SCCS/1521/13
Revision of 27 March 2014

Scientific Committee on Consumer Safety

SCCS

OPINION ON

Methylisothiazolinone (P94)

Submission II

(Sensitisation only)

The SCCS adopted this opinion at its 4th plenary meeting

on 12 December 2013

Revision of the opinion on methylisothiazolinone (P94)

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ACKNOWLEDGMENTS

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This opinion has been subject to a commenting period of eight weeks after its initial publication. Comments received during this time have been considered by the SCCS and discussed in the subsequent plenary meeting. Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged. Revised opinions carry the date of revision.

Keywords: SCCS, scientific opinion, cosmetic ingredients, methylisothiazolinone, MI, Regulation 1223/2009, contact allergy, epidemic, CAS no. 2682-20-4, EC 220-239-6

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1. BACKGROUND

The Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) adopted the first opinion in March 2003 on "Methylisothiazolinone" (SCCNFP/0625/02).

The SCCNFP adopted the second opinion on "Methylisothiazolinone" on April 2004 (SCCNFP/0805/04) with the following conclusion:

The SCCNFP is of the opinion that the proposed use of Methylisothiazolinone as a preservative at a maximum concentration of 0.01% (100 ppm) in the finished cosmetic product does not pose a risk to the health of the consumer.

Methylisothiazolinone (MI) has been listed in Annex V/57 of the Cosmetic Regulation 1223/2009/ECC to be used as preservative at maximum concentration of 0.01% (100ppm) in cosmetics products.

In the Cosmetic Regulation 1223/2009/ECC Annex V/39 we have also the mixture of Methylchloroisothiazolinone(MCI) and Methylisothiazolinone (MI) that is currently allowed as a preservative in all cosmetic products at a maximum concentration of 0.0015 % (15ppm) of a mixture in the ratio 3:1 of the two substances.

Several Member States raised concern on the use of Methylisothiazolinone (MI) as data demonstrates that MI is a sensitizer in animals and a contact allergen in human. The Commission received information on the issue of sensitising potential of MI starting from 2011. According to this information both MCI/MI and MI alone are used in cosmetics and body care products as well as in household products and industrial products, i.e. occupational contactants. However, for a number of years, MI is also increasingly being used alone, without MCI, or in combination with other biocides. Sensitisation to MI is becoming an increasing problem all over Europe, particularly with sensitisation in young children from moist toilet tissue/hygiene moist tissues or cosmetics and Several Member States have asked the Commission to request to SCCS a reassessment of the safety of the MI when it is used as preservative in cosmetics products at maximum concentration of 100ppm.

2. TERMS OF REFERENCE

1. *On the basis of the new evidence in relation to sensitising potential, does the SCCS consider Methylisothiazolinone (MI) still safe for consumers, when used as a preservative in cosmetic products up to concentration limit of 100ppm? If no, it is asked for the SCCS to revise this concentration limit on the basis of information provided.*

2. *Does the SCCS have any further scientific concerns with regard to the use of Methylisothiazolinone (MI) in cosmetic products?*

3. OPINION

3.1. Chemical identity

3.1.1. Primary name and/or INCI name

INCI methylisothiazolinone

3.1.2. Chemical names

Methylisothiazolinone

IUPAC 2-Methylisothiazol-3(2H)-one

Other 2-Methyl-4-isothiazolin-3-one

3.1.3. Trade names and abbreviations

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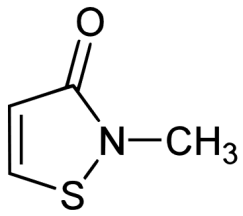
3.1.4. CAS / EC number

CAS no. 2682-20-4

EC 220-239-6

3.1.5. Structural formula

Methylisothiazolinone

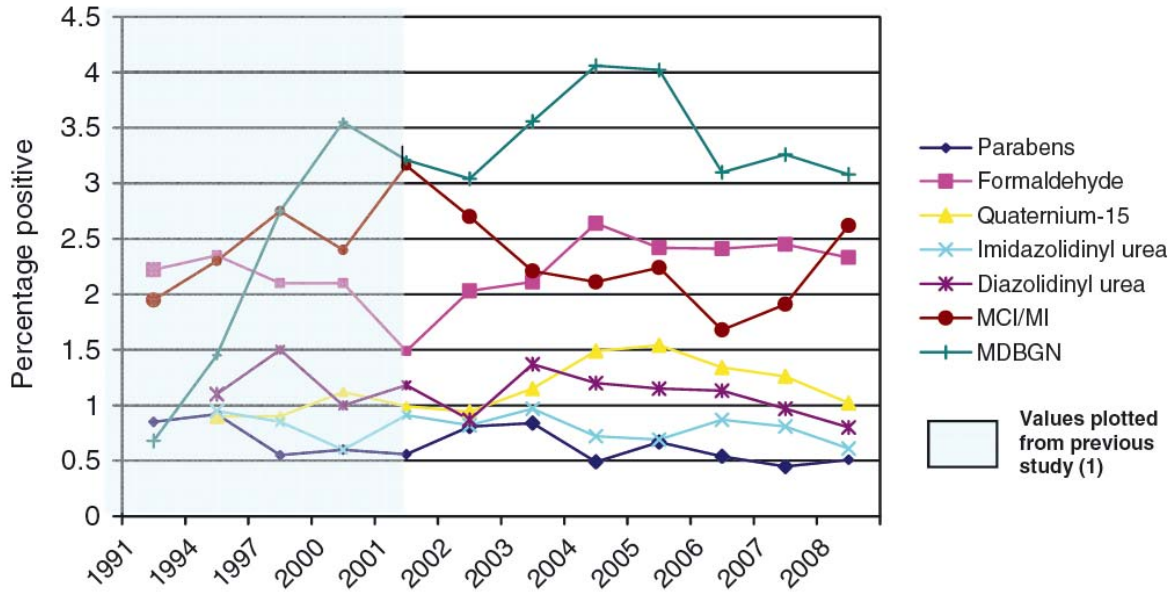


3.2. Epidemiology of Contact Allergy of Methylisothiazolinone

Normal exposures to preservative-containing products by the consumer can induce contact allergy, the elicitation phase of which manifests itself as allergic contact dermatitis.

Several preservatives are included in the European baseline series of contact allergens, used for diagnostic patch test investigations of individuals with eczema. Included in the series is methylchloroisothiazolinone and

methylisothiazolinone (MCI/MI in a 3:1 mixture). Data are available and published at intervals by dermatologists to monitor the trends in contact allergy to preservatives in Europe over time. Such recent pan-European data are illustrated below (Svedman C, Andersen KE, Brandão FM, *et al.* 2012):



For MCI/MI, stepwise risk management measures were introduced and following "safe" limits of this preservative in cosmetics in the EU (15 ppm), contact allergy to MCI/MI significantly decreased to around 2% of patch tested patients after the 90's.

MI was reported to be a weak sensitizer in the guinea pig (Bruze M, Fregert S, *et al.* 1987) but categorised as a strong sensitizer in the local lymph node assay with an EC3 of 0.4% in acetone: olive oil (AOO, see table from Basketter D A, Gilmour N J, Wright Z M, *et al.* 2003).

EC3 values (% v/v)

Vehicle	AOO	PG
Formaldehyde	0.4	2.8
Glutaraldehyde	0.07	1.5
MCI/MI	0.0082	0.063
MI	0.4	2.2

This latter information was not available for inclusion in the SCCNFP Opinion of March 2003 (SCCNFP/0625/02) or the updated opinion of April 2004 (SCCNFP/0805/04) and no LLNA information was included in these opinions. The sensitisation studies made available and considered by the SCCNFP for their Opinions are included within the present Opinion together with a review of the LLNA mentioned above.

The primary sensitising properties of MCI/MI have been attributed to MCI whereas MI was considered unable to sensitize individuals in concentrations below 1000 ppm (Burnett, CL, Bergfeld WF, Belsito DV *et al*. 2010).

MI alone (without MCI) was introduced as a preservative in industrial products in the early 2000's, and in 2005 was allowed as a preservative in both leave-on and rinse-off cosmetics at a maximum concentration of 100 ppm (0.01%) (Annex V/57 of the Cosmetic Regulation 1223/2009/ECC; Cosmetic Directive 2005/42/EC) with an increasing use since (Lundov M D, Krongaard T, Menné T L, Johansen J D. 2011; Castanedo-Tardana M P, Zug K A. 2013).

