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Sensitization to isothiazolinones in the Spanish Contact Dermatitis Registry (REIDAC): 2019–2021 epidemiological situation

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Abstract

Background: Current frequency and risk factors for sensitization to methylisothiazolinone (MI), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), benzisothiazolinone (BIT) and octylisothiazolinone (OIT) in Spain are not well known.

Objectives: To study the frequency of sensitization, risk factors and simultaneous sensitization between the four isothiazolinones.

Materials and Methods: We analysed all 2019–2021 consecutive patients patch-tested with MI (0.2% aq.), MCI/MI (0.02% aq.), BIT (0.1% pet.) and OIT (0.1% pet) within the Spanish Contact Dermatitis Registry (REIDAC).

Results: A total of 2511 patients were analysed. Frequencies of sensitization were: any isothiazolinone 15.7%, MI 6.8%, MCI/MI 4.8%, BIT 3.5% and OIT 0.5%. MI and MCI/MI sensitization was associated with being occupationally active, hand dermatitis, detergents and age over 40. BIT sensitization was associated with leg dermatitis and age over 40. About one in nine MI-positive patients were positive to BIT, whereas one in five BIT-positive patients were positive to MI.

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Conclusions: Sensitization to MI, MCI/MI and BIT is still common in Spain, while sensitization to OIT is rare. Currently, sensitization to MI and MCI/MI seems to be occupationally related. Although its origin is unknown, sensitization to BIT is more frequent in patients aged over 40 years. Simultaneous sensitization between MI and BIT is uncommon.

KEYWORDS
benzisothiazolinone, contact dermatitis, methylchloroisothiazolinone/methylisothiazolinone, methylisothiazolinone, octylisothiazolinone, patch tests, Spain, standard series

1 | INTRODUCTION

Methylisothiazolinone (2-methyl-4-isothiazolin-3-one, MI) (CAS no. 2682-20-4) and the mixture methylchloroisothiazolinone/methylisothiazolinone (5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one, MCI/MI) (CAS no. 55965-84-9) are two derivatives of isothiazolinones widely used as preservatives in rinse-off cosmetics, household detergents, water-based paints and industrial products. Sensitization to both isothiazolinones takes place both in the domestic sphere, mainly due to exposure to cosmetics and household detergents, and in the workplace, especially in cleaning workers.[1] The epidemic of allergic contact dermatitis (ACD) by MI and MCI/MI has been improving in Europe in recent years, because of European regulatory measures, but sensitization is still significant.[2]

The role of ACD elicited by other isothiazolinones, such as benzisothiazolinone (1,2-benzisothiazol-3(2H)-one, BIT) (CAS no. 2634-33-5) and octylisothiazolinone (2-octyl-2H-isothiazol-3-one, OIT) (CAS no. 26530-20-1), is currently being evaluated. BIT is widely present in household detergents, water-based paints, adhesives and industrial products, whereas OIT can be found in leather and industrial products.[1] There is little information concerning the current frequency of sensitization to these isothiazolinones and risk factors linked to sensitization.[3–6]

The objectives of this study were to determine the frequency, relevance and risk factors for sensitization to MI, MCI/MI, BIT and OIT, as well as risk factors for sensitization and the frequency of simultaneous sensitization between the four isothiazolinones, in a 2019–2021 multi-centre Spanish registry (REIDAC).

2 | MATERIALS AND METHODS

The Spanish Contact Dermatitis Registry (REIDAC) prospectively recruits all consecutive patients patch-tested in participating centres in Spain. From January 1, 2019 to December 31, 2021, all patients were tested with the Spanish standard series plus the extension/recommended additions to the European baseline series.[7,8] We analysed patients simultaneously patch-tested with the following allergens: MI (0.2% aq.), MCI/MI (0.02% aq.), BIT (0.1% pet.) and OIT (0.1% pet).

The allergens were commercially obtained from Chemotechnique (Chemotechnique MB, Vellinge, Sweden) and allergEAZE (SmartPractice, Calgary, Canada), based on availability at each centre. Patch tests were performed following the ESCD guidelines; (+), (++) or (+++) were considered to be positive.[9] Relevance was considered after clinical examination and evaluation of patient's history of possible exposure to every isothiazolinone. Current relevance was presumed when sensitization could explain or contribute to the dermatitis.

