

Review Article

An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products

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Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) has been widely used during the last 20 years for the preservation of aqueous systems in cosmetics, toiletries and in various industrial applications. MCI/MI has a broad spectrum of activity against fungi and bacteria at very low concentrations. The allergic contact potential of MCI/MI has been known for many years. This paper provides a review of pre-clinical and clinical experimental studies as well as experience from dermatology clinics worldwide. This forms the basis for an update of the risk assessment for the use of MCI/MI in rinse-off products. The scientific data indicate that the actual sensitization rate observed with a contact allergen is extremely dependent on dose and type of exposure. This review of the data leads to the conclusion that, under normal use conditions, within the current permitted/recommended use concentrations for MCI/MI of up to 15ppm, the risk of primary sensitization from the use of rinse-off products is negligible, and elicitation of allergic contact dermatitis in MCI/MI-sensitized individuals rare, after exposure to MCI/MI-preserved rinse-off products.

Key words: methylchloroisothiazolinone/methylisothiazolinone; contact allergy; risk assessment; occupational; consumer products; rinse-off, Kathon CG®; preservatives; diagnostic patch test; cosmetics. © Munksgaard, 1999.

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Antimicrobial preservative agents are important in preventing the growth of pathogenic and non-pathogenic microorganisms in personal care, household and industrial products. The growth of micro-organisms in such products can occur during their manufacture and/or through their repeated use post-sale. It is now generally recognized that preservation is a necessary element of product formulation to prevent such microbial growth, both in terms of protecting human health and preventing product spoilage (1).

Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) are the active ingredients in a family of commercial microbiocides and preservatives which has a broad spectrum of activity against fungi, yeasts and both gram positive and gram negative bacteria. MCI/MI is highly effective at

very low concentrations (2). This preservative system has been widely used during the last 20 years for the preservation of aqueous systems in cosmetics, toiletries and in various industrial applications. It is not known to be used in food applications in Europe. As supplied to cosmetic manufacturers, MCI/MI is in the form of a commercial biocide in aqueous solution. The trade name of one such MCI/MI preservation system supplied to the cosmetics industry is Kathon® CG (3). A typical composition of Kathon® CG is provided in Table 1. In this review, all concentrations are cited as parts per million (ppm) of the combined active ingredients MCI and MI, unless otherwise stated.

MCI/MI, like many other preservatives, is a human contact allergen (4, 5). The strong sensitization potential of MCI/MI has been known for

Table 1. Typical composition of Kathon® CG* (3)

Active ingredients	
5-chloro-2-methyl-4-isothiazolin-3-one	1.15%
2-methyl-4-isothiazolin-3-one	0.35%
total	1.50%
Inert ingredients	
magnesium salts (chloride and nitrate)	23.00%
water	to 100%

* This composition applies only to material supplied by the Rohm and Haas Company and does not apply to other sources of MCI/MI.

many years (6). Research in contact allergy caused by MCI/MI has significantly increased the understanding of the dose-response relationship for both induction and elicitation of contact allergy in humans. Although the primary sensitization data, as with other allergens, is difficult to obtain in the clinical setting, limited information is available. In contrast, considerable elicitation data are available. Since the introduction of MCI/MI, additional information has become available which is useful for updating the risk assessment.

Essentially, the risk assessment process uses a comparative toxicological approach (7). This involves integration of the data available on inherent toxicity of a material and exposure to it that allows for comparison with data generated on a benchmark material of similar chemistry, product application or both. Fundamental to this process is the updating of the risk assessment as new data on inherent toxicity and/or exposure to a material becomes available. This review serves as an update of the risk assessment for the use of MCI/MI in rinse-off products and focuses on key areas of induction, elicitation and dose per unit area analysis for such products containing MCI/MI.

Uses of MCI/MI

MCI/MI occurs as a preservative in a number of household products as well as in cosmetics and toiletries (Tables 2, 3) (3). In the European Union (EU) and United States of America (USA) cosmetics will be labelled with the International Nomenclature of Cosmetic Ingredients (INCI) name of methylisothiazolinone, methylchloroisothiazolinone (15). The permissible level of MCI/MI in cosmetic products in the EU is 15 ppm in both leave-on and rinse-off products (16). In the USA, the permissible level of MCI/MI in cosmetic products is 7.5 ppm in leave-on products and 15 ppm in rinse-off products (6). In Japan MCI/MI is approved for use in rinse-off products at 15ppm and no approval has been sought for use in leave-on products. In Hungary, the permissible level of

MCI/MI is 7.5 ppm in leave-on products and 15 ppm in rinse-off products. In Poland, it is additionally approved at 7.5 ppm for baby-care products. In countries where no regulatory approval is required, one manufacturer recommends 15 ppm for rinse-off products and 7.5 ppm for leave-on applications (3). The use of MCI/MI in skin care products has been widespread (8, 9, 11). MCI/MI is also used in paints, printing, cooling oils, polishes, pigments, fabric softeners, pesticides, adhesives, curing agents, binders, products of sanitation and in other applications, either directly as an ingredient or as the result of its presence in raw materials (17). Such industrial applications are summarized in Table 4 (3). Although the changes in worldwide human exposure to MCI/MI in the last 10 years are not known, there has been a substantial rise in the sales of Kathon® in the USA during this time period (3). The sales figures of the other companies that also manufacture MCI/MI have not been requested.

