ISSN 2521-7321

REVIEW ARTICLES

ISOTHIAZOLINONES AND CONTACT ALLERGY

Edlira NEZA

Department of Pharmacy, Faculty of Medical Sciences, Aldent University
(Corresponding author: edlira.neza@ual.edu.al)

Abstract

BACKGROUND: Isothiazolinones appears to be a frequent cause of dermatitis in European countries.

OBJECTIVES: The aim of this review was to investigate the prevalence of contact allergy from methylisothiazolinone and methylchlorothiazolinone/methylisothiazolinone in different countries.

METHODS: Information on isothiazolinone allergy published during 2013-2017 was reviewed.

RESULTS AND DISCUSSION: The percentage of the positive reactions to the methylisothiazolinone in different countries were as follows: 3.7% in Denmark, 6.02% in Germany, 5.6 % in France, 12.94 % in Canada, 6.9 % in Italy, 5% Ireland, 7.2 % in Belgium and 6.8 % in United States. In most cases contact allergy was caused by use of cosmetics, cleaning agents, paints and baby wipes. The prevalence of the mixture MCI/MI was as follows: 9.4 % in United Kingdom, 9.41% in Canada, 9.04 % Italy, 6.3 % Ireland, 4.5% Belgium, 4.4% Germany, 8.3% British Isles and 10.3% Portugal. Dermatitis from isothiazolinones most frequently affected the hands, face, arms, legs, eyelids, anal-genital area, but also widespread areas on the body. Most cases have been caused by leave on cosmetic products.

CONCLUSIONS: An increase in prevalence of contact allergy to methylizothiasolinone and methylchlorothisolinone/methylisothiazoline was observed in European countries, Canada and US. The concentration of these preservatives in cosmetic products should be reduced to safer levels.

KEYWORDS: Isothiazolinones, methylisothiazolinone, Kanthon CG, contact dermatitis.

Introduction

The EU regulation 1223/2009 provides a list of allowed preservatives in cosmetic products with maximum concentration in ready for use preparation (Annex V). At the moment the list contains 57 chemical substances; however, only few of them are strongly represented on the market: formaldehyde, parabens, formaldehyde-releasers, methylchoroisothiazolinone (MCI) /methylisothiazolinone (MI). Preservatives are known as one of the two most relevant allergens found in cosmetic products (Timm-Knudson et al., 2006; Maier et al., 2009) and there is a significant increase in the level of reactivity (Schnuch et al., 2011).

Isothiazolinones are a group of broad spectrum preservatives with good antimicrobial activity against gram-positive, gram-negative, bacteria, yeast and fungi used in different products to inhibit the growth of microorganisms. The most widely used isothiazolinones in cosmetics, household and industrial products are: methylisothiazolinone (MI), methyl-chloroisothiazolinone (MCI), methylisothiazolinone/ methylchloroisothiazolinone (MI/MCI), benzi-sothiazolinone (BIT), octylisothiazolinone (OIT) and methyltrimethyleneisothiazolinone. MI and BIT are used as preservatives in cleaning agents and MI in cosmetics and body care products. BIT and OIT are used in industrial products (Friis et al., 2014). They are all classified as skin sensitizers.

Methylisothiazolinone and methylchloroisothiazolinone (MI/MCI 3:1) are also used together but the mixture is highly allergenic (Smith et al., 2016). In the early 1980s MI/MCI was introduced into personal care products at levels of up to 50 ppm. Kathon CG was a preservative system contaning as active ingredients MCI and MI, widely used in the early 1980s. Rapid increase in contact allergy to Kathon CG was observed in different European countries during 1985-1989. The prevalence of allergy was: 4.6 % in Finland (Hannuksela 1986), 4.4% in Sweden (Björkner et al. 1986), 3.43% in Germany (Frosch and Schulze-Dirks, 1987), 0.8% in Denmark (Hjorth and Petersen, 1986), 3.6 % in USA (Fransway 1986), 3.5 % in Spain (Hasson et al. 1990) and 5.5 % in Switzerland (Pasche and Hunziker 1989).