The first reports on contact allergy from MI appeared in 1987 (Bruze M, Dahlquist I, Fregert S, *et al*. 1987). After 2000, MI was introduced in industrial products (e.g., paints, adhesives, varnishes and cooling fluids), and due to its weaker preservative effect was used at higher concentrations than in MCI/MI. Allergic contact dermatitis from MI in the occupational setting was reported in 2004 (Isaksson M, Gruvberger B, Bruze M. 2004). Several cases of occupational allergic contact dermatitis from MI were then reported from paints (Thyssen, J. P., Sederberg-Olsen, N., Thomsen, J. F. & Menné, T.2006; Mose, A. P. *et al.* 2012).

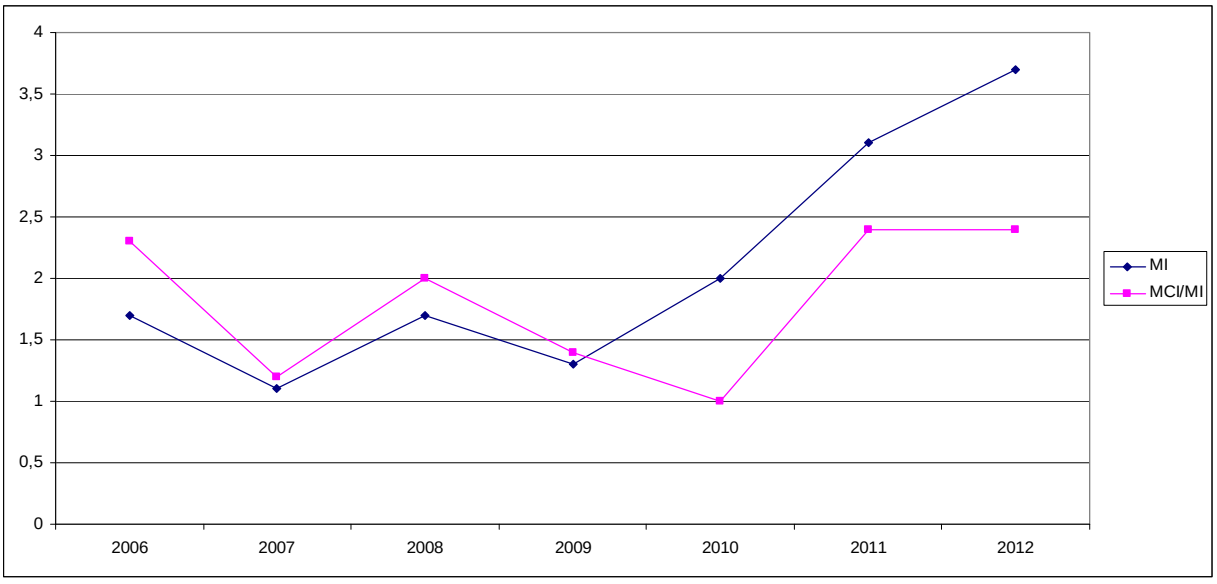
The first reports from cosmetics began in 2010 (García-Gavín J, Vansina S, Kerre S, *et al.* 2010) mainly due to wet wipes for hygiene (baby wipes, moist tissues, moist toilet paper), hair cosmetics (shampoos), facial cosmetics (Lundov, M. D., Thyssen, J. P., Zachariae, C. & Johansen, J. D. 2010; Lundov, M. D., Krongaard, T., Menné, T. L. & Johansen, J. D. 2011) , deodorants (Amaro, C., Santos, R. & Cardoso, J. 2011) and sunscreens (Castanedo-Tardana, M. & Zug, K.2013).

Airborne exposure to MI has caused severe cases of airborne allergic contact dermatitis and systemic contact dermatitis particularly from recently painted walls (Aerts, O. *et al.* 2013; Lundov M. D., Zachariae, C., Menné, T. & Johansen, J. D. 2012) or from toilet cleaners (Lundov, M. D. & Menné, T. 2013), including a case in a 4-year-old child most probably sensitized to MI through baby wipes (Aerts, O. *et al.* 2013).

Accompanying the increasing number of published cases of allergic contact dermatitis from MI, particularly since 2009, a rise in contact allergy to MCI/MI has been observed in Europe.

In Germany, with more than 12 000 patients tested/year, positive patch tests to MCI/MI increased from 2.3% in 2009 to 3.9% in 2011 (Geier J, Lessmann H, Schnuch A, Uter W. 2012) similar to Leeds, UK (increase from 0.9 to 4.9%) (Urwin, R. & Wilkinson, M. 2013) and in Amersham, UK (from < 3% to >8%) (Orton D & Willis C. 2013*).* In Coimbra, Portugal, reactivity to MCI/MI rose from 1.5% (in 2006/7) to 2.9 and 3.6% respectively in 2011 and 2012 (Gonçalo M, Goossens A. 2013). Similar figures are being observed elsewhere in Europe, with alerts particularly during late 2012 in France and Belgium at REVIDAL, a system to collect alerts in contact dermatitis (Hosteing S, Meyer, N; Waton, J. *et al.* 2013).

The rise in contact allergy to MCI/MI cannot be explained by a change in exposure to MCI/MI in cosmetics (the permitted maximum concentration has been 15 ppm since February 1989 (89/174/EEC), and phasing out of its use in leave-on cosmetic products may enter into force in 2014, see below), but is due to the increasing exposure to MI, present in concentrations very near 100 ppm both in leave-on and rinse-off cosmetics, as illustrated from Denmark (Lundov M D, Krongaard T, Menné T L, Johansen J D. 2011). Further, there is some indication of the levelling-off of the frequency of reactions to MCI/MI whilst MI continues to increase (Lundov M D, Morten S, Opstrup MS, Johansen J D. 2013).



Prevalence of methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI)/MI patch test positive patients at Gentofte Hospital from 2006 to 2012. (Lundov M D, Mortsen S, Opstrup M S, Johansen J D. 2013)

MI has only recently been tested as a single allergen, separate from MCI/MI in the European baseline series, in the local baseline series in several countries. Reactivity was around 1.5% until 2008 in Denmark (Lundov, M. D., Krongaard, T., Menné, T. L. & Johansen, J. D. 2011) but values increased from 0.9% in 2006 to 1.8% in 2008 in Finland (Ackermann, L. *et al.* 2011*)* and very high values were detected in 2011/12 in Leeds (4.6%) (Urwin, R. & Wilkinson, M. 2013), London (6%), Coimbra (4.5%) and Leuven, Belgium (5.8%), with a very high percentage of relevant reactions (Gonçalo M, Goossens A. 2013).

In Germany, although in selected patients with suspected cosmetic or occupational exposure, MI reactivity rose from 1.9% in 2009 to 4.4% in 2011, particularly in female patients (188% increase) and in patients with facial dermatitis (200% increase), suggesting that increase in reactivity is most probably related to cosmetic exposure (Geier, J., Lessmann, H., Schnuch, A. & Uter, W. 2012). In the USA a similar situation seems to have occurred as MI was considered the allergen of the year 2013 (Castanedo-Tardana, M. & Zug, K. 2013).

Testing with standard patch test preparations of MCI/MI contain too low a concentration of MI to properly demonstrate contact allergy to MI. A patch test concentration of 300 ppm MCI/MI fails to detect almost half of the cases of contact allergy to MI. Increasing to 1000 ppm MCI/MI is not irritating and detects more and relevant cases with subjects reacting in the repeated open application test (ROAT) with a cream containing 100 ppm MI, the highest allowed concentration in cosmetics (Ackermann, L. *et al.* 2011). MI has now been recommended to be included in the European baseline patch test series and tested at 2000 ppm (0.2%). (Bruze M, Engfeldt M, Gonçalo M and Goossens A. 2013).

Contact allergy to MI has been reported in consecutively tested dermatitis patients in Sweden, Denmark, Germany, Finland, and the UK. The contact allergy rates reported vary between 0.5% and 6% in 2012. The highest rates were from the UK, where an increase was noticed in Amersham from 2.5% in 2009 to 6.0% in 2011 (Orton D, Willis C. 2013) and in Leeds from 0.6% in 2009 to 4.6% in 2012 (Urwin R, Wilkinson M. 2013). In Denmark an increase from 1.4% in 2009 to 3.1% in 2011 was recorded (Lundov M D, Zachariae C, Menné T, Johansen J D. 2012). Aimed testing of MI has been performed in Germany where MI has been tested at 500 ppm in water respectively (Geier J, Lessmann H, Schnuch A, Uter W. 2012; Schnuch A, Lessmann H, Geier J, Uter W. 2011). This testing has identified an increasing contact allergy rate to MI from 0.5% before 2009 to 4.4% in 2011.

