

Outbreak of contact sensitization to methylisothiazolinone: an analysis of French data from the REVIDAL-GERDA network

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Summary

Background. The preservative methylisothiazolinone (MI) is used in combination with methylchloroisothiazolinone (MCI), but the MCI/MI mixture has been identified as highly allergenic. MI is considered to be less allergenic, and since the mid-2000s has been widely used alone, but is now clearly identified as a contact allergen. The French Vigilance Network for Dermatology and Allergy of the Study and Research Group on Contact Dermatitis (REVIDAL-GERDA) added MI to its baseline patch testing series in 2010.

Objective. To evaluate the change in the proportion of MI-positive tests in France between 2010 and 2012.

Patients/materials/methods. We conducted a nationwide, multicentre, retrospective study of all MI-tested patients between 2010 and 2012.

Results. Sixteen centres participated in the study (7874 patients were tested). Patch tests were performed mainly at a concentration of MI 200 ppm aqua. We observed a significant increase in the proportion of MI-positive tests in 2012 and 2011 as compared with 2010 (5.6%, 3.3%, and 1.5%, respectively; $p < 0.001$).

Conclusions. We report a significant increase in the number of MI-positive tests. MI is confirmed to be a rapidly emerging allergen, as also observed in other European countries.

Key words: contact dermatitis; cosmetics; France; methylchloroisothiazolinone; methylisothiazolinone; preservative; REVIDAL-GERDA; sensitization.

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Preservatives and fragrances are recognized as the main skin sensitizers, particularly in cosmetics. The methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) mixture in a 3:1 ratio was introduced as a preservative in the early 1980s. MCI/MI is used extensively, has a broad antibacterial and antifungal spectrum, and is effective at low concentrations over a wide pH range. The use of MCI/MI resulted in an epidemic of allergic contact dermatitis in Europe, with a prevalence ranging from 3% to 8% (1, 2). This allergen has been included in the European baseline series at a concentration of 100 ppm. European experts made stricter recommendations for the MCI/MI concentration levels permitted in cosmetic products, with a maximum of 15 ppm (3). These recommendations led to a reduction in the contact sensitization rate. In 1992, the United States recommended an even lower concentration threshold of 7.5 ppm (4) for leave-on products, but, despite this measure, the prevalence of sensitization remained unchanged, at 1–4% (5). For 10 years, MCI/MI has been one of the most common causes of sensitization and allergic contact dermatitis resulting from the use of preservatives (6).

Over the past decade, there has been strong consumer pressure to abandon the use of preservatives such as parabens and formaldehyde; methyl-dibromoglutaronitrile has been banned in all cosmetics since 2008, owing to its sensitization potential in cosmetics. In this context, one alternative in the mid-2000s was to use MI alone, as it was considered to be a weaker sensitizer than MCI/MI, despite being categorized as a moderate to strong sensitizer in several classifications (7, 8). It was first used as a preservative in aqueous industrial products (water paints, inks, adhesives, lacquers, varnish, cutting oils, cooling fluids, various aqueous emulsions, etc.). Then, in 2005, its use was permitted for use in all cosmetics, and it was also introduced in other consumer products, such as household detergents.

MI is now commonly used in household products, being found, for example, in 16.5% of these products in Sweden (9). Additionally, it has been increasingly used in leave-on products, such as wet wipes for various purposes (intimate hygiene or domestic use) and cosmetics. Baby and intimate wipes are applied under occlusion, increasing penetration of the allergen (10). Since the introduction of this preservative, the emergence of allergic contact dermatitis has been reported (11–13).

MI permitted concentration levels are higher than those for MCI/MI. The maximum authorized concentration in cosmetics, whether rinse-off or not, is 100 ppm in Europe and the United States (14), corresponding to ~25 times the level for MCI/MI. In the case of

industrial products, there is no maximum concentration level.

Until the end of 2013, MI was not included in the European baseline series (15), unlike MCI/MI. As the MCI/MI test does not reliably detect MI sensitization, since 2010 the French REVIDAL-GERDA group (Vigilance Network for Dermatology and Allergy of the Study and Research Group on Contact Dermatitis) has routinely tested MI alone. The main aim of our study was to describe the change in the proportion of MI-positive tests among patients tested between 2010 and 2012. Further objectives were to define the demographic characteristics of the sensitized population (age and sex), to quantify the proportion of MI-positive cases not detected with the MCI/MI test and the rate of clinically relevant test results, and finally to identify the products and occupations responsible for the allergy.