Atopic dermatitis on hand, face and lower leg was the most common of skin disorders. Prevalences of allergy symptoms are shown in Table I. Cosmetics were found to be the major cause of sensitization. MCI/MI has been limited at a concentration of 15 ppm. From July 2015 MCI/MI mixture is not allowed in leave-on cosmetics.

MI was used alone in cosmetics since 2005 at concentrations up to 100 ppm. Methyisothiazolinone is an important cause of contact dermatitis in European countries and USA. Also other preservatives have shown to be relevant sensitizers. Perrenoud et al. (1994) studied the frequency of sensitization of 13 common preservatives on 2295 Swiss patients.

Table 1. Kathon CG allergy in different countries.

Country	Prevalence of allergy from Kathon CG		Symptoms	Reference
Finland	Kathon CG 100 ppm	0.7% 1985 to 4.6% 1986	Atopic dermatitis, chronic hand dermatitis, lower leg dermatitis.	Hannuksela 1986
Sweden	Kathon CG 300 ppm	4.4 % 1986	Contact dermatitis	Björkner et al. 1986
Germany	Kathon CG 100 ppm	3.43% 1986	Contact dermatitis on the face and hands.	Frosch and Schulze-Dirks
Denmark	Kathon CG 100 ppm	0.8% 1986	Contact dermatitis	Hjorth and Petersen 1986
USA	Kathon CG	3.6% 1986	Allergic contact dermatitis	Fransway 1986
Spain	Kathon CG	3.5 % 1988-1989	Contact dermatitis	Hasson et al. 1990
Denmark	Kathon CG	1.3 % 1988	Contact dermatitis	Menné and Hjorth 1988
Switzerland	Kathon CG 100 ppm	5.5 % 1986-1987	Contact dermatitis	Pasche and Hunziker 1989

The percentages of positive reaction to the preservatives studied were as follows: formaldehyde 5.7%, benzalkonium chloride 5.5%, Kathon CG 5.5%, thiomersal 4.2%, chlorhexidine digluconate 2.0%, DMDM hydantoin 1.7%, paraben mix 1.7%, chloroacetamide 1.5%, bronopol 1.2%, imidazolidinyl urea 1.0%, quaternuim 15 1.0%, triclosan 0.8%, 2,4 – dichlrobenzyl alcohol 0.4 %. According to Mose et al. (2013) and Aerts et al. (2016) octylisothiazolinone is also a relevant sensitizer. Cases of occupational

allergic contact dermatitis caused by benzisothiazolinone are also reported (Meysman and Groossens 2017). Benzisothiazolinone is widely used in paint and varnishes, but also in household cleaning products but is not allowed in cosmetic products. Schwensen et al. (2015) have reported high concentration of BIT in paints (0.1 to 462.5 ppm). Friis et al. (2014) reported that the most widely isothiazolinones (in Danish markets) are benziisothiazolinone, methylisothiazo-linone and methylchloroisothiazolinone and may occur in high concentrations.

Materials And Methods

Information on isothiazolinone allergy published in the period 2013-2017 was reviewed. Keywords used were: isothiazolinone allergy, methylisothiazolinone allergy and methylchloroisothiazolinone allergy.

Results And Discussion

Few years ago, a higher prevalence of contact allergy was registered in different countries. In Europe, USA and Canada several groups have documented the frequency of allergy to methylisothiazolinone and to the mixture methylisothiazolinone/ methylchloro-thiazolinone. In the EU, MI was approved as a preservative in cosmetics and household products in 2005 at a concentration of 100 ppm. Since then, several cases of MI contact allergy have been reported. The prevalence of contact allergy has reached the levels: 3.7% in Denmark (Lundov et al. 2013), 6.02% in Germany (Uter et al. 2013), 6.0% in some European countries (Schwensen et al. 2016), 5.6 % in France (Hosteing et al. 2014), 12.94 % in Canada (Wilford et al. 2017), 6.9 % in Italy (Gallo et al. 2016), 5% Ireland (Murad and Marren 2015), 7.2 % in Belgium (Aerts et al. 2014) and 6.8 % in United States (Yu et al. 2015). More detailed data are presented in the Table II.