Some manufacturers' declarations of the preservatives in cosmetic products may not always have been accurate. Recently, Gruvberger et al. investigated the presence of 9 common preservatives in 100 moisturizers sold in Sweden, using high-performance liquid chromatography (14). With focus on MCI/MI, out of 100 moisturizers commercially available in Sweden, 6 were found to contain MCI/MI and, in one of these, MCI/MI was neither declared by the manufacturer/supplier nor stated to be present on the product label. The concentration of MCI/MI was 14.7 ppm in this particular moisturizer and was at a higher concentration than in the other moisturizers although not exceeding the maximum concentration allowed in Swedish legislation. The authors of this study did not discuss how MCI/MI found its way into the moisturizer. Other instances of mislabelling for some of the other preservatives investigated in this study were also identified. This led the authors to conclude that "this information (product labelling) is for too many moisturizers erroneous and misleading" (14).

Induction of MCI/MI Contact Allergy

Evidence of MCI/MI as a strong allergen is deduced from experimental evidence in animals and humans, from observations in industry and from accumulated case reports associated with MCI/MI in consumer products.

EXPERIMENTAL STUDIES

Animal studies

Animal studies have demonstrated that MCI/MI is a strong contact allergen; for example, 100% of

Table 2. The ratio of MCI/MI-preserved products relative to product type and country

Product surveyed	Country	Year	Product type	Ratio of MCI/MI-preserved product/Total	Use concn. (ppm)	Ref.
cosmetics, toiletries, consumer products	Sweden	1986	leave-on	16/56	1–15	(8)
			rinse-off	22/67	1–15	
cosmetics and toiletries*	Netherlands	1988	leave-on	44/211	ns	(9)
			rinse-off	15/42	ns	
moistened toilet tissues	Netherlands	1991	various brands	10/13	5.9–23.4	(10)
cosmetics and toiletries	Denmark	1990	leave-on	15/49	**	(11)
			rinse-off	51/107	**	
household products	Denmark	1992	carpet cleaners	4/29	ns	(12)
			shampoo	54/200	ns	
			skin cleaners	40/224	ns	
			fabric softeners	9/67	ns	
			floor polishes	13/94	ns	
			general cleaners	34/509	ns	
moistened toilet tissues	Spain	1996	various brands	11/19	10–15	(13)
moisturizers	Sweden	1998	moisturizers	6/100	3.6–14.7	(14)

* Products picked at random. ** 10% < 10 ppm, 4.5% > 15 ppm. ns: not stated.

animals were sensitized to MCI/MI when induced and then elicited with 2,000 ppm of MCI/MI, using a modified Buehler method in guinea pigs (4). MCI/MI was also shown to be sensitizing by a modified Magnusson-Kligman guinea pig maximization test, with MCI being a potent sensitizer and MI a weak sensitizer when these compounds were tested in equimolar concentrations (18). A possible contaminant present at a low concentration in some batches, 4,5-dichloro-2-methyl-4-isothiazolin-3-one, was also shown to be an equally potent sensitizer by the same technique (19). It has been established that it is the parent compounds and not the degradation products which are the sensitizers (20).

Human studies

Human repeat insult patch testing (HRIPT) is a risk assessment tool used in assessing the skin sensitization potential of ingredients and products (21). 2 of 104 subjects manifested a skin response consistent with contact allergy, using a modified Draize technique, when patches containing 100 ppm MCI/MI were applied to the upper arm or back 3× a week for 3 weeks, but none of 96 subjects were sensitized when 50 ppm was used with the same technique (22). In another series of experiments, a number of volunteers had patches containing 6–20 ppm MCI/MI in various vehicles applied to the outer lateral arm 3× a week for 3 weeks. Allergy was defined as

having a positive patch test when a similar pad was applied 2 weeks later. Using this definition, none of 1121 patients were sensitized at less than 10 ppm, but 1/84 (1.2%) at 12.5 ppm and 2/45 (4.4%) at 20 ppm were sensitized (23). When a patch test concentration of 1,000 ppm was used for diagnostic purposes, 5 of 40 patients (13%) had a delayed reaction suggesting patch test sensitization (24). Patch test sensitization from 300 ppm has also been reported (24).

OCCUPATIONAL

There have been many reports of occupational allergic contact dermatitis caused by isothiazolinones used as biocides in water-based processes in industry. Examples include cooling tower water, latex emulsions and metalworking fluids

Table 3. Use of Kathon® biocide in household products (3)

Application	Maximum use level (ppm active ingredient)
liquid dishwashing detergents	15
liquid cleaners	15
liquid laundry products	15
fabric softeners	15
automotive and floor polishes	15
air fresheners	15
carpet shampoos	15
premoistened sponges and mops	15

Table 4. Use of Kathon[®] biocide in industrial applications (3)

Application	Maximum use level (ppm active ingredient)
metalworking fluids	
- maintenance	15
- curative [to clean heavily fouled systems]	35*
hydraulic fluids	25
metal cleaning fluids	25
industrial cooling towers	15
industrial air washers with efficient mist elimination systems	15
electrodeposition paint systems	15
- curative	35*
paper mill slimicide	15
oil field water injection	15
commercial photoprocessing	15
inks and printing fluids	15
polymer latex	30
aqueous paint	30
biopolymers	25
dispersed organic pigments	25
adhesives and tackifiers	25
textile processing fluids	25

* It is recommended that curative dosing is conducted over a weekend or vacation period where the potential for exposure is lowest.

(25). The active ingredients are supplied and often stored at high concentrations of 1.5–13.5% in water and diluted on site to 0.0015%–0.0050% (15–50 ppm). The product labels and material safety data sheets supplied with these products stipulate that the material is corrosive and a contact allergen, and not meant to come into contact with the skin (26).