A male predominance has been reported from the UK (Orton D, Willis C. 2013), Denmark (Lundov M D, Thyssen J P, Zachariae C, Johansen J D.

2010), Germany (Schnuch A, Lessmann H, Geier J, Uter W. 2011), and Sweden (Isaksson M, Gruvberger B, Bruze M. 2013).

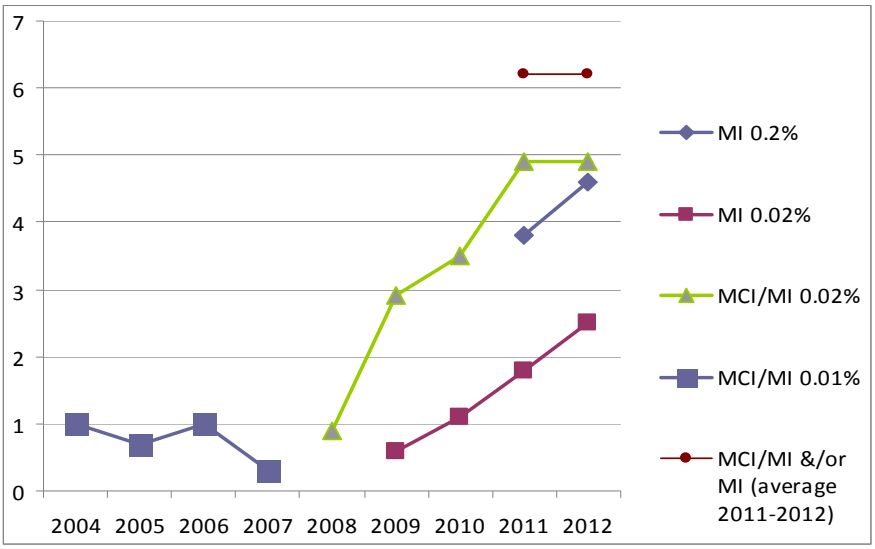
The table below (adapted from: Bruze M, Engfeldt M, Gonçalo M and Goossens A. 2013) shows data on patch test preparations used and contact allergy rates to MI in various European publications. The data above the thick line concerns consecutively tested dermatitis patients, while the information below the thick line concerns aimed testing of groups of patients.

Member State	Conc. in ppm (all aq. except when stated)	Dose in µg/cm^2	Number tested	MI allergy rate %	% of MI positive, MCI/MI negative	Years	Ref
Germany	500	NA	2167	0.8	0.2	2005	A
Denmark	2000	60***	2536	1.5	0.8	2006-2010	D
Finland	300	NA	10 821	0.6		2006-2008	E
	1000	NA	10 821	1.4	0.5	2006-2008	E
UK	500	NA	1337	4.0(2.5-6)	0.1*	2009-2011	B
	200	NA	349	0.6	NA	2009	C
	200	NA	771	1.1	NA	2010	C
	200	NA	611	1.8	NA	2011	C
	200	NA	325	2.5	NA	2012	C
	2000	NA	238	3.8	1.6**	2011	C
	2000	NA	325	4.6	1.6**	2012	C
Sweden	475	14.3	100	1.0	0*	2003	G
	950	28.5	1457	0.7	0	2003-2005	G
	1000	30.0	181	0.5	0	2005	G
Germany	500 pet.	NA	13 433	1.5	0.5	(2005) 2008-2009	F
	500	NA	6789	1.9	1.2	2009	A
	500	NA	7193	3.4	1.2	2010	A
	500	NA	7292	4.4	1.2	2011	A

NA = not available
* = MCI/MI tested at 200 ppm
** Figure is only given for 2011 and 2012 together. MCI/MI was tested at 200 ppm.
*** unpublished, JD Johansen (Denmark)

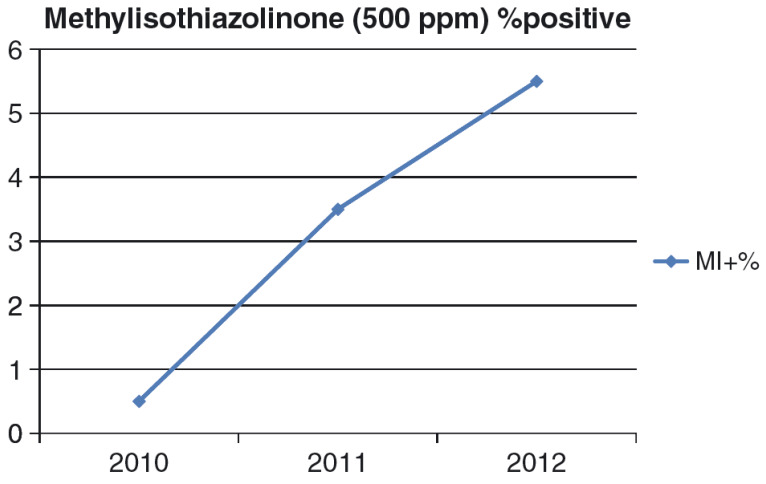
A. Geier J, Lessmann H, Schnuch A, Uter W. 2012
B. Orton D , Willis C. 2013
C. Urwin R, Wilkinson M. 2013
D. Lundov M D, Thyssen J P, Zachariae C, Johansen J D. 2010
E. Ackermann L, *et al*. 2011
F. Schnuch A, Lessmann H, Geier J, Uter W. 2011
G. Isaksson M, Gruvberger B, Bruze M. 2013

The graph below illustrates the rising frequency of contact allergy to MI in a single centre in the UK (Leeds) (Urwin R, Wilkinson M. 2013):

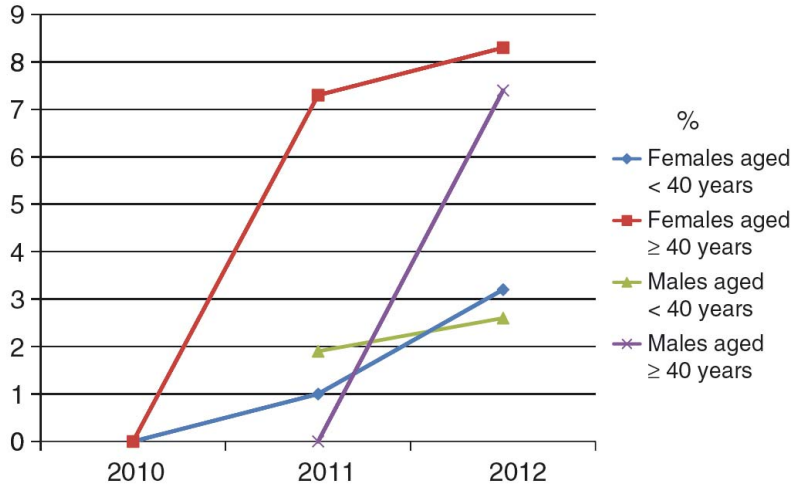


Percentage (y-axis) patch test sensitivity at day 4 (D4) to methylisothiazolinone (MI) and methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) mix at The Leeds Centre for Dermatology January 2004 - June 2012

The graph below illustrates the rising frequency of contact allergy to MI in a further single centre in the UK (London) with consecutive testing of patients with 500 ppm MI (McFadden JP, Mann J, White JML, Banerjee P, White IR. 2013):

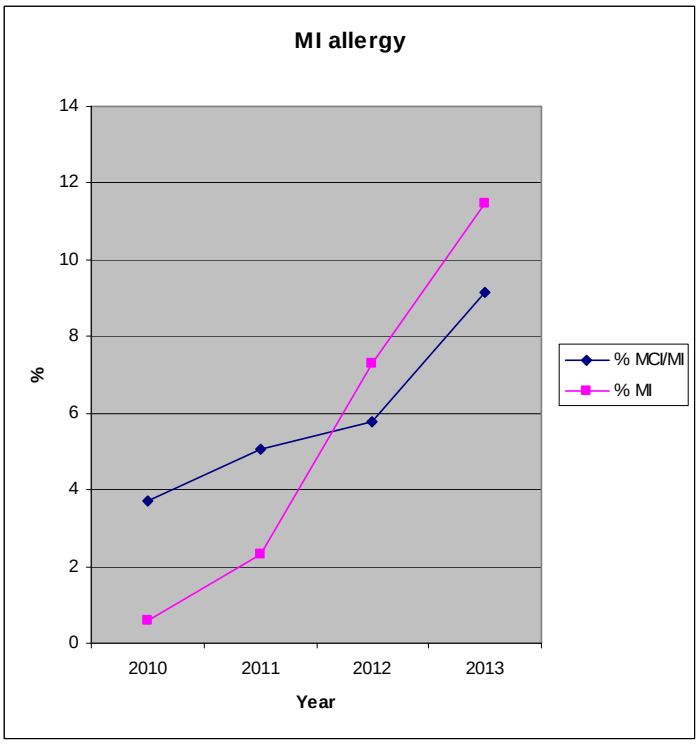


The same data extracted for age and sex shows that males and females $\geq$ 40 years old were the first to be sensitised in the recent emergence of MI as an important allergen. Possible immuno-mechanistic reasons for this observation have been discussed. (McFadden JP, White IR, Basketter D, Puangpet P and Kimber I. 2013).