MI is also an emerging allergen in the pediatric population (Madsen et al., 2014). Wet wipes with MI were frequently the cause of atopic contact dermatitis (Chang et al., 2014). Frequently these are misdiagnosed as eczema, impetigo, or psoriasis.

The prevalence of the mixture MCI/MI was as follows: 9.4 % in United Kingdom (Ali et al. 2014), 9.41% in Canada (Wilford et al. 2017), 9.04 % Italy (Gallo et al. 2016), 6.3 % Ireland (Murad and Marren 2015), 6.3 % (Madsen and Andersen 2014), 4.5% Belgium (Aerts et al. 2014), 4.4% Germany (Molin et al. 2014), 8.3% British Isles (Johnston 2014), 10.3% Portugal (Gameiro et al. 2014).

As we can see from the Table II, there is an increase in the prevalence in the period from 2010/2011 to 2013. Studied conducted in Canada (Wilford et al. 2017) showed that prevalence of contact allergy from MCI/MI has had very high values in 2015 (12.94%). However we should take in consideration the fact that different methods, number of patients and allergen concentration are used by different groups.

Table 2. Methylisothiazolinone and methylchloroisothiazolinone prevalence of contact allergy in different countries.

Country	Prevalence of contact allergy		Symptoms	Publication
Denmark	MI MCI/MI	2.0% in 2010 to 3.7% in 2012 1.0% in 2010 to 2.4 % in 2012	Hand and face dermatitis	Lundov et al. 2013
Germany	MI	1.94% in 2009 to 6.02% in 2012	Face and ano-genital dermatitis	Uter et al. 2013
European countries	MI	6% in 2015	Hand, face, arms, eyelids dermatitis	Schwensen et al. 2016
France	MI 200 ppm	1.5 % (2010) to 5.6 % (2012)	Contact dermatitis	Hosteing et al. 2014
Sweden	MI	0.55 to 6.5%	Contact allergy	Isaksson et al. 2015
Europe	MCI/MI 100 ppm MCI/MI 200 ppm	1.2% 2.1%	Contact allergy	Bruze et al. 2014
Canada	MCI/MI MI 2000 ppm	9.41% (2015) 6.6% (2013) to 12.94 % (2015)	Contact allergy	Wilford et al. 2017
Italy	MI 2000 ppm MCI/MI	2.3 % (2012) to 6.9% (2013) 6.76% (2012) to 9.04% (2013)	Hand and face dermatitis	Gallo et al. 2016
Ireland	MCI/MI 200 ppm MI 2000 ppm	6.3 % (2012-2014) 5.0 % (2012- 2014)	Facial dermatitis	Murad and Marren 2015
Denmark	MI MCI/MI 0.02% MI 0.02%	4.8% (2011) to 6.5% (2013) 5.1% (2011) to 6.3% (2013) 3.1 % (2011) to 3.8% (2013)	Contact allergies	Madsen and Andersen 2014
Belgium	MCI/MI MI	4.5 % (2012) 6.0% (2012) to 7.2% (2013)	Hand and facial dermatitis.	Aerts et al. 2014
France-Belgium	MI	6.0% (2012) to 7.0% (2013)	Facial and hand dermatitis	Aerts et al. 2015
Germany	MCI/MI	4.4 % (2013)	Skin allergy	Molin et al. 2014
British Isles	MCI/MI MI	4.3 % (2010) to 8.3 % (2013) 1.7% (2010) to 11.1 % (2013)	Contact allergy	Johnston 2014
United Kingdom	MCI/MI	9.4 % (2011-2013)	Skin allergy	Ali et al. 2014
United States	MI	2.5 % 2012 to 6.8 % 2014	Hand and face allergy	Yu et al. 2015
Finland	MI	10.3% 2012 to 13.2% 2014	Contact allergy	Lammintaustra et al.2014
Portugal	MI (500 ppm) and MCI/MI (100 ppm)	5.15% 2012 to 10.9 % 2013	Contact allergy	Gameiro et al. 2014
United Kingdom	MI (500 ppm)	0.5 % 2010 to 5.7 % 2012	Contact allergy	Mc.Fadden et al.2013