In prospective surveys of specific industries and certain workplaces, isothiazolinones are well-recognized allergens (27–29). 150 metal workers in a factory using MCI/MI in a coolant oil were offered patch testing, and of the 27 who were tested to 50 ppm, 44% had a positive patch test to MCI/MI, which means, at a bare minimum, that 7% of the factory personnel were sensitized (27). Over a period of 1 year, 8 participating dermatological centres in Germany reported patch testing of metal workers as part of a study conducted by the Information Network of Dermatological Clinics (IVDK). In all, 424 metal workers were patch tested with 1 or 2 test series containing additives (mainly biocides) of industrial fluids. Results showed that, of the 253 patients patch tested with Kathon[®] in 1 of the test series, 3 patients demonstrated a + patch test reaction on day (D) 3. In addition, some of the allergens from the standard series showed a higher sensitization rate in male

patients of the study group compared to the average of all males, e.g., for Kathon[®] CG this equated to 4.9% versus 3.1%. (30). 299 members of a painters organization were sent a questionnaire and 202 of these were patch tested. 3 painters were deemed to have a probably relevant contact allergy to MCI/MI, as well as 2 with a doubtful reaction (28). In a factory making acrylate-based paint and glue binders, 9/51 (17.6%) of the current production workers who were patch tested were allergic to MCI/MI, with 4 of these workers having current dermatitis (3 hands and 1 leg). All 9 had a history of an itchy eruption after occupational exposure to an MCI/MI-preserved emulsion (29).

Individual cases of allergic contact dermatitis have also been reported in hairdressers (31), printers (32), radiology technicians (33), photographic developers (34) and 2 cosmetic cream makers (35). Allergic contact dermatitis has also been reported in a researcher investigating its allergenic properties, when attempting to purify MCI/MI to its solid state. The researcher was working with concentrated/solid MCI and MI (36).

There have been a number of reports of an initial chemical burn with a concentrated solution of MCI/MI resulting in contact allergy (25, 37, 38). Initially, there is a single painless exposure, followed hours later by a erythematous plaque, which can be bullous, vesicular or even necrotic (38). Days to weeks later this resolves with hyperpigmentation. No permanent scarring has been reported. In such cases, the level of exposure to MCI/MI is sufficient also to cause induction or elicitation of contact allergy. In the small number of reported cases, clinically relevant allergic contact dermatitis has subsequently occurred.

There have been some reports of sudden outbreaks of contact dermatitis in a workplace shortly after the introduction of MCI/MI to the manufacturing process (39, 40). In a flax spinning mill, where irritant contact dermatitis was already prevalent, 7 workers had patch-test-confirmed allergic contact dermatitis 2 months after the introduction of MCI/MI to the mill. The exposure concentration was between 7.5 and 22.5 ppm. It was postulated that 20% of the workers exposed to MCI/MI had developed allergic contact dermatitis (39). In a nylon mill, 6 out of 40 workers developed patch-test-confirmed allergic contact dermatitis 2 months after MI/MCI was introduced to the manufacturing process. None of these workers had a past history of dermatitis (40).

CONSUMER PRODUCTS

Most cases of contact allergy to MCI/MI in the general population probably result from exposure

to cosmetic and household products. It should be noted that the direct relationship can be difficult to prove in individual cases for people with contact allergy to MCI/MI. Exposure to cosmetic products can be traced, but specific products are difficult to identify. Pre-existing dermatitis was present in about half of patients (41). Studies during the time period of MCI/MI introduction in leave-on cosmetics supports such a view, as the sensitization frequency in certain areas increased (42).

Case Reports of Contact Allergy

Examples of product types that have been reported to elicit allergic contact dermatitis are listed in Table 5, along with the concentration of MCI/MI as stated in the case report, when known. Moisturizers have been the commonest source of elicitation and other cosmetics and skin care products, especially leave-on products, are also common sources of MCI/MI in those allergic to this substance (41, 42, 49, 54). The reported case of elicitation due to a fabric softener occurred after inappropriate use of a product containing 300 ppm MCI/MI, a level which is 20× the recommended use level (43). Moist toilet tissues have been implicated in a number of cases, including as the source of sensitization (10, 13, 55, 56). Shampoos preserved with MCI/MI have been implicated as a cause of hand eczema in hairdressers sensitized to MCI/MI (31). A few studies implicate shampoos as a possible source of elicitation of scalp, eyelid, and facial dermatitis (42, 52, 57). There has been an unusual case

report of one patient who could not tolerate being in a room which had been painted with paint containing 32.5 ppm MCI/MI, but could wash her hair once a week with a shampoo containing 2.24 ppm MCI/MI (controlled provocation tests were not done) (44). A single case is reported in the literature in which an individual (engine worker) developed a skin reaction from the use of a cleansing cream containing 10 ppm MCI/MI (45).

Diagnostic Patch Test Experience

Diagnostic patch test concentration

The current concentration of MCI/MI in the European standard series is 100 ppm (aq.), i.e., 0.01% (w/v) or 3 $\mu\text{g}/\text{cm}^2$. Usually this is a non-irritating and non-sensitizing concentration. The use of aqueous vehicle is standard (58, 59). In a group of volunteers sensitized by the Draize technique, there was no positive reaction in 80 people tested to 100 ppm (aq.) MCI/MI in petrolatum (22). More positive reactions were observed when the TRUE Test™ system was compared with MCI/MI 100 ppm (aq.) and no late reactions were seen (60). TRUE Test™ uses 4 $\mu\text{g}/\text{cm}^2$, which is equivalent to 150 ppm MCI/MI (60). D2 readings will miss 40–50% of those positive on D3–D4 (61). Ring-shaped positive reactions are common with MCI/MI, presumably because of the aqueous vehicle (62). Determination of the ideal concentration for patch testing with MCI/MI is not straightforward, as has been reviewed previously (63). Problems include the morphology of the allergic response and its differentiation from an irritant reaction, the ideal concentration and vehicle for the allergen, and the risk of patch test sensitization.

