

SENSITISATION TO THE PRESERVATIVES METHYLCHLOROISOTHIAZOLINONE/METHYLISOTHIAZOLINONE AND METHYLISOTHIAZOLINONE

Anna Fourie¹

Hilary Carman²

Tanusha Singh^{1,3}

¹ National Institute for Occupational Health, National Health Laboratory Service, Johannesburg

² Consultant Dermatologist at NIOH Occupational Skin Disease Clinic, Johannesburg

³ Department of Clinical Microbiology and Infectious Diseases, School of Pathology, University of the Witwatersrand, Johannesburg

Email | annaf@nioh.ac.za

ABSTRACT

Introduction: Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and methylisothiazolinone (MI) are preservatives commonly used in water-based products to prevent microbial overgrowth. They are used in industrial products such as paints, glues, lacquers and cutting oils as well as in cosmetics and household-cleaning products. Allergic reactions to MCI/MI were reported in the 1980s and this resulted in the review of the concentration of the preservative in products, and its maximum concentration being legislated in Europe in 2016. The concentration of MCI/MI in industrial products and household-cleaning products is not regulated and there are no labelling requirements in terms of product composition. MI was introduced as a preservative on its own and, since its introduction, reactions to this preservative are increasing to the extent that in the United States it was named allergen of the year in 2013.

Methodology: Data from the National Institute for Occupational Health (NIOH) Occupational Dermatology Clinic, South Africa for the period January 2006–January 2018 were analysed to determine the prevalence of sensitisation reactions to MCI/MI and MI.

The records of 829 referrals to the NIOH clinic were reviewed retrospectively. MCI/MI and MI-sensitised cases were identified as patients with a positive patch test (1+; 2+ or 3+ reaction) to MCI/MI and/or MI in the European Standard Series (590 tests) and/or the cosmetic (110 tests) series of patch tests.

Results: Of 590 patients tested with MCI/MI, 30 had positive reactions (5.1%; 30/590). When testing MCI/MI as a 0.01% solution from January 2006 to August 2015, 21/445 (4.7%) of those tested were positive, whereas using double the concentration (0.02%) from September 2015 to January 2018, 9/145 (6.2%) were positive. Sensitisation to MI (0.2%) alone, tested since July 2014, was 15/84 (17.9%) of patients tested, with 7/84 (8.3%) reacting to both MI and MCI/MI. Since the introduction of MI, 13.2% (31/234) of patients tested with these preservatives were sensitised to either MCI/MI and/or MI.

Conclusion: Sensitisation to MCI/MI and MI was shown to increase over the years. Although patch testing with more sensitive reagents may contribute to this, the number of patients sensitised to the two preservatives, both occupational and non-occupational, has increased, and this is in line with international studies. Since these are commonly used preservatives, their concentration in industrial and self-care products needs to be reduced and properly labelled. The concentration for testing is also important to prevent false-positive or -negative reactions.

Keywords: methylchloroisothiazolinone/methylisothiazolinone (MCI/MI); methylisothiazolinone (MI); Kathon™ CG; Euxyl® K 100; isothiazolinones; patch test; sensitisation; occupational exposure; contact dermatitis

INTRODUCTION

Isotiazolinones are a group of preservatives including methylisothiazolinone (MI), methylchloroisothiazolinone (MCI), octylisothiazolinone (OIT) and benzisothiazolinone (BIT) that are used in various industrial and household water-based products (see Table I) to inhibit microbial overgrowth and prevent degradation of the product by microorganisms.¹

MCI and MI in a ratio of 3 : 1 are preservatives commonly used in the manufacture of products for industrial use, household-cleaning products and cosmetics (see Figure 1).² The MCI/MI combination, also known as Kathon™ CG or Euxyl® K 100, was introduced in the 1980s. The frequency of contact sensitisation to this preservative rose to 8% due to its use at a high concentration (30 ppm, 0.003%),³ especially in leave-on products (moisturisers, deodorants, etc). In order to reduce the frequency of allergic reactions, European legislation was introduced in 2016 which lowered the maximum allowable concentration of MCI/MI in all rinse-off cosmetic products to 15 ppm (0.0015%). Also, its use in leave-on products was prohibited. The United States reduced the concentration of MCI/MI even further in leave-on products (7.5 ppm; 0.00075%). These restrictions did not seem to have a significant impact on the prevalence of sensitisation in the general population.² This may be due to alternate exposures as documented in Table I. It may also be due to the application of several cosmetics, which may cause a summation of concentrations of MCI/MI and MI to which people are exposed. Alternatively, patients with pre-existing dermatitis are one of the major consumers of self-care products and having an impaired barrier increases the penetration of the allergens and increases the risk of sensitisation.² The concentration of MI in industrial products is not regulated in Europe.³ Initial research done on MCI and MI showed that MCI was 30 times more potent as a sensitizer than MI.⁴