Patients and Methods

This was a multicentre, retrospective, report-based study involving an analysis of all cases reported by French doctors belonging to the REVIDAL-GERDA group and performing patch tests in private practice or in hospitals from January 2010 to December 2012.

During this period, the members of the REVIDAL-GERDA group were invited to report all MI-sensitized cases that they observed, specifying age, sex, clinical relevance and concomitant sensitization to MCI/MI for each positive test. If possible, the product(s) responsible for the allergic contact dermatitis and the subject's professional occupation were specified.

Patch tests with MI were performed with concentrations of 200 ppm aqua, 2000 ppm (Chemotechnique[®], Malmö, Sweden), or 500 ppm (Stallergènes[®], Anthony, France). The tests were read after 2 and 3–4 days.

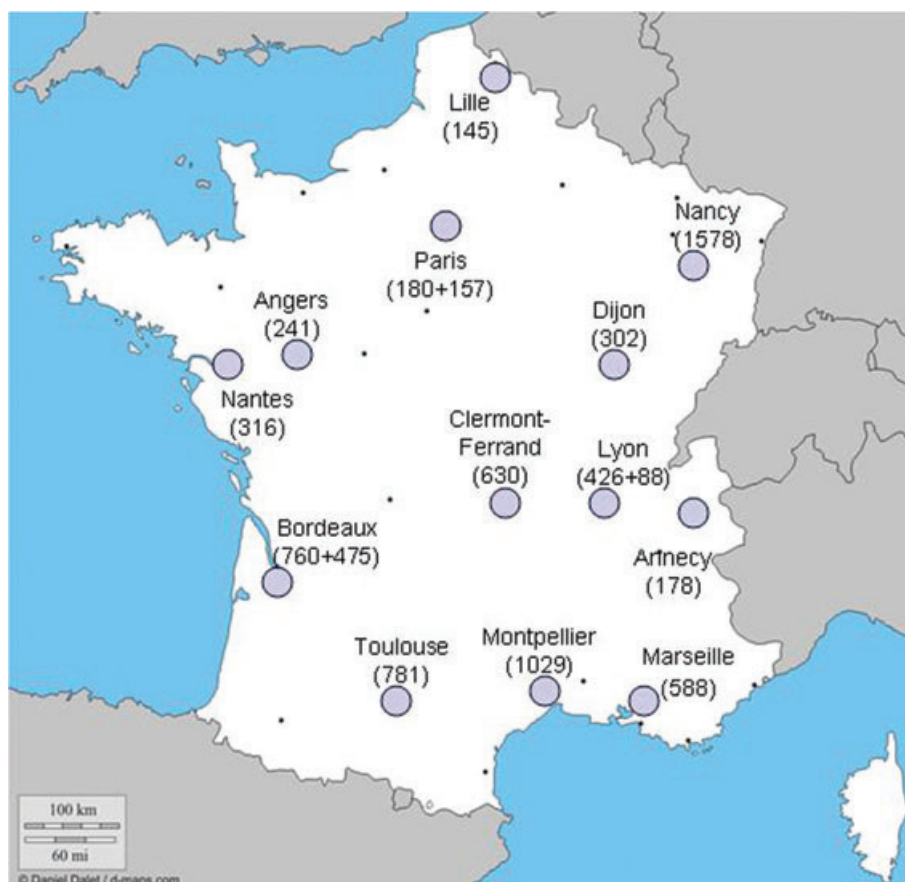
We calculated the median proportion of MI-positive tests. The Kruskal–Wallis test was used for comparison of the medians of the 3 years. We compared the years two by two using the Mann–Whitney test. The significance level was defined as $p < 0.05$.

Results

Sixteen centres participated in the study (Fig. 1). A total of 7874 patients were tested with MI. The number of centres testing MI increased from seven in 2010 to 14 and 16 in 2011 and 2012, respectively. The number of tested patients also increased, from 1875 in 2010 to 2792 and 3207 in 2011 and 2012, respectively.

In most cases, the test concentration was 200 ppm (69–72% of cases); alternatively, 500 ppm was used

Fig. 1. Centres of the REVIDAL-GERDA group that participated in the study. The figures in parentheses under the centres correspond to the numbers of tested patients. Two centres participated in Bordeaux, Lyon, and Paris.



(21–29%). One centre tested for sensitization to MI with 2000 ppm in 2011 and 2012 (Fig. 2). One centre tested with 200 ppm at the beginning of 2012, and then with 500 ppm at the end of the year. For this centre, we adopted a concentration of 500 ppm for 2012. In fact, patients who are positive at 200 ppm may also be considered to be positive at 500 ppm.