It is controversial whether 200 ppm diagnoses more cases than 100 ppm (64, 65). In the study by Fewings and Menné, in which 200 ppm was compared with 100 ppm, there were no more + or greater results but there were more dubious (?+) patch test reactions (66). 300 ppm produces more positive reactions than 100 ppm, but this is not a suitable patch test concentration because of the significant risk of patch test sensitization (24).

Patch testing with moist toilet tissue, as is, or with moisturizers, can give a positive reaction (10, 56). However, the end-use concentration of MCI/MI is now less than 15ppm so testing, as is, with the actual product, is estimated to miss between 79% (67) and 100% (49) of patients with allergic contact dermatitis from moisturizers.

There have been a number of studies where patients with a positive patch test have been patch tested with serial dilutions of MCI/MI (24, 54, 68, 69, 70, 71, 72, 73, 74) (Fig. 1). Between 30–50% of those with a positive patch test to 100ppm MCI/

Table 5. Products reported as eliciting allergic contact dermatitis in MCI/MI-sensitized individuals and the concentration of the MCI/MI

Product type	Concentration (ppm)	Ref.
clothing wool softener	300	(43)
house paint	32.56	(44)
"hair balm"	ns	(43)
cleansing cream	10	(45)
house paint	ns	(46, 47)
minoxidil lotion	15	(48)
moist toilet paper	10–15	(13)
moist toilet paper	ns	(10)
moisturizer	<14–30	(49)
moisturizer	12	(9)
moisturizer	19	(42)
barrier cream	9	(50)
plasticine	39	(51)
powder carpet shampoo	ns	(43)
shampoo	ns	(52)
shampoo	25	(6)
shampoo	5	(42)
sunscreen	ns	(53)

ns: not stated.

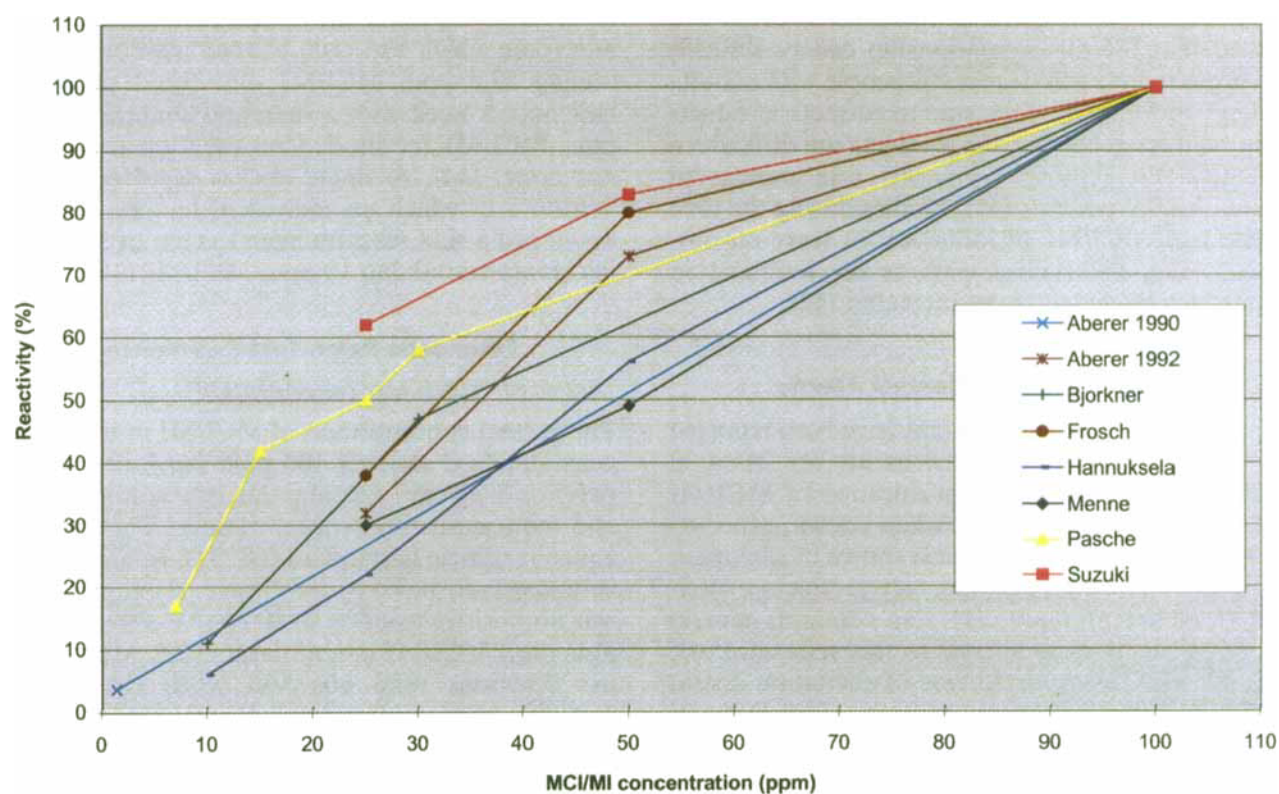


Fig. 1. Dose-response in patients with a positive patch test to 100 ppm MCI/MI.

N.B. The study by Aberer, 1990 (68) is based on 2 concentrations only.

X-axis: concentration of MCI/MI (ppm). Y-axis: (%) of patients with a positive patch test

References: Aberer et al. 1990 (68); Aberer et al. 1992 (69); Björkner et al. (24); Frosch et al. (70); Hannuksela & Salo (71); Menne et al. (54); Pasche & Hunziker (72); Suzuki & Hayakawa (73).