Dermatitis most frequently affected the hands, face, arms, legs, eyelids, anal-genital area, but also widespread areas on the body. In most cases, patients were aged >40 years, both males and females. Cosmetics were the most common products causing allergy. According to Madsen and Andersen (2014) sources of exposure from methylisothiazolinone or methylchloroisothiazolinone were different consumer products such as: cosmetics (43%), cleaning agents (7%), paints (14%) and baby wipes (1%). Other authors suggest that primary source of exposure are cleaning agents and paints. Leave-on cosmetic products were the most allergic. Allergic reaction from wet wipes (baby wipes) were frequently reported with hand dermatitis in parents, chronic perianal and facial dermatitis in babies.

Different authors suggest that high prevalence is related with increasing use of MI and MCI/MI in cosmetic products. Other authors suggest that higher concentrations of MI are used in cosmetic products. Alvarez-Rivera et al. (2012) revealed higher isothiazolinone content for some rinse off products (baby care products). Methylisothiazolinone (0.025%-0.36%), benzalkonium chloride (1%) and triclosan (0.4%) were found in cosmetic products sold in European markets in concentrations higher than the limit allowed by European Regulation 1223/2009 Banned preservatives such as methyldibromo glutaronitrile were also found (Neza and Centini, 2016).

Conclusions

This review shows the increasing prevalence of methylisothiazolinone and methylchloroiso-thiazolinone/methylisothiazolinone contact allergy in different European countries , Canada and US. The concentration of these preservatives in cosmetic products should be reduced to safer levels.

Acknowledgments

No funding source was obtained for this work.