MI was incorrectly classified as a 'moderate sensitizer' that could be used safely below a concentration of 600 ppm (0.06%) as it was thought that only beyond this concentration would it result in sensitisation.⁶ This research contributed to the Cosmetic Ingredient Review Expert Panel in 2010 publishing the final report on the safety of MI. The report recommended that MI could be used commercially as a preservative in cosmetics and household-cleaning products up to a concentration of 100 ppm, with mandatory labelling.⁷ These regulations do not account for multiple-product usage or cumulative exposure over time which may explain the ongoing reactions. The regulations are not applicable to industrial products, therefore no maximum limits for the concentration of MI in industrial products or labelling requirements exist. This means that the levels in workplaces could be high and aerosolisation may trigger, not only sensitisation, but also allergic contact dermatitis (ACD) in sensitive workers.²

Concurrent with the increased use of MI, an increase in cases of sensitisation to the chemical started to appear⁸ to the extent that, in 2013, MI was pronounced the 'allergen of the year' by the North American Dermatitis Society.^{3, 9–11}

Occupational exposure to these preservatives in industrial products is becoming an increasing cause of ACD. The first reports of occupational sensitisation to MI were from exposure to wallpaper glue¹² and paints.¹³ In Finland, Vauhkala et al showed a six-fold increase in sensitisation to the preservative over two periods: 2002–2008 and 2008–2013. The most common occupational groups in this study were hairdressers and beauticians. Common exposures included rinse-off products such as detergents, liquid soaps and industrial hand cleansers among other products.¹⁴ In England, from 1996–2012, there has been a 4.1% increase in occupational ACD from exposure to

TABLE I: EXAMPLES OF THE USE AND OCCURRENCE OF COMMON AND LESS REPORTED PRODUCTS CONTAINING MCI/MI OR MI⁵

COMMON NON-COSMETIC SOURCES	LESS REPORTED SOURCES
Water-based paints and varnishes	Antibacterial insoles for shoes
Glues (eg for wallpaper, shoes, plasters) and glue removers	Animal-care products (eg dog shampoo)
Industrial and household detergents (including wet wipes, dishwashing and machine-washing liquids, fabric softeners, textile sprays)	Medical devices (eg 'waist-reduction belts', wet wipes for skin care, products to decontaminate MRSA, ultrasound gels)
Fillers (eg plaster and floor-tile work; pottery)	Toilet fresheners
Gloss and polish products (eg maintenance products for cars, boats)	Cosmetics such as solid soap cubes, hand barrier creams, liquid makeup products
Metal-working fluids (cooling fluids and oils; cooling tower waters)	Mouth washes, maintenance products for dental prostheses
Textile and leather shoes, fur, carpet and mattress industry (aqueous pigment liquids)	Gel (mattresses) and waterbeds
Printing inks and toners	Products for gardening
Rubber industry (latex emulsions)	Antifungal coatings for car tyres and seats
Plastics industry (polymer solutions, chopping boards, rubbish bags)	Radiographic materials
Paper and cardboard industry (eg as a biocide in paper pulp, in aqueous pigment liquids)	In medium density fibreboard (MDF)
Wood cleaning and maintenance products	Fuels (gasoline, diesel)
Pesticides	Ironing waters
As a bactericide, fungicide and algicide in various industries (eg water softeners, air fresheners, milk and water industry) and in laboratories	Articles, objects and textiles 'contaminated' with isothiazolinones, for example, due to a detergent (sofas, toilet seats, towels, garments)

the preservative per annum.¹ A few reports of severe allergic reactions to MI have primarily identified occupational exposures to paints and glues – known causes of MI sensitisation.¹

The objective of this article is to describe the extent of the increase in sensitisation to MCI/MI and MI in patients seen at the NIOH Occupational Dermatology Clinic. Demographics of patient referrals and patch-test results using the European standard and cosmetic series for the period January 2006 to January 2018 were analysed.