MI will have a positive patch test to 25 ppm. The lowest dose which will not produce a response in any individual has not been determined, although the interesting observations of Aberer are noteworthy (68). Patients were tested with a solution that was subsequently found to contain 1.35 ppm MCI/MI, which yielded a 0.2% (12/6402) positive patch test frequency rate. When patients were simultaneously tested with the 1.35 ppm solution and a 100 ppm solution, 1 of 28 reacted to both (68). In Lund, Sweden, none of 2006 patients were positive when similarly tested to 7 ppm (24). As with other allergens, patch test positivity can persist for at least 5 years (75).

Prevalence of a positive patch test in populations without dermatitis

Table 6 illustrates the prevalence of a positive patch test to MCI/MI in populations without dermatitis. The frequency is less than in patch test clinics, which implies that positive patch tests are relevant in the investigation of allergic contact dermatitis.

Patch test clinic frequency rates

The first reported cases of MCI/MI allergy were reported in 1984–5 (80, 81). In the mid to late 1980s, large numbers of patients suddenly began to present with contact allergy to MCI/MI (Table 7). This was attributed to leave-on products, especially moisturizers, which in some instances often occurred with one specific product in certain geographical areas (42, 49). Most of the products contained a concentration of MCI/MI that was within the recommended limits of that time. A rapid increase from 0.7% to 4.6% in patch test frequency, in a 12-month period, was seen in Oulu, Finland, due to the introduction of a popular moisturizer containing MCI/MI at 19 ppm (42). In Italy, 52 patients in Bologna were seen in a 2-year period with allergic contact dermatitis associated with a moisturizer preserved with MCI/MI. 14 patients had used a popular moisturizing cream found to contain more than 30 ppm MCI/MI when measured by HPLC using 2 different samples. 8 had used products with a measured concentration between 16.9–24.2 and in 20 patients various brands

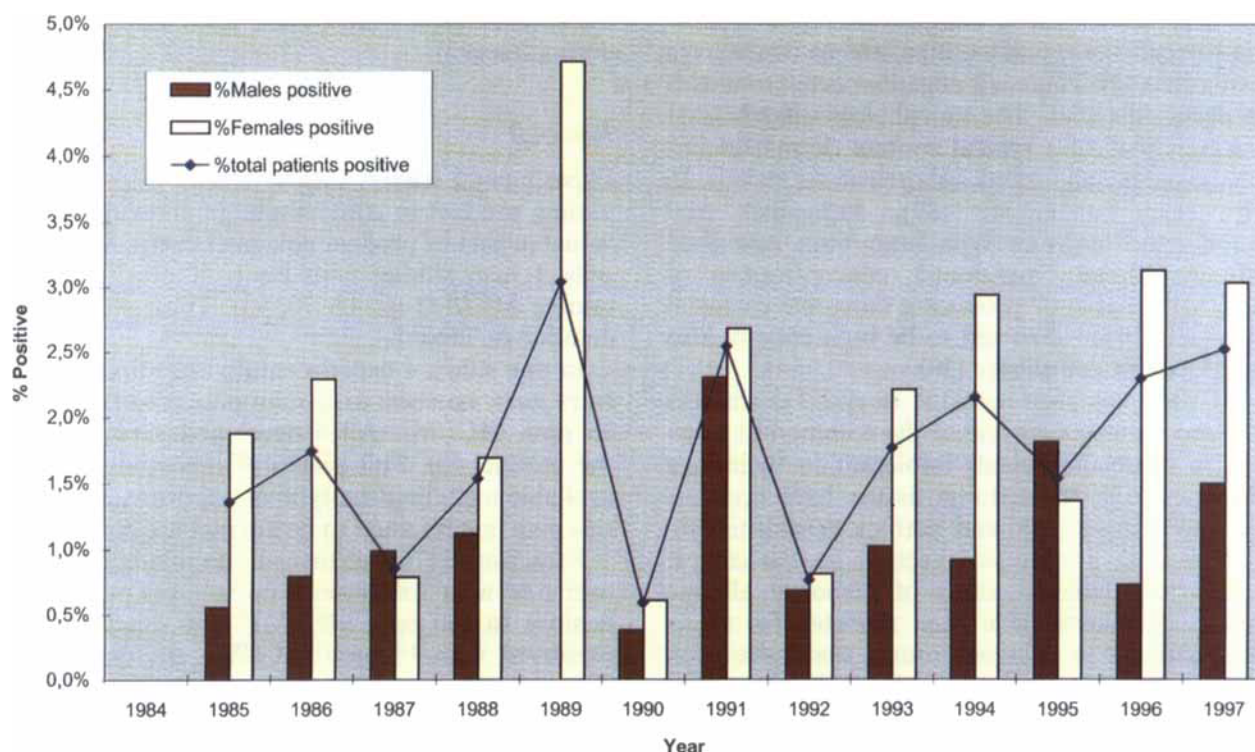


Fig. 2. Patch test frequency rates of contact allergy to MCI/MI in Copenhagen 1985–1997 (88).

of cosmetic creams containing less than 14 ppm MCI/MI were implicated as the cause of allergic contact dermatitis. For perspective, in the products with less than 30 ppm MCI/MI the proprietary names, method of measurement and the age of the specimens measured were not specifically mentioned in the report (49).

Table 7 summarizes more recent patch test studies. In most studies the prevalence is between 1 and 3%. This may be because of the use of lower concentrations in products, or because less leave-on products contain MCI/MI than previously (14).