REIDAC collects online data using the OpenClinica platform (OpenClinica LLC and collaborators, Waltham, MA, USA, RRID: SCR_019223), as previously described.[10] Positive, irritant and doubtful reactions were collected, as well as relevance (current, past, unknown), age, gender, occupation-related dermatitis, atopic dermatitis, site(s) affected, occupations and sources of sensitization.

2.1 | Statistics

Continuous variables (age) are reported as means (standard deviations), and categorical variables are reported as numbers (proportions). Factors associated with sensitization were expressed as odds ratios (OR) with 95% confidence intervals (95%CI). Significance was calculated with Fisher's exact test. Results were considered significant when the *p*-value was 0.05 or lower. For data analysis, the statistical package Stata 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC, RRID: SCR_012763) was used.

3 | RESULTS

A total of 2511 patients were patch-tested with the four allergens and included in this analysis. Table 1 describes the clinical-demographic characteristics of the population and the odds ratio of each variable studied for sensitization. The frequency of global sensitization to any isothiazolinone was 15.7% (394/2511). The number of patients sensitized to each was: MI 172 (6.8%), MCI/MI 120 (4.8%), BIT 89 (3.5%) and OIT 13 (0.5%). The frequency of current relevance for the four allergens was: MI 77%, MCI/MI 68%, BIT 39% and OIT 38.5%.

As factors associated with a higher risk for sensitization (risk factors), we identified that MI was significantly associated with being occupationally active (OR: 2.3; 95%CI: 1.6–3.3), hand dermatitis (OR: 2.4; 95%CI: 1.7–3.3) and the use of detergents (OR: 3.8; 95%CI: 2–6.8). As factors significantly associated with a lower risk for sensitization (protective factors), we identified female sex (OR: 0.7; 95%CI:

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TABLE 1 Clinical-demographic characteristics of the population and odds ratio for sensitization.