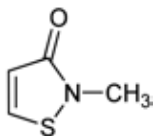
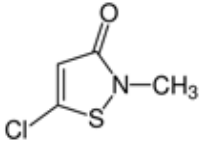
Methylisothiazolinone (MI) 	CAS: 2682-20-4 Example of trade name: Neolone™ Restrictions: forbidden in leave-on cosmetics in the European Union (as of January 2017), but still allowed in rinse-off cosmetics up to 100 ppm; cosmetics and detergents should always be labelled; chemical products require specific labelling if MI present >1.5 ppm, and an additional warning 'risk of sensitisation' if MI >15 ppm.
Methylchloroisothiazolinone (MCI) 	CAS (MCI): 26172-55-4 / CAS (MCI/MI): 55965-84-9 Example of trade name: Kathon™ CG (3 : 1 ratio of MCI to MI) Restrictions: forbidden in leave-on cosmetics in the European Union (as of April 2016), but the mixture MCI/MI is still allowed in rinse-off cosmetics up to 15 ppm; cosmetics and detergents should always be labelled; chemical products require specific labelling if MCI/MI present >1.5 ppm, and an additional warning 'risk of sensitisation' if MCI/MI >15 ppm.

Figure 1: Chemical structure and restrictions of MI and MCI.⁵

METHODS

PATIENTS

The NIOH Dermatology Database is an adaptation of the database created by the British Contact Dermatitis Society and is used for capturing routinely referred patient patch-test data. Patients are examined by a dermatologist and if it is suspected that they may have an occupational allergy, patch testing is done with relevant allergens as per the safety data sheets (SDS) provided by the worker's companies or from the occupational history taken. Patients are also referred from private dermatologists and from dermatology departments at

government hospitals – specifically for patch testing. Of the 829 patients seen at the Occupational Dermatology Clinic between January 2006 and January 2018, 590 were patch-tested with the European Standard Series (ESS) and/or the cosmetic series including the preservatives MCI/MI and/or MI. Initially, MI was provided with the cosmetic series of allergens and therefore only patients where self-care products were thought to play a role were tested with the MI. MI was later added to the ESS. The patients would sometimes be tested only with selected allergens that were thought relevant to their exposures, for example metals in miners working in the platinum/gold/chrome mines. Information available from the database included gender, age, occupation, medical history, exposures and patch-test results.

PATCH TESTING

Patch tests were prepared, in house, from commercial patch-tests series allergens (Chemotechnique MB Diagnostics, Sweden) depending on likely sensitisations anticipated from history and examination.

Initially MCI/MI at a concentration of 0.01% was used for testing. In July 2014, MI was introduced as a single allergen at a concentration of 0.2%.¹⁷ In September 2015, the MCI/MI concentration was doubled from 0.01% to 0.02% (see Figure 2).¹⁸

Patch tests were applied to the upper back in IQ chambers. The occlusion time was 48 hours, and readings were performed on day three. Patch-test reactions are read according to the International Contact Dermatitis Research Group criteria.¹⁹ Reactions of strength 1+, 2+ and 3+ were interpreted as positive responses.

To investigate the frequency of reactions to MCI/MI and MI, reactions to these two allergens in the ESS and cosmetic series were identified.

STATISTICS

The data were exported from the Access database to Excel for analysis. Descriptive statistics were applied. Percentages were used to determine the difference in sensitisation to MCI/MI, MI, or the combinations of the two preservatives. The effect of change in MCI/MI concentration from 0.01% to 0.02% and the introduction of the MI on its own on the percentage of positive reactions over the study period are reported.

RESULTS

A total of 829 cases were referred to the clinic between January 2006 and January 2018. Of these 590 were patch-tested

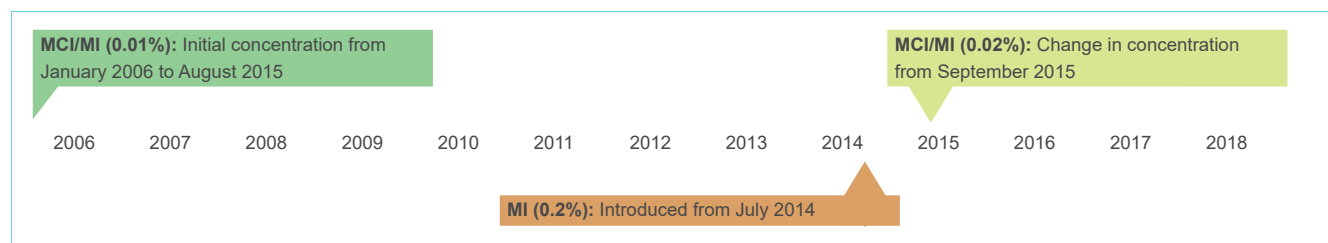


Figure 2: Timeline highlighting the changes in the concentration of MCI/MI and MI preservatives for patch testing.