Fig. 2 illustrates the patch test frequency in the same clinic over a long period of time (88). It is known that a large proportion of this population is exposed to MCI/MI (12). The average frequency is 2–3%. In this context, it is interesting to note

that the frequency of MCI/MI positive patch tests in the background population with no skin disease in the area from which the university clinic receives patients is known to be 0.7% (78).

Clinical Features

Allergic contact dermatitis from MCI/MI in the non-occupational setting usually presents as a facial and/or hand dermatitis and is more common in females (49, 54). Allergy to MCI/MI may present as an acute dermatitis of rapid onset or as an exacerbation of pre-existing dermatitis (42). In 40%, MCI/MI is the only contact allergen, 28% have 1 more, 14% have 2 more and 11% have 3 more contact sensitivities (54). There can be a more widespread dermatitis, with abrupt onset,

Table 6. Prevalence of positive patch tests to MCI/MI in populations without dermatitis

Source	Age (years)	Test concentration	Positive/no. tested	Country	(%)	Ref.
school children	5–14	0.01% ³	0/562	Portugal	0	(76)
military recruits ¹	18–28	0.01%	1/593	Italy	0.17	(77)
random	15–74	0.015%	4/567	Denmark	0.7	(78)
elderly volunteers ²	68–85	0.01%	3/82	USA	3.6	(79)

¹ Excluded those with past/present history of dermatitis. ² 1 patient only with dermatitis. ³ Assumed by the authors.

over a period of 1 to 2 weeks, which may necessitate topical therapy as an inpatient to control the dermatitis (42). There is a negative correlation with leg dermatitis (54). The morphology of MCI/MI allergy is that of a typical contact dermatitis but may be patchy and mimic seborrheic dermatitis. In rare cases, urticarial (89), lupus-like and lymphocytic infiltrate type have been described (90). As already mentioned, concentrations of MCI/MI capable of producing corrosive chemical burns have been reported to be high enough also to induce contact allergy (38).

MCI/MI has been reported in eyelid dermatitis (91) and identified as one of the commonest allergens in those individuals intolerant to their own cosmetics (67). Moist toilet tissues have been associated with perianal and buttock dermatitis (10, 56) and with a vesicular reaction on the central palms (55). Isolated cases of airborne allergic contact dermatitis have been reported for sensitized patients in enclosed rooms that have been recently painted with an MCI/MI containing paint (44, 46).

Exposure studies

A number of in-use exposure studies for rinse-off and leave-on products containing MCI/MI have been conducted. A similar number have not been conducted with any other allergen. It is important to note that these studies have been conducted on normal skin, although in some cases patients with healed eczema have been included. It is important to be aware that the threshold for reaction will differ whether it is normal skin, skin for which there has been an earlier allergic contact dermatitis for

the specific hapten, or if there is an active contact dermatitis (92).

Rinse-off

Experimental studies with a defined allergen-containing product in contact-allergic individuals is a valuable part of product risk assessment. There are only 4 such studies with rinse-off products containing MCI/MI (6, 45, 70, 93). These studies are detailed in Table 8.

In one study, 4 experimentally sensitized volunteers were exposed to a shampoo preserved with 25 ppm MCI/MI. All 4 developed a reaction to the product (6). Full details of this study are not available including the type of exposure, although this may be presumed to be normal use conditions.

Frosch et al. (70) performed a double-blind cross-over trial with 2 shampoos on subjects patch-test-positive to 100 ppm MCI/MI. One shampoo was preserved with 15 ppm MCI/MI, the other with 0.3% imidazolinyl urea (IU). 27 subjects from 5 European centres participated. 1 subject discontinued use after severe adverse reactions (vesicles and scaling on scalp, neck and hands) to the MCI/MI preserved shampoo after 4 washings and did not evaluate the other shampoo. 2 more subjects reported severe reactions on the scalp and neck while using the MCI/MI-preserved shampoo. These subjects discontinued its use after 2 and 4 washings, respectively. The same subjects tolerated the other shampoo without any adverse effects for the full 2-week period. 1 subject experienced a flare up of hand eczema after the use of the MCI/MI-preserved shampoo, but this was not of sufficient severity to cause discontinuation before 2 weeks. A slight flare of hand eczema with the MCI/MI-preserved shampoo was also noted in another subject.

2 subjects discontinued use after 1 or 2 washes following severe adverse reactions to the IU-preserved shampoo. One subject experienced itching and transient oedema of the face whilst the second experienced slight flare of hand eczema. An additional subject continued use of the IU-preserved product. However, the majority of subjects had negative findings on the skin for both shampoos. The physician's global evaluation of the data indicated that there was no significant difference between adverse effects to the 2 shampoos. 35% of the subjects had no skin problems with either preservative. Owing to the rarity of positive skin reactions, the number of subjects included in the study was too low to give statistical power either to prove or disprove the original hypothesis. Furthermore, it is a weakness in the methodology that not every patient was tested with all ingredients of the shampoos, in order to detect any pre-sensitizations

Table 7. Frequency of positive patch tests to MCI/MI in various patch-test clinics

Country	Dates	Positive/tested	(%)	Ref.
USA	1984-5	13/1152	1.2%	(82)
	1988-9	18/949	1.9%	(74)
	1991-2	23/1259	1.8%	(83)
Denmark	1983-4	13/1511	0.8%	(84)
	1985-8	18/1396	1.3%	(52)
Netherlands	1986-7	155/3114	5.0%	(41)
	1994	94/2943	3.2%	(85)
UK	1990-93	62/5167	1.2%	(86)
Sweden	1982-85	43/976	4.4%	(24)
	1987-90	31/918	3.4%	(64)
Germany	1986	23/671	3.4%	(50)
	1990-94	717/27,331	2.6%	(87)
Japan	1989	6/493	1.2%	(73)
	1990	5/500	1.0%	(73)
	1991	5/830	0.6%	(73)
	1992	8/975	0.82%	(73)

Table 8. Provocative use tests in MI/MCI-allergic individuals with rinse-off products

Product type	No. applications	Duration (days)	Concn (ppm)	Reacted	Tested	Reactions in controls ¹	Ref.
shampoo	6	14	15	3	27	2	(70)
shampoo	ns	ns	25	4	4	no controls	(6)
multiple ²	ns	21–42	4–6	0	18	0	(93)
cleansing cream	35	7	10	1	1	0	(45)

¹ No. those who also reacted with a non MI/MCI-preserved shampoo.² These were experimentally-sensitized volunteers and not eczema patients.