	MI (%)	OR (95%CI)	MCI/MI (%)	OR (95%CI)	BIT (%)	OR (95%CI)	OIT (%)	OR (95%CI)	Total (*n*: 2511) (%)
Reactions									
Positive (any)	**172 (6.8)**		**120 (4.8)**		**89 (3.5)**		**13 (0.5)**		**394 (15.7)**
Positive (+)	39 (22.7)		31 (25.8)		52 (58.4)		5 (38.5)		127 (32.2)
Positive (++)	73 (42.4)		60 (50)		27 (30.3)		7 (53.8)		167 (42.4)
Positive (+++)	60 (34.9)		29 (24.2)		10 (11.2)		1 (7.7)		100 (25.4)
Irritative	4		3		0		0		
Doubtful (−/+)	9		5		22		3		
Relevance									
Current	132 (76.7)		82 (68.3)		35 (39.3)		5 (38.5)		
Past	17 (9.9)		12 (10)		4 (4.5)		0 (0)		
Unknown	23 (13.4)		26 (21.7)		50 (56.2)		8 (61.5)		
Demographics									
Age (years), mean (*SD*)	47.9 (18.2)		50.9 (15.2)		55.3 (16)		54.1 (10.7)		48.5 (18.4)[a]
Female sex	106 (61.6)	0.7 (0.5–0.95)	78 (65)	0.8 (0.5–1.2)	49 (55.1)	0.5 (0.3–0.8)	7 (53.8)	0.5 (0.1–1.8)	1750 (69.7)[a]
Occupational	47 (27.3)	2.3 (1.6–3.3)	38 (31.7)	2.8 (1.9–4.3)	16 (18)	1.3 (0.7–2.2)	3 (23.1)	1.7 (0.3–6.7)	372 (14.8)[a]
Atopic dermatitis	32 (18.6)	1.2 (0.8–1.7)	22 (18.3)	1.1 (0.7–1.8)	6 (6.7)	0.4 (0.1–0.8)	4 (30.8)	2.3 (0.5–8.2)	417 (16.6)[a]
Hand dermatitis	80 (46.5)	2.4 (1.7–3.3)	58 (48.3)	2.5 (1.7–3.7)	20 (22.5)	0.7 (0.4–1.2)	4 (30.8)	1.1 (0.3–4.1)	700 (27.9)[a]
Leg dermatitis	8 (4.7)	0.9 (0.4–1.8)	6 (5)	0.9 (0.3–2.2)	12 13.5)	3 (1.5–5.8)	0 (0)	0	132 (5.3)[a]
Facial dermatitis	29 (16.9)	0.6 (0.4–0.97)	17 (14.2)	0.5 (0.3–0.9)	13 (14.6)	0.5 (0.3–0.99)	2 (15.4)	0.6 (0.1–2.7)	593 (23.6)[a]
Age over 40 years	119 (69.2)	1.1 (0.8–1.6)	96 (80)	2 (1.2–3.3)	75 (84.3)	2.6 (1.5–5.1)	12 (92.3)	5.8 (0.6–247.3)	1686 (67.1)[a]
Occupations									
Retiree	21 (12.2)	0.6 (0.3–0.9)	17 (14.2)	0.7 (0.4–1.2)	22 (24.7)	1.4 (0.8–2.4)	2 (15.4)	0.8 (0.1–3.6)	
Office worker	20 (11.6)	1.1 (0.7–1.8)	16 (13.3)	1.3 (0.7–2.3)	8 (9)	0.8 (0.3–1.7)	2 (15.4)	1.6 (0.2–7.1)	
Cleaning worker/ housekeeper	18 (10.5)	0.7 (0.4–1.2)	15 (12.5)	0.9 (0.5–1.6)	12 (13.5)	1 (0.5–1.9)	3 (23.1)	2 (0.3–7.7)	
Health worker	20 (11.6)	1.5 (0.9–2.5)	16 (13.3)	1.8 (0.96–3.1)	5 (5.6)	0.6 (0.2–1.6)	0 (0)	0 (0–3.2)	
Student	19 (11)	1.1 (0.6–1.8)	7 (5.8)	0.5 (0.2–1.1)	3 (3.4)	0.3 (0.1–0.9)	0 (0)	0 (0–2.6)	
Others	74 (43)	1.2 (0.9–1.7)	49 (40.8)	1.1 (0.7–1.6)	39 (43.8)	1.2 (0.8–2)	6 (46.2)	1.3 (0.4–4.8)	
Possible sources of allergen exposure									
Leave-on cosmetics	35 (20.3)	1.2 (0.8–1.8)	27 (22.5)	1.4 (0.9–2.2)	16 (18)	1 (0.6–1.8)	4 (30.8)	2.1 (0.5–7.6)	
Rinse-off cosmetics	23 (13.4)	1.3 (0.8–2)	17 (14.2)	1.4 (0.8–2.3)	6 (6.7)	0.6 (0.2–1.3)	0 (0)	0 (0–2.4)	
Detergents	16 (9.3)	3.8 (2–6.8)	18 (15)	7 (3.7–12.5)	5 (5.6)	1.9 (0.6–4.7)	0 (0)	0 (0–9)	
Others	89 (51.7)	0.9 (0.6–1.2)	52 (43.3)	0.6 (0.4–0.9)	50 (56.2)	1.1 (0.7–1.7)	8 (61.5)	1.3 (0.4–5.1)	
Unknown	9 (5.2)	0.3 (0.2–0.7)	6 (5)	0.3 (0.1–0.7)	12 (13.5)	1 (0.5–1.9)	1 (7.7)	0.5 (0–3.6)	

Note: Statistically significant variables highlighted in bold. Those acting as risk factors are highlighted in red, whereas those acting as protective factors are highlighted in green.

Abbreviations: BIT, benzisothiazolinone; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MI, methylisothiazolinone; OIT, octylisothiazolinone.

[a]Data from the whole population (*n*: 2511).