TABLE II: PATIENT DEMOGRAPHICS AND PATCH TESTS CONDUCTED AT THE NIOH OCCUPATIONAL DERMATOLOGY CLINIC

PATIENT REFERRALS (N = 829)	
Occupational referrals	609 (73.5%)
Non-occupational referrals	220 (26.5%)
GENDER	
Males	295 (50.0%)
Females	295 (50.0%)
Age (median, range)	42.3 (10–73)
PATCH-TEST SERIES*	
European Standard (MCI/MI) tested	590
Cosmetic	110

* Patch test series that contained the MCI/MI and MI preservatives that were tested on all referrals considered to have a possible ACD

with the ESS and 110 with the cosmetic series (see Table II), including MCI/MI and/or MI. Other series tested include the metalworking oil (n = 73), epoxy (n = 57), shoe (n = 48), rubber (n = 33) and the hairdressing series (n = 20) to identify possible sensitisation to other occupational allergens where relevant, if multiple sensitisation was suspected.

During the period January 2006 to January 2018, 30/590 (5.1%) sensitisation to MCI/MI were detected and it was the fifth most prevalent allergen following nickel (103/590; 17.5%), chromate (57/590; 9.7%), cobalt (37/590; 6.3%) and fragrances (34/590; 5.8%). From January 2006 to August 2015, 4.7% 21/445 of patients tested were sensitised to MCI/MI [0.01%] (see Tables III and IV). From September 2015 to January 2018, 6.2% (9/145) of patients tested were sensitised to MCI/MI (0.02%) (see Tables III and IV).

In July 2014, MI (0.2%) was tested on its own. Initially, the MI was added to the cosmetic series, and hence only if the cosmetic series was requested, was MI tested. Later, it was included in the ESS and MI was tested if the entire ESS was tested. Occasionally, only specific allergens from the ESS were tested so MI may not have been tested, therefore only 84/234 (35.9%) patients were tested with MI. Of the 84 patients tested with MI, 15 (17.9%) were sensitised to MI only, seven patients (8.3%) were sensitised to both the MI and MCI/MI, and nine (10.7%) patients were sensitised to MCI/MI alone (see Table III). It should be noted that in this period the MCI/MI was tested at 0.01% up to September 2015 when the new allergen concentration of 0.02% was introduced. The total number of patients sensitised to the preservatives (MCI/MI (0.01% and then 0.02%) and MI (0.2%) from July 2014 was 13.2% (31/234) (see Table III).

From January 2006 to January 2018, 30 patients were sensitised to the mix MCI/MI. From July 2014 to January 2018 among the 234 people tested, 31 were sensitised to MCI/MI and/or MI, nine reacted to MCI/MI alone, seven to both MCI/MI while 15 to MI alone. From 2006 to 2009 there were no reactions to MCI/MI. The reason for this may be that the preservative was not commonly used in South Africa.

TABLE III: POSITIVE REACTIONS TO MCI/MI AND MI DETECTED BY PATCH TESTING WITH THE ESS AND THE COSMETIC SERIES

PRESERVATIVE	PERIOD OF TESTING	FREQUENCY OF POSITIVE SENSITISATIONS
MCI/MI combined [#]	January 2006–January 2018	5.1% (30/590)
MCI/MI (0.01%)	January 2006–December 2009	0.0% (0/147)
MCI/MI (0.01%)	January 2010–August 2015	7.0% (21/298)
MCI/MI (0.01%)	July 2014–August 2015	5.6% (5/89)
MCI/MI (0.02%)	September 2015–January 2018	6.2% (9/145)
MI (0.2%) only	July 2014–January 2018	17.9% (15/84)
MCI/MI and MI*	July 2014–January 2018	8.3% (7/84)
MCI/MI and/or MI [^]	July 2014–January 2018	13.2% (31/234)