Methylisothiazolinone allergy by age and sex. (McFadden JP, Mann J, White JML, Banerjee P, White IR. 2013)

The trend is further illustrated by multicentre data from the British Society for Cutaneous Allergy (BSCA) (Johnson G 2014; reproduced with permission from the author), which includes available 2013 data from contributing centres in the British Isles (UK and Republic of Ireland).



(Johnson G. 2014, combined multicentre date from British Isles). Percentage of patients having contact allergy to MI.

Detailed data from the IDVK in Germany also illustrates the rise in the frequency of MI sensitisation reported from their contributing centres up to 2012 (Uter W, Geier J, Bauer A, and Schnuch A. 2013).

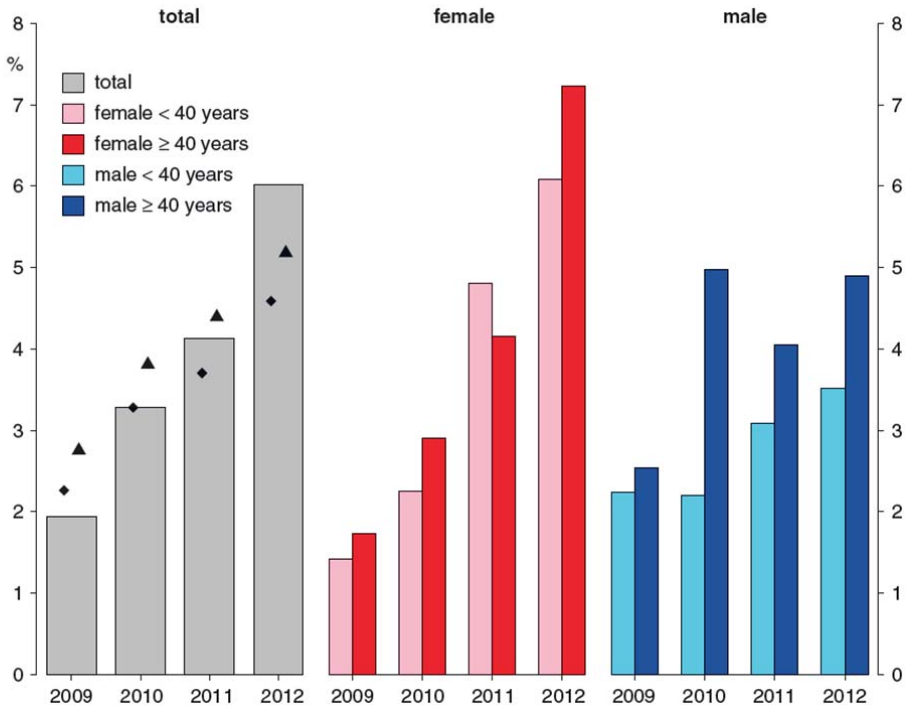


Fig. 1. Annual proportions of positive reactions to methylisothiazolinone (MI), 500 ppm aqua, between 2009 and 2012 in departments of the IVDK. Diamonds: the prevalence of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (100 ppm aqua, tested in the baseline series) sensitization among consecutively tested patients. Triangles: the results with MCI/MI in patients tested with the cosmetic preservatives series [see also (3)].

These IVDK authors observed a strong association between female sex and face dermatitis, resulting from the use of various cosmetic products.

A significant association was also found with hand eczema as well as face dermatitis. Ano-genital dermatitis was observed in 2.8% of the patients emphasizing the importance of intimate hygiene wipes as a source of exposure to MI. (Uter W, Geier J, Bauer A, and Schnuch A. 2013).

SCCS Comment

Recent and current clinical data, from widely distributed geographical areas within Europe, demonstrate a rapidly increasing frequency of contact allergy to MI.

Below (with typographical errors in the original corrected) are the relevant MI sensitisation report summaries reproduced from SCCNFP Opinion (SCCNFP/0625/02) which suggested that MI 100 ppm to be safe in both leave-on and rinse-off cosmetic products. The reference numbers are those used in the original Opinion (SCCNFP/0625/02) but the full references are

included below each reference number. There is no attempt to re-interpret the data or otherwise comment on the conclusion of the Opinion.

3.3 Irritation and corrosivity

3.3.1. Skin irritation

From SCCNFP 0625/02

2-Methyl-4-isothiazolin-3-one was applied undiluted by a single application of 0.5 ml to the shaved intact skin of 7 New Zealand White rabbits. Contact time was 3 minutes for 5 animals, 1- hr (and 3 min.) for one animal, 4-hrs for one animal. The application sites were semi-occluded. After removal of the patch, the animals were observed for 14 days for signs of irritation.
No mortality or clinical signs of systemic toxicity were observed during the study.
On the 4 and 1 hr sites, skin irritation indicative of corrosivity was observed on day 14 and 7, respectively.
On the 3 min. site, very slight to well defined erythema was noted through day 7 and slight oedema was noted at 1 hr.
For the 5 animals exposed during 3 min., very slight to well defined erythema was noted through 48 hrs in most rabbits. Very slight to moderate oedema was noted at 1 and 24 hrs. Very slight to slight oedema was noted in one rabbit at 48 and 72 hrs.

2-Methyl-4-isothiazolin-3-one is corrosive to the skin when applied undiluted.

Ref.: 5 (SCCNFP 0625/02)

Rohm and Haas Report No 96R-123, RH-573T (undated)- Skin Irritation Study in Rabbits

0.5 ml of an aqueous solution of Neolone™ 950 (100 ppm a.i. [MI] was applied to the skin of a group of six New Zealand White rabbits. Contact time was 4 hours and the application was semi occluded. After removal of the patch, the animals were observed for 72 hours for signs of irritation.

No mortality or clinical signs of systemic toxicity were observed during the study. There was no erythema or oedema present at any observation period. The Primary Irritation Index (PH) was 0.

An aqueous solution of MI is non-irritating to rabbit skin at proposed recommended use concentrations of 100 ppm active ingredient.

Ref.: 6 (SCCNFP 0625/02)

Rohm and Haas Report No OOR-006 (2000) Neolone^{Tm} 950 Preservative (100 ppm aqueous solution) Skin Irritation Study in Rabbits.

Human study (modified HRIPT)

The cumulative irritation potential of 2-Methyl-4-isothiazolin-3-one (RH-573; MI) was - investigated in a 21 day test with human volunteers. Aqueous dilutions of MI (0.1 ml) were applied to the back under occlusive patches, for a contact period of 23 hours on 21 consecutive days. On completion of the dosing phase, the subjects were rested without further dosing for 10 - 14 days. Following the rest period, 24 hour patch(es) of the appropriate test material(s) were applied to a naive site. Subject induced with 50, 100 and 250 ppm MI were challenged with the same respective concentrations of test material as well as distilled water and sodium lauryl sulphate. Subjects induced with 500 ppm MI were challenged with 100,250 and 500 ppm MI as well as with distilled water and SLS. Four of the subjects induced with 1000 ppm were not only challenged with 1000 ppm but also with 250 and 500 ppm.

Group	Number of subjects	Introduction concentration of MI (ppm)	Total Reactions during dosing	Cumulative irritation	Challenge concentration of MI (ppm)	Reactions on challenge
I	16	50	11/16	0/16	50	0/16
11	15	100	4/15	0/15	100	0/15
III	17	250	6/17	0/17	250	0/17
IV	15	500	7/15	0/15	500	1/15
					250	1/15
					100	0/15
V	16	1000	15/16	1/16	1000	2/16
					500	1/4
					250	1/4

During the introduction phase, a number of irritant reactions (to both MI and vehicle control - distilled water) were observed, these were mainly graded as 1 and were transient in nature. The total reactions for vehicle controls were 7/16, 4/15, 4/17, 4/15 and 12/16 for the groups I, II, III, IV and V respectively. No reactions were noted on challenge for the vehicle controls in any group.