Table 9. Provocative use tests in MI/MCI-allergic individuals with leave-on products

Product type	Applications/day	Duration (days)	Concn (ppm)	Tested	Reacted (%)	Control reactors	Ref.
skincare lotion	b.d.	7	15	101	31%	8	(54)
skincare lotion	b.d.	14	7	52	100%	ns	(49)
Rohm & Haas							
skincare preparation	b.d.	7	15	20	40%	nil	(94)
skincare lotion	b.d.	7	15	13	54%	nil	(24)
generic skincare							
lotion	daily	5	8.6	11	0%	nil	(84)
skincare lotion	daily	7	15	10	50%	1	(74)
skincare lotion	daily	7	15	19	53%	ns	(69)
skincare cream	b.d.	7	7	10	50%	ns	(42)
skin lotion	b.d.	7	15	7	57%	nil	(50)
barrier cream	b.d.	7	9	7	42%	nil	(50)

b.d.: 2× daily.

ns: not stated.

Table 10. Exposure levels to MCI/MI using different patch test methods

Method	($\mu\text{g}/\text{cm}^2$)	Allergic reactions	Ref.
diagnostic patch test	3.0 ^{a)}	induction not reported	(58)
TRUE Test TM	4.0	induction not reported	(60)
repeat insult patch test	1.6–2.8 ^{c)}	induction 2/45 ^{b)}	(23)
repeat insult patch test	0.4–0.7 ^{c)}	no induction in 0/416 ^{b)}	(23)
repeat insult patch test	0.8–1.4 ^{d)}	no induction in 0/602 ^{b)}	(23)

^{a)} 100 ppm (100 $\mu\text{g}/\text{ml}$) in 15 μl water is 1.5 μg over 0.5 cm^2 (Finn Chamber area) or $\mu\text{g}/\text{cm}^2$.^{b)} Not formally patch tested, see explanation in text for how induction was defined.^{c)} 0.3 ml of 20 ppm MCI/MI (6 μg) over 3.6 cm^2 or 0.5 ml 20 ppm MCI/MI (10 μg) over 3.5 cm^2 .^{d)} 0.3 ml of 5 ppm MCI/MI (1.5 μg) over 3.6 cm^2 or 0.5 ml of 5 ppm over 3.5 cm^2 .

other than MCI/MI. On the other hand, reactions were observed in a few subjects with the MCI/MI-preserved and/or IU-preserved shampoos. The authors therefore concluded that it would be prudent for the clinician to advise alternative products to patients with proven sensitivity to a shampoo or cosmetic ingredient. Full ingredient labeling will ensure that this is possible.

In another study, 18 experimentally induced MCI/MI-allergic volunteers used various combination products which were preserved with MCI/MI. These included liquid soap (5 ppm), shampoo (4 ppm), hair conditioner (5 ppm), liquid fabric softener (6 ppm), and a bath & shower foam (5 ppm) for 3–6 weeks. In all but 1 instance, the subjects used multiple product types concurrently. At least 1 of the test products was used at least 1×

daily. No skin reactions indicative of allergic contact dermatitis elicitation were observed amongst any of the subjects (93).

A single case is reported in the literature in which an individual (engine worker) developed a skin reaction that he attributed to the use of a cleansing cream containing 10ppm MCI/MI. He had used the cleansing cream up to 5× a day for 2 years. He presented with a partly exudative dermatitis on his hands and forearms. Patch testing with the standard series, a cutting fluid series and products from his workplace (including the cleansing cream) revealed hypersensitivity to Kathon[®] CG and 2 coolants. A controlled use test with the MCI/MI-containing cleansing cream elicited skin responses such as itching, erythema and papules. The cleansing cream with a different preservative

(2-bromo-2-nitropropane-1,3-diol) produced no skin responses after 35 applications over the course of a week. The authors concluded that the patient's exposure ($5\times$ a day) to the MCI/MI-containing cleansing cream was unlikely to have been the primary factor involved, but rather served to aggravate the dermatitis likely to have been caused by industrial exposure to coolants (45).

Leave-on

There have been a number of studies involving use tests of leave-on products (24, 42, 49, 50, 54, 69, 74, 84, 94). These studies are summarized in Table 9. The protocols have varied to some degree, but usually an MCI/MI lotion was applied to uninvolved skin, such as in the antecubital fossa, and left in place. The response was between typically 30–57% with 100% obtained when a 7 ppm lotion was applied b.d. for 2 weeks (49) and 0% when a 8.6 ppm lotion was applied daily for 5 days (84).