[#]Total number of positive reactions to both MCI/MI (0.01%) and MCI/MI (0.02%)

*Patients reacted to both MCI/MI and MI

[^]Patients reacted to MCI/MI and/or MI

Sensitisation to MCI/MI and/or MI was detected among 18 of 590 (3.1%) cases of occupational contact dermatitis that were patch tested (see Table IV). Several of the workers referred to the NIOH clinic were exposed to high concentrations of the preservatives, for example, when diluting concentrated solutions of the preservatives (23–46%) or adding concentrate to cooling fluids, and this may have resulted in sensitisation. In some cases, no clear link to MCI/MI could be found in products used at work although items such as soaps and detergents are known to commonly contain MCI and MI as preservatives.¹ It is well documented that sensitisers are regularly omitted from safety data sheets,¹⁹ making it difficult to associate sensitisation to workplace exposure. In some cases, the reactions continued even if away from work, since these preservatives can also be found in many self-care and household-cleaning products. In addition, skin reactions were typically on exposed areas of the body, for example the hands, which are the primary site of involvement in 80% of occupational contact dermatitis cases, compared to non-exposed areas such as covered areas, in non-occupational exposures.²⁰

Positive reactions to MCI/MI or MI were also detected among non-occupational contact dermatitis cases, 28/220 (12.7%) of those tested. These cases had reactions on the face and/or generalised reactions all over the body. MCI/MI or MI were listed on the bottles of the self-care products used by these patients.

DISCUSSION

In line with many international studies,^{9–11,14} the prevalence of sensitisation to MCI/MI and MI at the NIOH occupational dermatology clinic (which does include non-occupational cases) has shown an increase over the years. Although the increase may be partly due to optimised testing, the number of cases of sensitisation to the preservatives detected, both in the occupational and non-occupational setting, is of concern.

A sensitisation prevalence of 8.3% to MCI/MI and MI is similar to that reported by Scherrer, in a study in Brazil which showed an increase in reactions to MCI/MI from 3.35% in 2006 to 2009,

TABLE IV: OCCUPATIONAL REFERRALS SENSITISED TO MCI/MI AND/OR MI WITH EXPOSURES, PATCH-TEST RESULTS AND INFORMATION RELEVANT TO DIAGNOSIS.

OCCUPATION	EXPOSURES	POSITIVE PATCH TESTS	COMMENTS
Fitter	H, N, H ₂ SO ₄ , NaCl, Cl ₂ NaOH, HCl, CaCl ₂ , greases	MCI/MI 3+, formaldehyde 2+, fragrance mix 2+, potassium dichromate 2+, fragrance mix 2+, carba mix 1+	Improves away from work, all reactions may contribute to ACD diagnosed
Nail technician	Acrylates, nail gel, MCI/MI, colour pigment	MCI/MI 3+, nickel sulphate 3+, nail gel IR	Improves away from work
Artisan millwright	Hydraulic oil, gear lubricant	MCI/MI 1+	No mention of MCI/MI
Chemical mixer	Shower soap, detergents, antibacterial handsoap, multipurpose cleaner, car shampoo	MCI/MI 3+	No mention of MCI/MI on SDS; but MCI/MI are common preservatives
Packer books	Books, plastic, cardboard, laundry soap in previous job	MCI/MI 2+, nickel sulphate 1+, potassium dichromate 1+	Possibly laundry soap as problem started at laundry
Filter worker water plant	Wears gloves, water	MCI/MI 2+, thiuram mix 2+, mercapto mix 2+, mercaptobenzothiazole 3+, Quaternium 15 1+	Gloves, Non-occupational case
Hairdresser	Perms, tints, shampoos, conditioners, bleaches	PPD 2+, MCI/MI 1+	Shampoos, conditioners, hair dyes
General worker	Phosphoric acid, sulphuric acid, Kathon™ CF1400 biocide	MCI/MI 1+	Occurred after spill of Kathon™, poured concentrate into cooling fluids
Cleaner	Cleaning chemicals, detergents	MCI/MI 2+	Improves when not at work
IT officer on cruise liner	Hand sanitisers, soaps	MCI/MI 3+, MI 3+, Quaternium 15 2+, nickel sulphate 3+	Only improves on treatment
Cleaner/porter	Hand lotion foam soap (MCI & MI), cleaning agents	nickel sulphate 3+, MI 2+	Not better away from work
Professional nurse	Disinfectants, hand sanitisers, latex gloves	MCI/MI 3+, MI 3+, Lyril 3+, nickel sulphate 2+	Latex allergic
Nurse	Disinfectants, hand sanitisers, latex gloves	MCI/MI 2+	Started in current job, not better away from work
Dental technician	Denture glue, dental cement, impression putty, instrument steriliser, powders to prepare for fillings	MCI/MI 2+	Not sure if it improves away from work
Weighing operator	Acids, NaOH, Kathon™	MCI/MI 2+, MI 1+, Kathon™ (CS0035) (0.02%) 3+, Kathon™ (C0013) (0.02%) 1+	Improves away from work
Site operator chemical company	MCI/MI containing preparation (23–26%) for addition to cooling fluids	MCI/MI 2+, MI 2+	Improved away from work
Hygiene technician-Cleaning company	Disinfectants, sanitiser, deodoriser, soaps, air fresheners	MI 3+	MCI/MI common in these products Improves away from work
Medical Intern	Gloves, disinfectants, sanitisers	formaldehyde 1+, MCI/MI 3+, MI 2+	Improves away from work