Cumulative irritation was only observed in one individual from the 1000 ppm induction group.

Ref: 8 (SCCNFP 0625/02)

Rohm and Haas Report No. 92RC-097A. (1994) RH-573 - Evaluation of 21-Day Cumulative Irritation Potential in Humans

3.3.2. Mucous membrane irritation

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3.4 Skin sensitisation

The skin sensitisation potential of 2-Methyl-4-isothiazolin-3-one [MI; RH-24,573] was determined using the closed patch method of Buehler [OECD 406]. Four groups of outbred Hartley guinea pigs [5/sex/group] received ten 6-hr induction doses [3 doses/week for 3.5 weeks] of 0.4 ml at concentrations of 1000, 5000, 15,000 and 30,000 ppm a.i. in distilled water. Two weeks after the last induction dose these animals, together with a group of uninduced control animals, were challenged with 1000, 5000, or 15,000 ppm MI in distilled water.

No erythema reactions were observed in the non-induced control animals at any challenge concentration of MI.

	Challenge dose (ppm a.i.)		
Induction dose **[ppm** a.i.]	**1000**	**5000**	**15000**
0			
1000	0/10	0/10	1/10
5000	0/10	2/10	6/10
15000	1/10	1/10	3/10
30000	0/10	2/10	5/10

The concentration of MI required to induce and elicit a response in 50 % of the animals (EC_{50}) was estimated to be ≥ 5000 ppm a.i. for induction at a challenge concentration 15,000 ppm a.i. and ≥ 15,000 ppm a.i. for challenge at an induction concentration of 30,000 ppm a.i.

Ref 9: SCCNFP 0625/02

Rohm and Haas Report No. 88R-052. (1989) RH-24,573: Delayed Contact Hypersensitivity Study in Guinea Pigs.

Human Repeated Insult Patch test

One subject, from the 500 ppm induction group (see table above), was found to react on challenge. This individual was found to react to the marker pen and also to a number of consumer products; this reaction was therefore considered to equivocal. Two subjects from the 1000 ppm

induction group showed a mild reaction upon challenge and were considered to be sensitised.

Based on this data the threshold for sensitisation appears to be at around 1000 ppm 2-Methyl- 4-isothiazolin-3-one.

Re: 8 SCCNFP 0625/02

Rohm and Haas Report No. 92RC-097A. (1994) RH-573 - Evaluation of 21-Day Cumulative Irritation Potential in Humans

In an intensified Shelanski and Shelanski Repeated Insult Patch Test, ninety-eight [98] adult volunteers, patch test negative to 100 ppm Kathon® CG, were enrolled into the study. Kordek™ 50C (Methyl-4-isothiazolin-3-one; MI), 0.15 ml of a 100 ppm aqueous solution, was applied to a webril pad and the pad applied to the back of the volunteers under occlusion. Patches were applied four times a week for three weeks [induction phase]. After a week free of dosing, the subjects were challenged on a fresh site with MI, 0.15 ml of a 100 ppm aqueous solution applied to a webril pad. One of the 98 subjects showed a positive response [grade 4] on the fifth day of the induction phase. This subject was judged to be pre-sensitised. Of the remaining 97 subjects none reacted to challenge [elicitation] with 100 ppm aqueous MI.
Under the conditions of this test, 100 ppm Methyl-4-isothiazolin-3-one did not induce skin sensitisation in human volunteers.

Ref: 10 SCCNFP 0625/02

Rohm and Haas Report No. 99RC-0138. (2000) A Patch Test to Determine the Skin Irritation and Sensitisation Propensities of Kordek TM 50C (study conducted at 100 ppm active ingredient)

In a Repeat Insult Patch Test, 113 adult volunteers (12 males and 101 females), were enrolled in the study. 0.2 ml of an aqueous solution of 200 ppm 2-Methyl-4-isothiazolin-3-one, was applied by occlusive patches for a contact period of 24-hr per day. Patches were applied three times a week for three weeks [induction phase]. After a week free of dosing, the subjects were challenged on a fresh site with MI, 0.2 ml of a 200 ppm aqueous solution applied to a webril pad.

There was no adverse effect reported in the 100 subjects who completed the study. 13 out of 113 enrolled in the study either violated the protocol or withdrew from the study.

Under the conditions of this test, 200 ppm Methyl-4-isothiazolin-3-one did not induce skin sensitisation in human volunteers.

Ref: 11 SCCNFP 0625/02

Rohm and Haas Report No. 00RC-099A. (2000) Repeat Insult Patch Study with 2-methylisothiazolin-3-one at an Aqueous Concentration of 200 ppm Active Ingredient.

In a Repeat Insult Patch Test, 107 adult volunteers (19 males and 88 females), were enrolled in the study. 0.2ml of an aqueous solution of 300 ppm 2-Methyl-4-isothiazolin-3-one, was applied by occlusive patches for a contact period of 24-hr per day. Patches were applied three times a week for three weeks [induction phase]. After a week free of dosing, the subjects were challenged on a fresh site with MI, 0.2 ml of a 300 ppm aqueous solution applied to a webril pad. There was no adverse effect reported in the 98 subjects who completed the study. 9 out of 107 enrolled in the study either violated the protocol or withdrew from the study.

Under the conditions of this test, 300 ppm Methyl-4-isothiazolin-3-one did not induce skin sensitisation in human volunteers.

Ref: 12 SCCNFP 0625/02

Rohm and Haas Report No. OORC-099B. (2000) Repeat Insult Patch Study with 2-methylisothiazolin-3-one at an Aqueous Concentration of 300 ppm cove Ingredient.

Sensitisation Potency of MI in relation to MCI/MI

Animal Data

In a study using the Buehler method (Ref. 9 (*Rohm and Haas Report No. 88R-052. (1989) RH-24,573: Delayed Contact Hypersensitivity Study in Guinea Pigs*)), the concentrations of RH-24,573 [MI] required to induce and elicit a response in 50% of guinea pigs [EC_{50}] (the effective concentration producing the effect under study in 50% of the test population) were estimated. The EC50 for induction was determined to be > 5000 ppm a.i. at a challenge concentration of 15,000 ppm a.i. For elicitation, the EC_{50} was 15,000 ppm a.i. at an induction concentration of 30,000 ppm a.i. A similar study (Ref. 28 (*Chan, P. K., Baldwin, R. C., Parsons, R. D., Moss, J. N., Stiratelli, R., Smith, J. M. and Hayes, A. W. [1983] Kathon Biocide: Manifestation of Delayed Contact Dermatitis in Guinea Pigs is Dependent on the Concentration for Induction and Challenge. Journ.Investigat. Dermatol: 81: 409 - 411*)) performed with MCI/MI [3/1] determined the EC_{50} for induction to be 88 ppm a.i. at a challenge concentration of 2,000 ppm a.i., and the EC_{50} for elicitation to be 429 ppm a.i. at an induction concentration of 1,000 ppm a.i.

In a version of the Local Lymph Node Assay (Ref. 29 (*Potter, D. W. and Hazelton, G. A. [1995]. Evaluation of Auricular Lymph Node Cell Proliferation in Isothiazolone-Treated Mice. Fundamental and Applied Toxicology 24 165- 172*)), the PC_{200} [the concentration giving a 2-fold proliferate response over controls] for MI was 1506 µg and for MCI was 11 µg.

The sensitisation potential of methylchloroisothiazolinone

/methylisothiazolinone [3: 1] was compared to that of Methylisothiazolinone in the Open Epicutaneous test. The threshold for induction for MCI/MI was 58 ppm (Ref. 30 (*Wiemann, C. and Hellwig, J. [2001]. Methylisothiazolinone 20% - Open Epicutaneous Test in Guinea Pigs*)). For MI the induction threshold was in the range of 3000 ppm. (Ref. 31 (*Wiemann, C. and Hellwig, J. [2001].]. Chloromethylisothiazolinone/Methylisothiazolinone 3:1 Open Epicutaneous Test in Guinea Pigs*))

Human Data

Although no comparative Human Repeat Insult Patch tests have been performed on MCI/MI and MI, it is possible to compare the sensitisation potential based on existing studies of the two substances. The available data, taken partly from Company reports and partly from the open literature, is summarised in the table below.