References

1. Timm-Knudson V.L.; Johnson J.S.; Ortiz K.J.; Yiannias J.A. (2006), Allergic contact dermatitis to preservatives. Dermatol.Nurs. 18, 130-6.
2. Maier L.E.; Lampel H.P.; Bhutani T.; Jacob S.E. (2009), Hand dermatitis: a focus on allergic contact dermatitis to biocides. Dermatol.Clin.. 27, 251-64.
3. Schnuch A.; Lessmann H.; Geier J.; Uter W. (2011), Contact allergy to preservatives. Analysis of IVDK data 1996-2009. Br. J. Dermatol. 164, 1316-25.
4. Friis, U. F., Menné, T., Flyvholm, M.-A., Bonde, J. P. E., Lepoittevin, J.-P., Le Coz, C. J. and Johansen, J. D. (2014), Isothiazolinones in commercial products at Danish workplaces. Contact Dermatitis, 71: 65–74. doi:10.1111/cod.12235.
5. Smith V.; Clark Sh.; Wilkinson M. Allergic contact dermatitis in children: trends in allergens, 10 years on. A retrospective study of 500 children tested between 2005 and 2014 in one Uk centre. Contact Dermatitis. 2016. 74, 37-43.
6. Hannuksela, M. (1986), Rapid increase in contact allergy to Kathon® CG in Finland. Contact Dermatitis, 15: 211–214.
7. Björkner, B., Bruze, M., Dahlquist, I., Fregert, S., Gruvberger, B. and Persson, K. (1986), Contact allergy to the preservative Kathon® CG. Contact Dermatitis, 14: 85–90.
8. Hjorth, N. and Roed-Petersen, J. (1986), Patch test sensitivity to Kathon® CG. Contact Dermatitis, 14: 155–157.
9. Fransway, A. F. (1988), Sensitivity to Kathon CG: findings in 365 consecutive patients. Contact Dermatitis, 19: 342–347.
10. Hasson, A., Guimaraens, D. and Conde-Salazar, L. (1990), Patch test sensitivity to the preservative Kathon CG in Spain. Contact Dermatitis, 22: 257-261.
11. Menné, T. and Hjorth, N. (1988), Kathon® CG reactivity in 1396 consecutively patch tested patients in the Copenhagen area. Contact Dermatitis, 19: 260–262.
12. Perrenoud, D., Bircher, A., Hunziker, T., Sutter, H., Bruckner-Tuderman, L., Stäger, J., Thürlimann, W., Schmid, P., Suard, A., Hunziker, N. and SWISS CONTACT DERMATITIS RESEARCH GROUP (1994), Frequency of sensitization to 13 common preservatives in Switzerland . Contact Dermatitis, 30: 276–279. doi:10.1111/j.1600-0536.1994.tb00597.x
13. Mose, A. P., Frost, S., Öhlund, U. and Andersen, K. E. (2013), Allergic contact dermatitis from octylisothiazolinone. Contact Dermatitis, 69: 49–52. doi:10.1111/cod.12068
14. Aerts, O., Meert, H., Romaen, E., Leysen, J., Matthieu, L., Apers, S., Lambert, J. and Goossens, A. (2016), Octylisothiazolinone, an additional cause of allergic contact dermatitis caused by leather: case series and potential implications for the study of cross-reactivity with methylisothiazolinone. Contact Dermatitis, 75: 276–284. doi:10.1111/cod.12670
15. Meysman, T. and Goossens, A. (2017), Occupational allergic contact dermatitis caused by benzisothiazolinone in printing ink and soap. Contact Dermatitis, 76: 51–53. doi:10.1111/cod.12642
16. Lundov, M. D., Opstrup, M. S. and Johansen, J. D. (2013), Methylisothiazolinone contact allergy – a growing epidemic. Contact Dermatitis, 69: 271–275.
17. Uter, W., Geier, J., Bauer, A. and Schnuch, A. (2013), Risk factors associated with

methylisothiazolinone contact sensitization. Contact Dermatitis, 69: 231–238.