Exposure Levels

The amount of allergen per area of skin is one of the key factors in induction and elicitation of allergic contact dermatitis (95). Table 10 summarizes various exposure levels to MCI/MI expressed as $\mu\text{g}/\text{cm}^2$. Levels ranging up to $1.4 \mu\text{g}/\text{cm}^2$ did not induce contact allergy in a repeat insult patch test (RIPT) (23). In contrast, levels of 1.6 – $2.8 \mu\text{g}/\text{cm}^2$ did induce contact allergy in 2/45 subjects. The reported observations of Hannuksula (42) are of interest. 0.1 ml of a lotion preserved with 15 ppm MCI/MI was applied to an area of 25 cm^2 $2\times$ a day in 12 patients with contact allergy to MCI/MI. 6 patients demonstrated a positive skin reaction. Calculation of the exposure to MCI/MI per unit area of skin was determined as $1.5 \mu\text{g}$ over a 25 cm^2 area or $0.06 \mu\text{g}/\text{cm}^2$. In this study, $0.06 \mu\text{g}/\text{cm}^2$ was capable of eliciting dermatitis. In contrast, the diagnostic patch test concentration is 100 ppm per 0.5 cm^2 or $3.0 \mu\text{g}/\text{cm}^2$. An equivalent figure for exposure in use to MCI/MI from a shampoo preserved with this material can be determined. Using the following parameters:

Level of MCI/MI in shampoo:

- 15 ppm (0.0015 g MCI/MI/00 ml shampoo)=regulatory limit (16)
- surface area of the scalp and hands= 1035 cm^2 (96)
- 95th percentile shampoo use= 12 g/day (97)
- scalp deposition of applied product= 0.5% (97)
- dermal penetration= 100% (worst case assumption)

Exposure to MCI/MI through normal use of a shampoo preserved with this material is calculated

as $8.7\times 10^{-4} \mu\text{g}/\text{cm}^2$ for a product containing 15 ppm MCI/MI. This demonstrates that exposure to MCI/MI from the use of a shampoo preserved with 15 ppm MCI/MI is at least 3000 fold lower than the concentration ($3 \mu\text{g}/\text{cm}^2$) expected to elicit contact allergy under diagnostic patch test conditions (58).

Furthermore, the exposure data provided above is calculated based on the assumption that a shampoo product is preserved with the maximum concentration of MCI/MI (15 ppm) allowed by regulatory authorities. This introduces an additional conservatism into the calculation, as a more typical level of MCI/MI required for antimicrobial efficacy is 5 ppm. Using this level, the exposure to MCI/MI through normal use of a shampoo is calculated as $2.9\times 10^{-4} \mu\text{g}/\text{cm}^2$, which is 10,000 fold lower than the concentration ($3 \mu\text{g}/\text{cm}^2$) expected to elicit contact allergy under diagnostic patch test conditions.

Discussion

Few contact allergens have been studied and discussed as much as MCI/MI. Shortly after the introduction of MCI/MI, collaboration between the original manufacturer and dermatologists was established and this has been the platform for much of the available data. The data presented in this review consist of pre-clinical and clinical experimental studies as well as experience from dermatology clinics worldwide. With focus on the human experience, the strength of such studies is the ability to describe both the size of the clinical problem and the clinical consequences. These types of study of MCI/MI have utilized the diagnostic patch test, and have described the dose-response phenomenon in humans.

The controlled patch test studies can help predict the proportion of MCI/MI-sensitized individuals in the population. The obvious weakness of these clinical studies is their inability to identify unequivocally the cause of primary sensitization and the risk factors associated with primary sensitization. The cause of primary sensitization is obvious in the rare event of a chemical burn. In addition, factory outbreaks of MCI/MI contact allergy have also been well documented. However, contact allergy to MCI/MI, in the main, is not related to such specific events. The majority of sensitized cases in the general population are believed to have stemmed from exposure to leave-on cosmetic products preserved with MCI/MI. In some cases, it is reported that the patient can identify the product involved, but more frequently it is a range of products or a product from the past which is relevant. Among all the clinical data,

rinse-off products, as a cause of primary sensitization and elicitation, are mentioned only rarely and/or anecdotally.

Use of data from experimental studies, clinical experience, consumer use and calculations of exposure to MCI/MI in consumer products provides the basis for an update of the risk assessment of MCI/MI use in rinse-off consumer products. There is no conclusive evidence, from the literature reviewed, that rinse-off consumer products preserved with MCI/MI in normal use induce contact allergy to this preservative. In clinical studies, cases of elicitation are rare. From clinical experimental studies, elicitation of MCI/MI contact allergy from rinse-off products is also documented only rarely. In addition, global dermatological experience historically indicates that the frequency of MCI/MI contact allergy at patch test centres is less where this preservative is used only in rinse-off products and not leave-on products, e.g., Japan versus USA and Europe. This is coupled with the information that MCI/MI continues to be used in many regions of the world as a highly efficacious preservative for consumer products. In those regions for which data are available, the data indicate that the MCI/MI positive patch test frequency has not significantly changed and remains at a stable level, with that for populations without dermatitis being even lower and similar to that of other preservatives used in rinse-off products. A key factor relevant to this update of the risk assessment is the introduction of exposure data for MCI/MI. Exposure to MCI/MI through use of a rinse-off consumer product preserved with this material is identified (even with the use of conservative data) as being extremely low and transitory. Exposure through use of a rinse-off product is several orders of magnitude lower than that known to induce and/or elicit skin reactions both by patch-testing and by use-testing.

The scientific data indicate that the actual sensitization rate observed with a contact allergen is extremely dependent on dose and type of exposure.

This review of the data leads to the conclusion that, under normal use conditions, within the current permitted/recommended use concentrations for MCI/MI of up to 15ppm, the risk of primary sensitization from the use of rinse-off products is negligible, and elicitation of allergic contact dermatitis in MCI/MI-sensitized individuals rare, after exposure to MCI/MI-preserved rinse-off products.

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