Comparison of Human Repeat Insult Patch Test data on MCI/MI and MI

	MCI/MI [3:1]			MI		
Concentration [ppm]	Dose [µg/cm^2]	Incidence	% Response	Dose [µg/cm^2]	Incidence	Response
	0.42	0/416	0.0	-	-	-
	0.50	0/103	0.0	-	-	-
7.5	0.75	0/184	0.0	-	-	-
10	0.83	0/602	0.0	-	-	-
12.5	1.04	1/84	1.2	-	-	-
15	1.25	0/200	0.0	-	-	-
15	1.34	2/189	1.1	-	-	-
20	1.67	2/45	4.4	-	-	-
50[b]	2.50	0/109	0.0	-	-	-
100[b]	5.00	5/1 16	4.3	5	0/97	0.0
150[c]	7.50	7/196	3.6	-	-	-
200	-	-	-	10	0/100	0.0
300	-	-	-	15	0/98	0.0
400	-	-	-	20	1/116	0.9
500	-	-	-	45	1/210	0.5
600[d]	-	-	-	30	0/75	0.0

b: Based on the summation of results of Draize tests conducted by Maibach cited in ref.6 p. 105
c: Subjects received six induction exposures at 150 ppm in petrolatum followed by four induction exposures at 300 ppm in water - Maibach cited in ref. 6 p 104
d: Study in progress; the results to date are reported.

Ref: 32, 33, 34 SCCNFP 0625/02

Cosmetic Ingredient Review (CIR) Expert Panel: Final Report on the Safety Assessment of Methylisothiazolinone and Methylchlororisothiazolinone, J. Amer. College Toxicol., Vol. 11 (1), 1992.

Fewings, J. and Menne, T.: An Update of the Risk Assessment for methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) with Focus on Rinse-Off Products, Contact Dermatits, Vol. 41, 1999.

Repeat Insult Patch Studies with 2-Methylisothiazolin-3-one at Aqueous Concentrations of 100 to 600 ppm Active Ingredient : Rohm and Haas Report Numbers: 99RC-01 38, OORC -099A, OORC-099B, OORC-099C, OORC099D, OORC-099E, OORC-099F; conducted:1999-2001.

Based on the results of the HRIPT data, there is at least a factor of 30 difference in the sensitisation [induction] potential of the two isothiazolinone products. This compares favourably with the Open Epicutaneous Test [OET] which shows a factor of 50 difference in sensitisation [induction] potential. Thus, on the basis of this data, the number of new sensitisations induced by exposure of people to MI through the use of cosmetic and toiletry products is predicted to be low.

Dose-elicitation studies of Methylisothiazolinone on individuals known to be allergic to Kathon® CG

In a study, 28 patients sensitised to MCI/MI were patch tested with MCI and MI and all individuals reacted to MCI at 300 ppm, whereas only 2 reacted to MI at 300 ppm [one also reacted to 100 ppm MI].

Ref: 35 SCCNFP 0625/02

Bruze, M., Dahlquist, I., Fregert, S., Gruveberger, B. and Persson, K. Contact allergy to the active ingredients of Kathon® CG. Contact Dermatitis 1987: 16: 183 - 188

Further studies showed that of 12 subjects previously sensitised to MCI/MI [all reacted to a 150 ppm patch of MCI/MI] 3 reacted to MI at 115 ppm with weak reactions, recorded by the authors as 'doubtful'.

Ref: 36 SCCNFP 0625/02

Bruze, M., Dahlquist, I. And Gruvberger, B. [1989] Contact allergy to dichlorinated methylisothiazolinone. Contact dermatitis 20: 219 - 239.

In a study, 85 subjects from the clinics of the IVDK identified as patch positive to MCI/MI, were patch tested with MI at concentrations of 500 ppm a.i or 1000 ppm a.i. in water. The allergic status towards MCI/MI was compared with the responses to the MI patches. The results are shown in tables 2 and 3.

Ref: 37 SCCNFP 0625/02

Schnuch, A. [1999] Testing the Frequency of Sensitisation to MI in MCI/MI (Kathon CG) sensitized subjects. Un-published study conducted for Rohm and Haas.

Table 2: Reactions of the MCI/MI-positive test subjects to MI

No. Subjects	Total MI negative	MI negative (500 ppm)	MI positive (500 +1000 ppm)
85	58 [68%]	9 [11 %]	27 [32%]

Table 3: Reactions of the MCI/MI-positive test subjects to MI graded by response to MCI/MI

No. Subjects	MI positive	MCI/MI (+) and MI positive	MCI/MI *(++1+++)* and MI positive	MCI/MI *(++1+++)* and MI negative
85	27 [32%]	12 [14%]	11 [13%]	7 [8%]

In the 73 subjects where the intensity of the MCI/MI reaction was reported, there is a highly significant correlation [$p<0.01$] between the intensity of MCI/MI sensitisation and the reaction to MI. See table 4.

Table 4: Relationship between the intensity of MCI/MI sensitisation and the reaction to MI

	MI (+/+++) positive	MI (+/+++) negative	Total
MCI/MI (++/+++) positive	11 [61%]	7 [39%]	18
MCI/MI (+) positive	12 [22%]	43 [78%]	55
Total	23	50	73

The results show that, at high concentrations of MI [500 to 1000 ppm], a proportion of the subjects with a known sensitivity to MCI/MI may also react to MI. Thus, from the available data, it cannot be excluded that patients previously sensitised to MCI/MI will react to products containing 100 ppm MI. However, the numbers are expected to be low and will be further reduced by the warning provided through ingredient labelling.

Importantly, based on the HRIPT data, the number of new sensitisations induced by exposure to MI through the use of cosmetic and toiletry products is expected to be low.

Sensitisation potential of degradation products

Degradation of MCI/MI involves opening of the isothiazolinone ring by nucleophilic attack on the ring sulphur. During the nucleophilic attack, the chlorine atom at position 5 of the isothiazolinone ring leaves, thus both MCI and MI will essentially follow the same metabolic/degradation pathways.

Once the ring has opened the electrophilic reactivity and biological action is lost.
This was confirmed by Bruze and Gruvberger who failed to find positive reactions when N- methylmalonamic acid, malonamic acid and malonic acid were tested in 10 MCI/MI sensitive patients. Further, inactivation of MCI/MI with sodium bisulphite destroys the sensitisation potential.

Ref: 38, 39 SCCNFP 0625/02

Bruze, M. and Gruvberger, B. Patch Testing with degradation products of Kathon CG. Contact Dermatitis 1989: 21: 124

Gruvberger, B. and Bruze, M. Can chemical burns and allergic contact dermatitis from higher concentrations of methyl chloroisothiazolinone/methylisothiazolinone be prevented? Am. J. Contact Derm 1998 31: 11-14.

Studies <u>not included or unavailable</u> for the SCCNFP Opinion (0625/02) are below:

Local Lymph Node Assay (LLNA)

Study 1

Guideline:	/
Species/strain:	female CBa/Ca mice
Group size:	4 per test dose
Test substance:	2-methyl-2H-isothiazol-3-one (MI)
Batch:	/
Purity:	19.7%-(the remainder water)
Vehicle:	acetone: olive oil, 4: 1 v/v (AOO) and propylene glycol (PG)
Concentration:	0.049, 0.099, 0.197, 0.493, 0.985 (AOO); 0.99, 1.97, 4,93, 9.85 (PG)
Positive control:	MCI/MI, formaldehyde, glutaraldehyde
GLP:	/
Study period:	2003 or earlier

Dosing solutions were freshly prepared each day immediately before treatment. Test concentrations were selected on the basis of the standard approach adopted for the local lymph node assay.
Groups of four mice received 25 µl, of various concentrations of 2-methyl-2H-isothiazol-3-one (MI) in vehicle or vehicle alone on the dorsum of both ears daily for 3 consecutive days. Five days following the initiation of treatment, all mice were injected intravenously with 250 µl, of 20 μCi ^{3}HTdR in PBS. Five hours later draining auricular lymph nodes were excised and a single cell suspension prepared. The incorporation of ^{3}HTdR was measured

by β-scintillation counting and is displayed in the table above as the mean dpm/node for lymph nodes pooled from each group of four mice and the stimulation index (SI) for two vehicles; AOO acetone: olive oil and PG propylene glycol.