The proportion of MI-positive tests more than tripled in 3 years, from 1.50% [95% confidence interval (CI) 0.93–1.92%] to 3.26% [95% CI 2.62–4.05%] and 5.56% [95% CI 4.50–9.49%] sensitized cases in 2010, 2011, and 2012, respectively. All centres but one specified the relevance of tests. The relevance was not specified for 2 of 24 positive patients in 2010 and for 10 of 86 positive patients in 2011. Clinical relevance of the tests was estimated for a total of 283 positive patients.

Tests were clinically relevant in 87.5%, 80.2% and 90.3% of cases in 2010, 2011, and 2012, respectively.

The difference in the proportion of MI-positive tests was significant between 2010 and 2011 ($p = 0.0025$), 2011 and 2012 ($p = 0.0134$), and 2010 and 2012 ($p = 0.0002$) (Fig. 3).

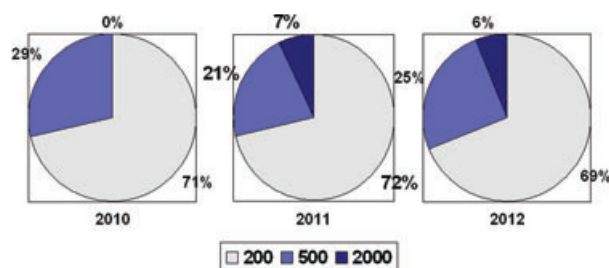


Fig. 2. Percentages of the methylisothiazolinone (MI) concentrations (200, 500 and 2000 ppm) used in MI patch tests in 2010, 2011, and 2012.

Women accounted for 75%, 69.8% and 77.8% of MI-positive patients in 2010, 2011, and 2012, respectively (Table 1).

The median age was between 39 and 43 years, with a range of 1–88 years. The age of 1 patient in 2012 was not available.

Among MI-positive patients, the MCI/MI test was negative in 29.2%, 32.6% and 33.5% of cases in 2010, 2011, and 2012, respectively, corresponding to

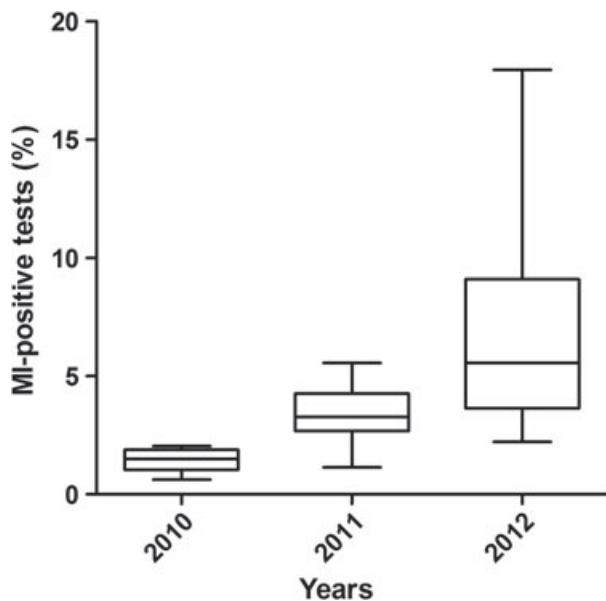


Fig. 3. Percentages of methylisothiazolinone (MI)-positive tests from 2010 to 2012. The graph shows the median of MI sensitization rate with 10th and 90th percentiles/minimum and maximum values.

Table 1. Demographic characteristics of methylisothiazolinone - positive patients

	2010	2011	2012
Women (%)	75	69.8	77.8
Median age (years)	39	41	43
25th percentile	29	28	32
75th percentile	50	51	53
Mean	42	41	43
Minimum	22	2	1
Maximum	88	72	82

approximately one-third of false-negative results with the MCI/MI test among MI-positive patients (Fig. 4).

Over the three complete years, information about the products used was available for 83.7% (247/295) of MI-positive patients. Among these, at least one product was responsible for allergic contact dermatitis caused by MI in 83.4% (206/247) of patients. Up to four products per patient were found to be responsible for allergic contact dermatitis caused by MI. Overall, a total of 245 products were implicated. Cosmetics accounted for 73.1% (179/245) of causative products (Fig. 5). Among the cosmetics that were specified, the majority were rinse-off, mainly soaps, particularly industrial soaps, toilet products, and hair products. Household products



Fig. 4. Photograph of patch tests in a patient who had a positive methylisothiazolinone (MI) test at 500 ppm and a negative MCI/MI test.