to 11.14% in 2009 to 2011.²¹ In Sweden, there was an increased frequency of reactions to MI from 2.9% in 2010 to 6.5% in 2012. Similarly, in the United Kingdom an increase from 0.6% in 2009 to 4.6% in 2012 was observed.²²

The finding of 18 cases where occupational exposures are linked to sensitisation to these preservatives is concerning. Although the international literature has shown that sensitisation to these two preservatives is on the decline in some countries such as Germany and France, other countries are still showing high levels of sensitisation especially to MI and particularly from work exposures.²³ Efforts must be made to increase awareness of this allergen as a cause of sensitisation in the workplace as well as from self-care and cleaning products.^{9–11,14}

The results also highlight the importance of testing with the appropriate allergens and/or at the appropriate concentration to prevent false-negative or false-positive results. It is also

important that the correct volumes are used for testing as large amounts could cause irritant reactions. Several patients reacted to the MI alone and not MCI/MI and these cases would not have been identified if testing with MI was not introduced. Castaneda-Tardana et al showed that the diagnosis of MI contact allergy was frequently missed as the concentration of MI in MCI/MI was too low to identify all patients with an allergy.²⁴ As shown by the data in this study, the identification of patients sensitised to the preservatives increased once the concentration of the MCI/MI was doubled and MI was introduced.²⁰ On the other hand, if the allergen is too concentrated or the amount applied in the testing chamber exceeds recommended limits, there is the possibility of causing strong irritant, false-positive reactions or it could increase the chances of sensitisation occurring due to patch testing.²⁰

The occupation of patients who were sensitised to these allergens varied from millwrights, beauticians, cleaners,

healthcare workers, caterers as well as occupations in chemical manufacturing plants. The possible exposures could be from the cooling oils, cosmetics used by beauticians, cleaning agents, disinfectants and soaps used in healthcare and various chemicals used in manufacturing processes. In the non-occupational setting, many homecare and self-care products contain these allergens. Identifying these allergens allows patients to avoid substances containing the chemicals, therefore improving their quality of life.

LIMITATIONS

One of the limitations of the study was that year-on-year reports of positive reactions to MCI/MI or MI were not done to show an increase in sensitisation unrelated to changing concentrations of allergens tested. Therefore, the results must be interpreted cautiously, acknowledging random fluctuations.

CONCLUSION

In conclusion, we have demonstrated the importance of adapting the allergens used for testing so that they remain relevant. MCI/MI and MI are commonly used preservatives that are known sensitisers and if not tested at the correct concentration sensitised patients may be missed during testing. It is also important that the concentration of these substances in industrial products as well as self-care products be reduced. Legislation should be introduced and enforced to regulate the use of non-sensitising levels of these preservatives in industrial settings. In companies where concentrated solutions of isothiazolinone are used, closed systems for handling the preservatives should be provided and all workers involved should receive proper education and personal protective equipment.

DECLARATION OF CONFLICT OF INTEREST

The authors have not conflict of interest.

This article has been peer reviewed.