Results

Vehicle/ concentration (%)	dpm/node	SI
AOO	355	
0.049	531	1.5
0.099	521	1.5
0.197	633	1.8
0.493	1348	3.8
0.985*	874	2.5
PG	281	
0.99	527	1.9
1.97	724	2.6
4.93	1978	7.0
9.85	2131	7.6

*It was noted that at 0.985%, the highest concentration of MI in AOO, the SI value was reduced, perhaps reflecting the distinct skin irritation observed at this concentration.

The estimated concentration of the test chemical required to induce an SI of 3 relative to concurrent vehicle-treated controls (the EC3 value) was calculated via linear interpolation of the dose response data.

	EC3 values	
	EC3 value	(% v/v)
Vehicle	AOO	PG
Formaldehyde	0.4	2.8
Glutaraldehyde	0.07	1.5
MCI/MI	0.0082	0.063
MI	0.4	2.2

Conclusion
MI has a similar sensitising potency as formaldehyde.

Ref:
Basketter D A, Gilmour N J, Wright Z M, *et al.* 2003

SCCS Comment
An EC3 value can depend on the vehicle. An EC3 of 0.4 categorises MI as a strong sensitizer. Parallel studies with other well-known skin sensitizers provide confirmation of the relative potency of MI.

Not all experimental information, normally expected when assessing original data, is included in the publication.

Study 2

Rohm & Haas investigated the sensitisation potential of 10.37% MI in Neolone™ 950 using female CBA/J mice in an LLNA. There were 5 mice in each of the 6 dose groups and the positive and negative (acetone/olive oil 4:1) control groups. The mice received 25 μL of topical solution consisting of 0%, 0.15%, 0.45%, 0.76%, 1.35%, 1.57%, or 1.80% MI or positive control on each ear for 3 consecutive days. On day 6 of the study, the mice were injected with 20 μCi of ^{3}H thymidine and killed 5 hours later.

The SIs were determined to be 2.08, 2.40, 2.23, 6.64, 4.73, and 6.62 for the 0.15%, 0.45%, 0.76%, 1.35%, 1.57%, and 1.80% MI dose groups, respectively. It was concluded that MIT is a sensitizer at concentrations greater than 0.76%. The EC3 was calculated to be 0.86%.

Ref:
Rohm & Haas, (2003) Report 06R-l002. Methylisothiazolinone: local lymph node assay (methylisothiazolinone 10.37% active ingredient). Unpublished data submitted by Rohm & Haas and referred to in Burnett, CL, Bergfeld WF, Belsito DV *et al.* (2010)

A review paper (Roberts DW, Patlewicz G, Kern PS, *et al*. 2007), in which the specific data source or date of acquisition is unreferenced, states an EC3 1.9% for MI (vehicle etc. not stated), but which would still categorise MI (#9 in the table below) as a strong sensitizer (SCCP/0919/05) and not as 'moderate' as indicated in the table. The same table gives an EC3 value of 0.009 to MI (source unreferenced) and which is similar to an EC3 0.0082 for MCI/MI (Basketter D A, Gilmour N J, Wright Z M, *et al.* 2003)

#	chemical name	CAS #	LLNA EC3%	potency category	group
1	clotrimazole	23593-75-1	4.8	moderate	
2	potassium dichromate	7778-50-9	0.08	extreme	
3	benzo[*a*]pyrene	50-32-8	0.0009	extreme	pro-SN2 PAH, via oxidation (*9*)
4	7,12-dimethylbenz[*a*]anthracene	57-97-6	0.006	extreme	pro-SN2 PAH, via oxidation (*9*)
5	5-chloro-2-methyl-4-isothiazolin-3-one	26172-55-4	0.009	extreme	compounds for which S_N2-reaction at the S-atom can be proposed (*9*)
6	1-methyl-3-nitro-1-nitrosoguanidine	70-25-7	0.03	extreme	*N*-nitroso derivatives, which act as hard S_N2 or pro-S_N2 electrophiles, discussed in some detail in (*9*)
7	*N*-methyl-*N*-nitrosourea, toxic	684-93-5	0.05	extreme	*N*-nitroso derivatives, which act as hard S_N2 or pro-S_N2 electrophiles, discussed in some detail in (*9*)
8	*N*-ethyl-*N*-nitrosourea	759-73-9	1.1	moderate	*N*-nitroso derivatives, which act as hard S_N2 or pro-S_N2 electrophiles, discussed in some detail in (*9*)
9	2-methyl-2*H*-isothiazol-3-one	2682-20-4	1.9	moderate	compounds for which S_N2-reaction at the S-atom can be proposed (*9*)
10	1,2-benzisothiazolin-3-one (proxel active)	2634-33-5	2.3	moderate	compounds for which S_N2-reaction at the S-atom can be proposed (*9*)
11	tetramethylthiuram disulfide	137-26-8	5.2	moderate	compounds for which S_N2-reaction at the S-atom can be proposed (*9*)
12	1-naphthol	90-15-3	1.3	moderate	we suggest that this acts as a Michael acceptor via its keto-tautomer

Ref:
Roberts DW, Patlewicz G, Kern PS, *et al.* 2007.

SCCS Comment

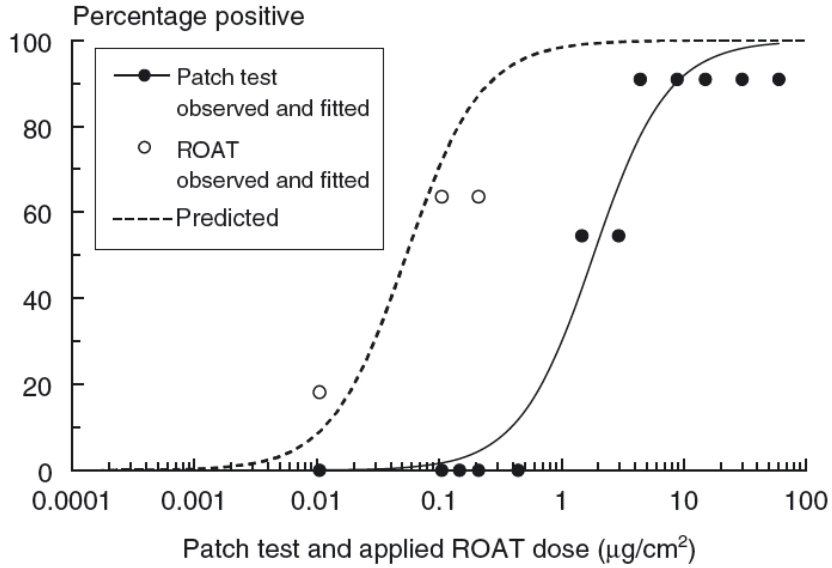
DW Roberts, in a personal communication, recalls that the information was obtained from an earlier paper (Estrada E, Patlewicz G, Chamberlain M *et al*. 2003), in which a so-called 'gold list' of reference EC3 values was published. In this earlier paper the EC3 of MI (item 23 in their list, see below) is given as 1.9; the source of this is unavailable in the paper. In an editorial (Roberts DW 2013) it is indicated that the error can be explained from a failure to take into account the dilution at which MI was tested in the LLNA. However, if one looks elsewhere in the Estrada *et al.* 'gold list', item 22 is given an EC3 0.4. This substance is a hair dye (Colipa A31) for which there is a SCCP Opinion (SCCP/0957/05, March 2006) that it is <u>not</u> a skin sensitiser in a properly performed LLNA.

22	2-methyl-5-hydroxyethylaminophenol	0.4
23	2-methyl-2H-isothiazol-3-one	1.9

Therefore, there appear to be at least two error(s) in the Estrada *et al*. paper. (Estrada, in a personal communication, was unable to comment on the observation). It is unknown whether there are other important errors in the 'gold list' of EC3 values.

The evidence concludes that only one published and properly described LLNA assay has been performed (Basketter D A, Gilmour N J, Wright Z M *et al*. 2003); the EC3 of MI is 0.4%.

Dose-response studies in man



Eleven MI-allergic individuals were patch tested with a dilution series of 12 doses of MI. The lowest eliciting dose in the patch test was 1.47 µgMI/cm^2. (49 ppm).

A repeat open application test (ROAT) mimicked the use of a cream preserved with 100, 50 and 5 ppm MI (corresponding to 0.21, 0.105 and 0.0105 µgMI/cm^2). In the ROAT, 7 patients (64%) reacted to 0.21 and 0.105 µgMI/cm^2 and 2 patients (18%) reacted to 0.0105 µgMI/cm^2, corresponding to a cream preserved with 5 ppm MI.

