration of Use (ppm)	Weight of Evidence NESIL (µg/cm^2)	Sensitization Assessment Factor (SAF)	Acceptable Exposure Level (AEL; µg/cm^2/day)	Consumer Exposure Level (CEL; µg/cm^2/day)	Margin of Safety (AEL/CEL)
Baby shampoo	12	0.83	300	0.0028	0.0027	1.15
Bubble baths	0.000019	0.83	100	0.0083	3.8×10^{-9}	> 2,000,000
Cologne and toilet waters	0.075	0.83	100	0.0083	0.0002	50.07
Hair conditioners	15	0.83	100	0.0083	0.0030	2.77
Hair sprays (aerosol)	7.5	0.83	30	0.0277	0.0104	2.65
Hair sprays (pump)	7.5	0.83	30	0.0277	0.0163	1.70
Permanent waves	7.5	0.83	100	0.0083	0.0315	0.26
Rinses (non-coloring)	11	0.83	300	0.0028	0.0019	1.48
Shampoos (non-coloring)	15	0.83	300	0.0028	0.0026	1.08
Tonics, dressings and other hair grooming aids (rinse-off)	7.5	0.83	100	0.0083	0.0007	11.18
Tonics, dressings and other hair grooming aids (leave-on)	7.4	0.83	100	0.0083	0.0073	1.13
Hair tints	0.4	0.83	100	0.0083	0.0004	20.96
Hair rinses (coloring)	11	0.83	100	0.0083	0.0012	6.92
Hair shampoos (coloring)	6	0.83	300	0.0028	0.0010	2.71
Bath soaps and detergents	15	0.83	300	0.0028	0.0002	18.44
Other personal cleanliness products (liquid hand soap)	15	0.83	100	0.0083	0.0030	2.77
Shaving cream	4.5	0.83	100	0.0083	0.0003	26.350
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	15	0.83	100	0.0083	0.0135	0.61

Shading indicates product categories that fall below a MOS of 1.

Table 4. Quantitative risk assessment of MCI/MI at the maximum recommended use concentrations in cosmetic products[76]

Product Category	Maximum Recommended Concentration of Use (ppm)	Weight of Evidence NESIL (µg/cm^2)	SAF	AEL (µg/cm^2/day)	CEL (µg/cm^2/day)	Margin of Safety (AEL/CEL)
Baby shampoo	15	0.83	300	0.0028	0.0030	0.92
Bath soaps and detergents	15	0.83	300	0.0028	0.0002	18.44
Bubble baths	15	0.83	100	0.0083	0.0030	2.77
Hair conditioners	15	0.83	100	0.0083	0.0030	2.77
Permanent waves	15	0.83	100	0.0083	0.0630	0.13
Rinses (non-coloring	15	0.83	300	0.0028	0.0026	1.08
Shampoos (non-coloring	15	0.83	300	0.0028	0.0026	1.08
Tonics, dressings and other hair grooming aids (rinse-off)	15	0.83	100	0.0083	0.0015	5.59
Hair tints	15	0.83	100	0.0083	0.0149	0.56
Hair rinses (coloring)	15	0.83	100	0.0083	0.0030	2.77
Hair shampoos (coloring)	15	0.83	300	0.0028	0.0026	1.08
Other personal cleanliness products – liquid hand soap	15	0.83	100	0.0083	0.0030	2.77
Shaving cream	15	0.83	100	0.0083	0.0011	7.90
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	15	0.83	100	0.0083	0.0135	0.61
Cologne and toilet waters	7.5	0.83	100	0.0083	0.0166	0.50
Hair sprays (aerosol)	7.5	0.83	30	0.0277	0.0104	2.65
Hair sprays (pump	7.5	0.83	30	0.0277	0.0165	1.68
Tonics, dressings and other hair grooming aids (leave-on)	7.5	0.83	100	0.0083	0.0074	1.12

Shading indicates product categories that fall below a MOS of 1.

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