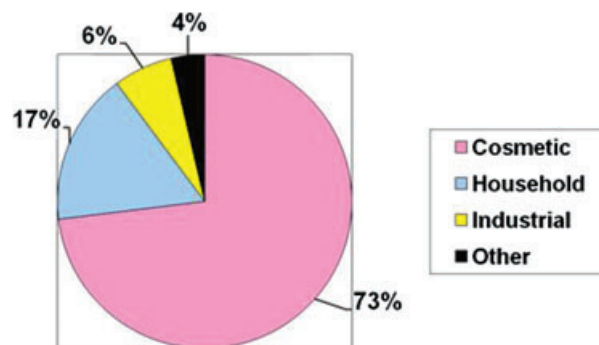


Fig. 5. Repartition of the categories of products responsible for methylisothiazolinone allergic contact dermatitis from 2010 to 2012.

constituted 16.7% (41/245) of the products implicated, the majority being specified as washing-up liquid. Finally, industrial products accounted for the final proportion of allergic products, constituting 6.5% (16/245) of the products implicated, and being predominantly cutting oils, followed by paint. The remaining 9 of 245 (3.7%) products are listed below: three products (do-it-yourself, gardening, and gloves) did not fit into any of the categories quoted above. For five products, classification was not possible in any category (wet wipes), because they could be classified as cosmetics or household products. Finally, an auxiliary nurse was exposed to MI in the course of her work, but the product was not specified. Wet wipes accounted for 7.3% (18/245) of the products implicated, and were considered to be more often used for cosmetic purposes than for domestic purposes.

Information about the occupational origin of MI sensitization was available for 177 of 295 (60%) patients over the total of 3 years. Of these cases, 54 of 177 (30.5%) were job-related: 20 of 54 (37%) were working in a paramedical or medical environment (mainly auxiliary nurses and nurses using soaps), 15 of 54 (27.8%) were using industrial products in the course of their occupation (painters, turners, mechanics, etc.), 7 of 54 (13%) used household products (restaurant staff, cleaners, etc.), and 5 of 54 (9.3%) used cosmetic products that were not soap (hairdressers, beauticians, etc.). Painters alone accounted for 5 of 54 (5.6%) of occupational cases. Four occupations were not specified, but the allergy was caused by the soap used in the course of work. Three trades did not fit into the categories quoted above (floodlight technician, logistician, and machinist), and the allergy was caused by work-related soap. Finally, soap was implicated in 22 of 54 work-related cases (40.7%).

Discussion

Increased incidence of sensitization and time-course

To our knowledge, this is the first study to investigate sensitization to MI in France. The proportion of MI-positive tests increased significantly from 2010 to 2012, and, among those tested for suspected allergic contact dermatitis, the figure rose to 5.6%.

The proportion of MI-positive tests, the number of centres and the number of patients tested increased over the 3 years. The test concentration was higher in 2011 and 2012, because of the inclusion of one test at 2000 ppm in one centre. However, there was the same proportion of tests at 200 ppm over the 3 years. Geier et al. also noted an increase in the proportion of MI-positive tests in a study by the Information Network of Departments of Dermatology (IVDK) of the German Contact Dermatitis Research Group, with 1.9% and 4.4% in 2009 and 2011, respectively, when testing was performed at 500 ppm (16, 17). This increased sensitization was surprising as compared with other preservatives, such as iodopropynyl butylcarbamate and 2-bromo-2-nitropropane-1,3-diol (bronopol), for which the proportion of cases of sensitization remained almost unchanged. Another study by the IVDK, published by Uter et al. (18), even more recently, also noted an increasing prevalence of MI sensitization, with 6.0% in 2012. There was a similar profile in other European countries, such as the United Kingdom, where the study by McFadden et al. (19) found 5.7% MI-positive patients in 2012 versus 0.5% in 2010 with a 500 ppm test, and Finland, with 1.8% sensitized cases in 2008 versus 0.9% in 2006 for

patients tested at 1000 ppm (13, 17) (Table 2). In the United States, the situation appears to be similar, because MI was considered to be the 'allergen of the year 2013' (20). This increase in sensitization may be related to the increase in the use of MI-containing products over the past 10 years. Indeed, in the United States, the Food and Drug Administration reported a more than twofold increase in the use of MI in cosmetic products between 2007 and 2010, with 1125 versus 2408 products, respectively (21, 22). Conversely, sensitization to MI may possibly have been underestimated previously, because it was poorly detected with the MCI/MI test and was rarely tested for alone.