Ref:
Lundov MD, Zachariae C and Johansen JD. (2011)

SCCS Comment
A relatively small number of subjects were investigated but the study does provide useful information on eliciting-doses of MI in sensitised individuals.

3.5 Discussion

The dramatic rise in the rates of reported cases of contact allergy to MI, as detected by **diagnostic patch tests**, is unprecedented in Europe; there have been repeated warnings about the rise (Gonçalo M, Goossens A. 2013). The increase is primarily caused by increasing consumer exposure to MI from cosmetic products; exposures to MI in household products, paints and in the occupational setting also need to be considered. The delay in re-

evaluation of the safety of MI in cosmetic products is of concern to the SCCS; it has adversely affected consumer safety.

Diagnostic patch tests offer 1) the first indication that exposure to a substance is causing allergy in the population; 2) a means to compare the relative importance of contact allergens in terms of the frequency of reactions and 3) a means of following contact allergy trends over time. (Basketter DA, White IR. 2012)

Diagnostic patch test data do not 1) prove what exposures caused the induction of contact allergy; 2) give any dose-response information or 3) inform on what types of exposure may be tolerated, either for induction or elicitation. (Basketter DA, White IR. 2012)

The elicitation of contact allergy under diagnostic patch test conditions is intended to show whether an individual patient has contact allergy to a substance or not; it is sensitive and specific as a diagnostic tool.

Part of the diagnostic procedure is also an exposure analysis, which provides information about exposures/products, which (may have) initiated the disease manifestation. It is from such analysis that it is known that cosmetic use is associated with MI contact allergy and it may be possible to identify the specific product responsible.

The characteristics of the multiple real life exposures (aggregate exposures) that have led to the induction of contact allergy are rarely well defined. However, they clearly have occurred; for MI, contact allergy has been induced to an alarming extent.

Sensitisation is a relevant toxicological endpoint. An obvious increase in the frequency of sensitisation in the consumer shows that there has been a failure of risk assessment and/or management of the risk.

In the 2009 SCCS Opinion on the mixture of 5-chloro-2-methylisothiazolin-3(2H)-one and 2-methylisothiazolin-3(2H)-one (SCCS/1238/09) it was concluded:

> "The mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one in a ratio of 3:1 is well recognised as an important skin sensitiser at current conditions of use and applications. Hitherto, it has been used in both leave-on and rinse-off products in Europe.
> Induction and elicitation would be less likely in a rinse-off product than when the same concentration is present in a leave-on product.
>
> "On the basis of the data submitted, the SCCS is of the opinion that the mixture of 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one in a ratio of 3:1 does not pose a risk to the health of

> the consumer when used as a preservative up to a maximum authorised concentration of 0.0015 % in rinse-off cosmetic products, apart from its sensitising potential."

However, despite the mandate on which the above Opinion is based, referring only to rinse-off cosmetic products, there remains no restriction on the use of the mixture (item 39, Annex V, Cosmetics Regulations 1223/2009 with updates) in leave-on cosmetic products. However, it is understood that there is a Commission proposal to restrict the use of MCI/MI in rinse-off products. Meanwhile MCI/MI appears to be now little used in leave-on cosmetic products in Europe.

A separate Opinion on the related preservative benzisothiazolinone (SCCS/1482/12; June 2012) raised concerns about MI:

> "As has been seen with MCI/MI and now with MI itself, these isothiazolinones are important contact allergens for the consumer in Europe. Within the mixture, MCI is known to be the more potent allergen (EC3 0.009%). MI is less potent (EC3 1.9%)* and is now permitted at up to 100 ppm in leave-on and rinse-off cosmetic products; contact allergy to MI itself is now a considerable problem in Europe and this is of concern.
>
> (* The EC3 value of 1.9% is incorrect; it is 0.4%. This is discussed above.)
>
> "It is recommended that the incidence of contact allergy to BIT (benzisothiazolinone) and other isothiazolinones be monitored at regular intervals (e.g. annually), by reference to dermatology clinic data in Europe. Necessary early interventions can then be introduced to reduce exposures and hence contact allergy and allergic contact dermatitis as required."

As present in the MCI/MI mixture, the consumer is being exposed to MI at *circa* 3.8 ppm in cosmetic products and this is now supported (by industry but not yet by regulation (SCCS/1238/09) for use only in rinse-off cosmetic products. Up to MI 100 ppm is currently permitted in leave-on (which includes wet wipes) and rinse-off cosmetic products. So, excluding aggregate exposures, the dose of MI per unit area of skin to which the consumer is exposed is *circa* 25x higher than with the MCI/MI mixture.

Leave-on cosmetic products

There is no adequate information to suggest a safe dose of MI in leave-on cosmetic products from the view of *induction* of sensitisation, although *circa* 3.8 ppm, as present in MCI/MI, may be indicative.

The wealth of clinical data demonstrates that 100 ppm MI sensitises.

There is no adequate information as to what doses of MI in leave-on cosmetic products an individual with contact allergy to MI may tolerate, although 5 ppm was not tolerated (*elicitation reactions*) by 2 subjects in the Lundov study (Lundov MD, Zachariae C and Johansen JD. 2011).

Rinse-off cosmetic products

For rinse-off products, it may be considered that *circa* 3.8 ppm MI (as in the MCI/MI mixture) is acceptable as this is the amount present when MCI/MI (3:1) is used at 15ppm for preservation of rinse-off cosmetic products, but it is unknown whether this concentration provides useful preservative activity. (Lundov (Lundov MD 2010) has shown that low concentrations of MI with phenoxyethanol produce active preservation). However, as MCI is a more potent allergen than MI and is the principal moiety in MCI/MI, the SCCS suggests that MI should be safe in rinse-off cosmetic products at 15 ppm (0.0015%). Permitted levels of MI in rinse-off cosmetic products should be safe for previously sensitised individuals but whose allergy has not been shown by formal investigation. Dose-elicitation studies of MI in rinse-off products on individuals with contact allergy to MI are not available.

It may be suggested that Quantitative Risk Assessment (QRA) could be applied to derive safe levels of MI in rinse-off cosmetic products. Although the SCCS considers QRA as a promising tool to prevent induction of contact sensitisation for people with normal skin, the SCCS has insufficient confidence in the model at present (SCCP/1153/08, June 2008).

Ingredient labelling may be used to protect the consumer with a known contact allergy to MI to avoid exposures which may elicit an allergic contact dermatitis. For the assessment of aggregate exposures and the safety evaluation of MI, information on the actual concentrations of MI in consumer products including cosmetics is needed. Since MI is widely used in other consumer products (eg. detergents, paints), exposures from such sources should also be assessed.

It is understood that cosmetic products containing MCI/MI (up to 15 ppm) may not include additional MI.

4. CONCLUSION

1. *On the basis of the new evidence in relation to sensitising potential, does the SCCS consider Methylisothiazolinone (MI) still safe for consumers, when used as a preservative in cosmetic products up to concentration limit of 100 ppm? If no, it is asked for the SCCS to revise this concentration limit on the basis of information provided.*

Current clinical data indicate that 100 ppm MI in cosmetic products is not safe for the consumer.

For leave-on cosmetic products (including 'wet wipes'), no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated.

For rinse-off cosmetic products, a concentration of 15 ppm (0.0015%) MI is considered safe for the consumer from the view of induction of contact allergy. However, no information is available on elicitation.

2. *Does the SCCS have any further scientific concerns with regard to the use of Methylisothiazolinone (MI) in cosmetic products?*

MI should not be used as an addition to a cosmetic product already containing MCI/MI.

More frequent review of data (than suggested in SCCS/1482/12) to monitor sensitisation frequencies of MI and related isothiazolinone preservatives is recommended. This permits trends in consumers' sensitisation to be observed and timely intervention to be taken.

Information on the actual concentration of MI present in individual cosmetic products will allow future evaluation of safe concentrations.

Labelling is only helpful to a consumer who has a known (established by diagnostic patch test investigations) allergy. It is unknown what proportion of the general population is now sensitized to MI and has not been confirmed as sensitized.

Since MI is widely used in other consumer products (eg. detergents, paints), exposures from such sources should also be assessed.

Consumers cannot find information on the presence of MI in products except in cosmetics and household detergents because, as yet, there is no harmonised classification of MI as a skin sensitizer. The risk for skin sensitisation by MI is at least equivalent to that of other substances which have received a harmonised classification according to the CLP Regulation.

5. MINORITY OPINION

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