REFERENCES

- Nielsen H. Occupational exposure to isothiazolinones. A study based on a product register. *Contact Dermatitis* 1994;31:18–21.
- Rodrigues-Barata AR and Conde-Salazar L. Methylisothiazolinone and Methylchloroisothiazolinone: new insights. *Eur Med J* 2014;2:101–105.
- Schnuch A, Mildau G, Kratz EM, et al. Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products. *Contact Dermatitis* 2011;65(3):167–174.
- Bruze M, Dahlquist I, Fregert S, et al. Contact allergy to the active ingredients of Kathon CG. *Contact Dermatitis* 1987;16(4):183–188.
- Aerts O. Contact allergy caused by methylisothiazolinone and related isothiazolinones, in Department of Dermatology, Faculty of Medicine and Health Sciences. 2017, Universiteit Antwerpen: Belgium, 1–216.
- Basketter DA, Gilmour NJ, Wright ZM, et al. Biocides: Characterisation of the allergenic hazard of methylisothiazolinone. *Cutan Ocul toxicol* 2003;22(4):187–199.
- The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman WFB, MD, FACP; Donald V Belsito MDRAH, PhD; Curtis D Klaassen, PhD; Daniel C Liebler, PhD; James G, Marks J, MD; Ronald C Shank, PhD; Thomas J Slaga, PhD; and Paul W Snyder, DVM, PhD. The CIR, et al Amended Safety Assessment of Methylisothiazolinone as Used in Cosmetics. *Cosmetic Ingredient Review*. 1620 L St NW, Suite 1200, Washington, DC 2014.
- Urwin R and Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: A new epidemic. *Contact Dermatitis* 2013;68:253–255.
- Geier J, Lessmann H, Schnuch A, et al. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: Is methylisothiazolinone the culprit? *Contact Dermatitis* 2012;67(6):334–341.
- García-Gavín J, Vansina S, Kerre S, et al. Methylisothiazolinone, an emerging allergen in cosmetics? *Contact Dermatitis* 2010;63(2):96–101.
- Aerts O, Goossens A, and Giordano-Labadie F. Contact allergy caused by methylisothiazolinone: the Belgian-French experience. *Eur J Dermatol* 2015;25(3):228–233.
- Isaksson M, Gruvberger B, Bruze M. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. *Dermatitis* 2004;15(4):201–205.
- Thyssen JP, Sederberg-Olsen N, Thomsen JF, et al. Contact dermatitis from methylisothiazolinone in a paint factory. *Contact Dermatitis* 2006;54(6):322–324.
- Vauhkala A, Pesonen M, Suomela S, et al. Occupational contact allergy to methylchloroisothiazolinone/methylisothiazolinone and methylisothiazolinone. *Contact Dermatitis* 2015;73:150–156.
- Urwin R, Warburton K, Carder M, et al. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: An occupational perspective. *Contact Dermatitis* 2015;72(6):381–386.
- Schwensen JF, Menne T, Andersen KE, et al. Occupations at risk of developing contact allergy to isothiazolinones in Danish contact dermatitis patients: From a Danish multicentre study (2009 - 2012). *Contact Dermatitis* 2014;71:295–302.
- Bruze M, Goossens A, and Isaksson M. Recommendation to increase the test concentration of methylchloroisothiazolinone/methylisothiazolinone in the European baseline patch test series – on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2014;71:35–40.
- Friis UF, Menne T, Flyvholm MA, et al. Isothiazolinone in commercial products at Danish workplaces. *Contact dermatitis* 2014;71:65–74.
- Keege TI, Saunders H, LaMontagne AD, et al. Are material safety data sheets MSDS useful in the diagnosis and management of occupational contact dermatitis? *Contact Dermatitis* 2007;57(5):331–336.
- Storrs FJ. Technical and ethical problems associated with patch testing. *Clinical Reviews in Allergy and Immunology* 1996;14:185–198.
- Scherrer MAR and Rocha VB. Increasing trend of sensitisation to Methylchloroisothiazolinone/methylisothiazolinone. *An Bras Dermatol* 2014;89(3):527–528.
- Isaksson M, Hauksson I, Hindsen M, et al. Methylisothiazolinone Contact allergy is rising to alarming heights also in Southern Sweden. *Acta Derm Venereol* 2015;95:31–34.
- Herman A, Aerts O, de Montjoye L, et al. Isothiazolinone derivatives and allergic contact dermatitis: A review and update. *J Eur Acad Dermatol Venereol* 2019;33:267–278.
- Castaneda-Tardana MP and Zug KA. Methylisothiazolinone. *Dermatitis* 2013; 24(1):2–6.