In Europe, many groups have observed the proportion of sensitization to be ~1.5%. In Denmark, Lundov et al. tested 2536 patients between 2006 and 2010 at 2000 ppm. Thirty-seven (1.5%) were positive. They classed it as the fourth most common contact allergen (11). In Germany, Schnuch et al. found 215 of 13 433 (1.54%) MI-positive patients tested at 500 ppm between 2005 and 2009 (12). In Finland, the series of Ackerman et al. between 2006 and 2008 found 147 of 10 821 (1.4%) MI-positive patients at 1000 ppm (13). Our study probably underestimated the proportion of sensitization, because we were testing at low concentrations as compared with these other countries. The figures are therefore very alarming. The recent English study by Urwin et al., like our study, found a high MI sensitization rate of 4.6% in 2012. The test concentration of 2000 ppm was higher, but patients were only tested over the first 6 months of the year, from January to June 2012 (23).

Furthermore, a Dutch cosmetovigilance study conducted from 2009 to 2011 showed that isothiazolinones (MI and MCI/MI) were the most frequently identified allergens in cosmetic products (23%) (24).

As a result, with > 1% of patients developing allergic contact dermatitis, MI has been included in the European baseline series since November 2013 (15).

Sensitized population

In our study, more women (75%) than men were sensitized to MI. However, data on the percentage of tested women were not available. In the study by Geier et al., the increase in the proportion of sensitization to MI from 2009 to 2011 was greater in women (+188%) than in men (+54%) (16). This female predominance could be explained by the more frequent use of cosmetics and the fact that women are more frequently tested than men.

The average age was between 41 and 43 years, and MI-sensitized patients were aged from 1 to 88 years, meaning

Table 2. Increase in the sensitization rate and the sensitization rate of methylisothiazolinone -positive tests in five European countries

Country	France	Germany	United Kingdom (18)	Finland (13)	Denmark (11)
Sensitization rate, % (year or period)	1.5 (2010)	1.5 (2005–2009) (15)	0.5 (2010)	1.4 (2006–2008)	1.5 (2006–2010)
Progression of the sensitization rate, % (period)	+ 4.8 (2010–2012)	+ 4.1 (2009–2012) (17)	+ 5.2 (2010–2012)	+ 0.9 (2006–2008)	+ 0.5 (2006–2010)
Test concentration (ppm)	200–500	500	500	1000	2000

that it is a ubiquitous environmental allergen capable of sensitizing even the youngest children. In the study by Lundov et al. (11), the age range of sensitized patients was narrower, being between 18 and 81 years. The average age of their patients (52.2 years) was therefore higher, probably because they did not test children. However, McFadden et al. (19) noted, in a study of 52 MI-positive cases (1289 patients tested) conducted between 2010 and 2012, that patients aged ≥ 40 years had a significantly higher sensitization rate ($p < 0.01$) than patients aged < 40 years, regardless of sex. The authors suggested that a breakthrough in immune tolerance in the older subgroup may, at least in part, explain this difference (25).

Among sensitized patients, 80–90% had a clinical history suggestive of allergic contact dermatitis caused by MI, showing the strong clinical relevance of this test.

Among the products responsible for allergic contact dermatitis, 73.1% were cosmetics and 16.7% were household products. In the study by Lundov et al., cosmetics, for the most part rinse-off products, were also the products most responsible for MI allergic contact dermatitis (32%). In most cases, these were hair care products, liquid soaps, and creams, which is consistent with our findings regarding products. Allergy resulting from household products accounted for 2.7% of cases (11). However, the percentages were more reliable than ours, which can be explained by the fact that the rate was calculated among all sensitized patients, as opposed to only those cases for which a product was identified.

Allergic contact dermatitis caused by MI was of occupational origin in 30.5% of cases. Similar results were reported in the study by Lundov et al. (11), with MI being the most common allergen associated with an occupational origin. In our study, painters accounted for 5.6% of occupational cases versus 45% in their study. MI is currently recognized as one of the most common occupational causes of contact dermatitis for painters (26). In addition, in painters, MI sensitization has been shown to be related to airborne exposure (27, 28). According to information from paint manufacturers,

the MI concentration in these products is high, at between 100 and 275 ppm.