18. Schwensen, J. F., Uter, W., Bruze, M., Svedman, C., Goossens, A., Wilkinson, M., Giménez Arnau, A., Gonçalo, M., Andersen, K. E., Paulsen, E., Agner, T., Foti, C., Aalto-Korte, K., McFadden, J., White, I., Johansen, J. D. and on behalf of the European Environmental Contact Dermatitis Research Group (2016), The epidemic of methylisothiazolinone: a European prospective study. Contact Dermatitis. doi:10.1111/cod.12733.
19. Hosteing, S., Meyer, N., Waton, J., Barbaud, A., Bourrain, J.-L., Raison-Peyron, N., Felix, B., Milpied-Homsi, B., Ferrier Le Bouedec, M.-C., Castelain, M., Vital-Durand, D., Debons, M., Collet, E., Avenel-Audran, M., Mathelier-Fusade, P., Vermeulen, C., Assier, H., Gener, G., Lartigau-Sezary, I., Catelain-Lamy, A., Giordano-Labadie, F. and On behalf of REVIDAL-GERDA network (2014), Outbreak of contact sensitization to methylisothiazolinone: an analysis of French data from the REVIDAL-GERDA network. Contact Dermatitis, 70: 262–269.
20. Bruze, M., Isaksson, M., Gruvberger, B., Andersen, K. E., Gonçalo, M., Goossens, A., Johansen, J. D., Maibach, H. I., Rustemeyer, T., Le Coz, C.-J. and White, I. R. (2014), Patch testing with methylchloroisothiazolinone/methylisothiazolinone 200 ppm aq. detects significantly more contact allergy than 100 ppm. A multicentre study within the European Environmental and Contact Dermatitis Research Group. Contact Dermatitis, 71: 31–34.
21. Wilford, E.J., Gannes, C.G. Methylisothiazolinone Contact allergy prevalence In Western Canada.(2017) Journal of Cutaneous Medicine and Surgery.
22. Gallo, R., Sgnori, A., Gervasio, S., Parodi, A. (2016), Prevalence of sensitization to methylisothiazolinone in an italian skin allergy unit.
23. Murad, A. and Marren, P. (2016), Prevalence of methylchloroisothiazolinone and methylisothiazolinone contact allergy in facial dermatitis: a single centre Irish study. J Eur Acad Dermatol Venereol, 30: 60–62.
24. Aerts, O., Baeck, M., Constandt, L., Dezfoulian, B., Jacobs, M.-C., Kerre, S., Lapeere, H., Pierret, L., Wouters, K. and Goossens, A. (2014), The dramatic increase in the rate of methylisothiazolinone contact allergy in Belgium: a multicentre study. Contact Dermatitis, 71: 41–48
25. Ali, F. R., Shepherd, E. L., Yell, L. C., Buckley, D. A. and Williams, J. D. L. (2014), Escalating methylisothiazolinone/methylchloroisothiazolinone allergy probably attributable to methylisothiazolinone in leave-on body cosmetics. Contact Dermatitis, 70: 316–317
26. Lammintausta, K., Aalto-Korte, K., Ackerman, L., Alanko, K., Berry, P., Hasan, T., Kaminska, R., Korhonen, L., Laukkanen, A., Liippo, J., Pesonen, M., Rantanen, T., Riekki, R. and Suuronen, K. (2014), An epidemic of contact allergy to methylisothiazolinone in Finland. Contact Dermatitis, 70: 184–185.
27. Yu SH, Sood A, Taylor JS. (2015), Patch Testing for Methylisothiazolinone and Methylchloroisothiazolinone-Methylisothiazolinone Contact Allergy. JAMA Dermatol..152(1):67-72.
28. McFadden, J. P., Mann, J., White, J. M. L., Banerjee, P. and White, I. R. (2013), Outbreak of methylisothiazolinone allergy targeting those aged ≥40 years. Contact Dermatitis, 69: 53–55
29. Madsen, J.T. and Andersen, K.E., 2016. Contact allergy to 1, 2-benzisothiazolin-3-one. Contact Dermatitis, 75(5), 324-326.
30. Schwensen, J. F., Lundov, M. D., Bossi, R., Banerjee, P., Gimenez-Arnau, E., Lepoittevin, J.-P., Lidén, C., Uter, W., Yazar, K., White, I. R. and Johansen, J. D. (2015), Methylisothiazolinone and benzisothiazolinone are widely used in paint: a multicentre study of paints from five European countries. Contact Dermatitis, 72: 127–138.
31. Aakhus A.E.; Warshaw E.M. Allergy to methyldibromoglutaronitrile/phenoxyethanol (Euxyl k 400): regulatory issues, epidemiology, clinical characteristics, and management. Dermatitis. 2011. 22, 127-40.
32. Admani S.; Matiz C.; Jacob S.E. Methylisothiazolinone: a case of perianal dermatitis caused by wet wipes and review of an emerging pediatric allergen. Pediatr. Dermatol. 2014. 31, 350-2.
33. Madsen J.T.; Andersen K.E. Airborne allergic contact dermatitis caused by methylisothiazolinone in a child sensitized from wet wipes. Contact Dermatitis. 2014. 70, 183-4.
34. Chang M., Nakrani R. Six children with Allergic Contact Dermatitis to Methylisothiazolinone in wet wipes (Baby Wipes). Pediatrics. 2014, 133,
35. Neza E.; Centini M. Microbiologically contaminated and over-preserved cosmetics according Rapex 2008-2014. Cosmetics. 2016. 3, 3.