False-negative test results with MCI/MI

In 2012, 33.5% of MI-sensitized patients had negative test results with MCI/MI 100 ppm. This could be explained by the low MI concentration in MCI/MI; hence the interest in testing MI alone. By comparison, there were 34% false-negative test results with MCI/MI in the Finnish study of 2006–2008 (13), and 33% in the German study of 2005–2009 (12). In the Danish study of 2006–2010, there were 59% false-negative test results with MCI/MI (11); however, the MI concentrations tested were higher (2000 ppm), and so detected more MI-positive patients than MCI/MI.

MI sensitization is often thought to be acquired by immunological cross-reaction after MCI sensitization. However, recent patch test data suggest that the prevalence of MI contact allergy is greater than the prevalence of MCI/MI contact allergy, suggesting that MI is the primary sensitizer, and that the increase in the prevalence of MCI/MI contact allergy is driven by the increase in MI exposure and MI contact allergy (16, 17).

MI concentration in patch tests and in products

In the current report of the European Surveillance System on Contact Allergy network on patch test results published in 2012, members concluded that MI should be included in the European baseline series (5). However, they did not specify the ideal patch test concentration. Indeed, there is currently no recommended concentration for MI patch tests. As with any other allergen, the ideal concentration should detect as many cases as possible without inducing either irritation or sensitization.

In France, MI was initially tested at 200 ppm, but it has recently been shown by Waton et al. that the patch test with 500 ppm detects more allergies without being irritant (29). In the study by Ackermann et al., among the 147 patients reacting to MI at 1000 ppm, only 47% reacted to 300 ppm (13). In the study by Urwin et al.,

the test at 2000 ppm detected 4.6% MI-positive patients versus 2.5% at 200 ppm in 2012, and the same difference was observed in 2011, with 3.8% versus 1.8% (23). A Danish study (30) showed that, even at 2000 ppm, the MI test did not cause an irritant reaction in healthy control cases. It appears to be necessary to test MI at a minimum concentration of 500 ppm, and preferably 2000 ppm, which seems to be the optimal patch test concentration (23). Since November 2013, the European Society of Contact Dermatitis (ESCD) and the European Environmental and Contact Dermatitis Research Group have recommended inclusion of MI at 2000 ppm in the European baseline test series (15).

The usual concentration of MI in cosmetics, whether rinse-off or not, is ~100 ppm, which is the maximum authorized concentration. However, a Danish study showed that a very large number of patients reacted to an MI concentration 20 times lower (30). The ESCD issued a warning in February 2013 to review the 'safe' maximum authorized MI concentration in cosmetics and other products, as to control occupational exposure (17). In December 2013, the Scientific Committee on Consumer Safety (SCCS) (31) adopted an opinion on the use of MI in cosmetics. It considers that 100 ppm MI in leave-on cosmetic products (including wet wipes) is not safe for the consumer. For rinse-off cosmetic products, a maximum concentration of 15 ppm MI is considered to be safe for the consumer with regard to the induction of contact allergy. No information is available on elicitation. At the same time, Cosmetics Europe (32) recommended to its member companies removal of MI from leave-on skin products, including cosmetic wet wipes, without waiting for regulatory intervention under the Cosmetics Regulation.

Potential bias of the study

There might be a centre effect in our study. Indeed, most of the French REVIDAL-GERDA centres that participated in the study were hospital departments, and tested a large number of patients. However, it may be noted that, geographically, the centres are homogeneously distributed across France. Therefore, our results reflect MI exposure trends over the whole of France.

In addition, the MI test from Chemotechnique® exists in two concentrations: 200 ppm (reference M035A) and 2000 ppm (reference M035B). One centre believed that it was testing with 200 ppm, whereas in fact it was using a 2000 ppm test from the same supplier. We corrected this, assuming the correct concentration to be 2000 ppm. After checking with the other centres, we found that none of them reported the same mistake.

Conclusion

We report a significant increase in MI-positive tests from 2010 to 2012, and confirm that MI is a rapidly emerging allergen. This study presents the first data available in France on this topic. Similar observations in other European countries have also been reported. Since November 2013, MI has been included at 2000 ppm aqua in the European baseline series. An opinion of the SCCS, European Commission, on the use of MI in cosmetics was issued in December 2013, and recommended removal from leave-on cosmetic products and restriction to 15 ppm in rinse-off products. Finally, it appears that essential and urgent regulatory intervention in Europe is needed to prevent new cases of sensitization and to protect those already sensitized.

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