0.5–0.95), facial dermatitis (OR: 0.6; 95%CI: 0.4–0.97) and being retired (OR: 0.6; 95%CI: 0.3–0.9). MCI/MI was significantly linked to being occupationally active, (OR: 2.8; 95%CI: 1.9–4.3), hand dermatitis (OR: 2.5; 95%CI: 1.7–3.7), age over 40 years (OR: 2; 95%CI: 1.2–3.3) and the use of detergents (OR: 7; 95%CI: 3.7–12.5), while, as a significant protective factor, facial dermatitis (OR: 0.5; 95%CI: 0.3–0.9).

Sensitization to BIT was significantly associated with leg dermatitis (OR: 3; 95%CI: 1.5–5.8) and age over 40 years (OR: 2.6; 95%CI: 1.5–5.1), whereas female sex (OR: 0.5; 95%CI: 0.3–0.8), atopic dermatitis (OR: 0.4; 95%CI: 0.1–0.8), facial dermatitis (OR: 0.5; 95%CI: 0.3–0.99) and being a student (OR: 0.3; 95%CI: 0.1–0.9) acted as significant protective factors. No factors were associated to OIT sensitization.

Figure 1 describes the concomitant sensitization frequencies between the four isothiazolinones. In the group of MI-positive patients, 11.6% (20/172) were also positive to BIT and 2.9% (5/172)

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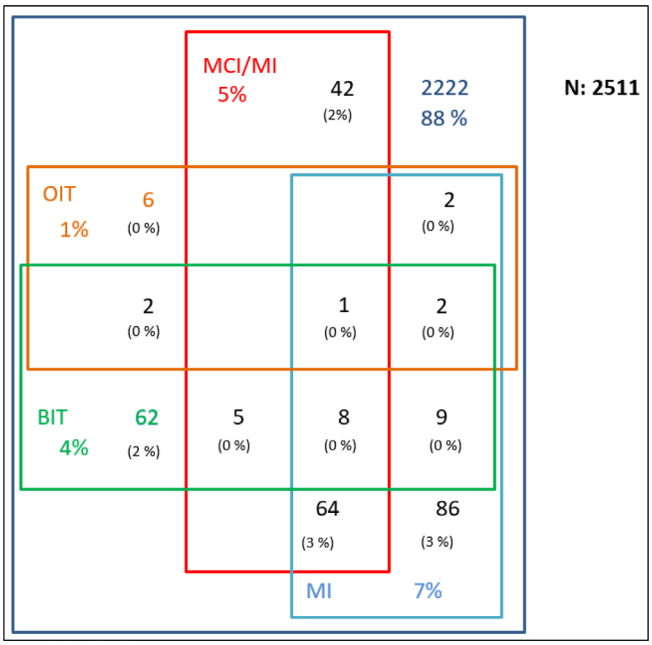

MI: Methylisothiazolinone
MCI/MI: Methylchloroisothiazolinone/methylisothiazolinone
BIT: Benzisothiazolinone
OIT: Octylisothiazolinone

FIGURE 1 Diagram illustrating simultaneous sensitization between the four isothiazolinones. BIT, benzisothiazolinone; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MI, methylisothiazolinone; OIT, octylisothiazolinone

to OIT. In the group of BIT-positive patients, 22.5% (20/89) were also positive to MI and 5.6% (5/89) to OIT. In the group of OIT-positive patients, 38.5% (5/13) were also positive to MI and 38.5% (5/13) to BIT.

4 | DISCUSSION

Overall, in our population we have found a high frequency of sensitization to any isothiazolinone (15.7%). Separately, the frequencies of sensitization to MI (6.8%), MCI/MI (4.8%) and BIT (3.5%) were high, while the frequency of sensitization to OIT (0.5%) was much lower. In addition, we found a high frequency of current relevance for MI (77%) and MCI/MI (68%), while low for BIT (39%) and OIT (38.5%).

4.1 | Methylisothiazolinone and methylchloroisothiazolinone/methylisothiazolinone

In the context of the MI sensitization epidemic, multiple studies have evaluated the frequency of sensitization to MI and MCI/MI in consecutive patients. Most recent European studies[2–4,11–13] have observed slightly lower frequencies of sensitization than ours (3%–5% for MI and 4% for MCI/MI). Minding the findings of studies from previous years,[5,14–19] there is an apparently progressive epidemic increase in the frequency of sensitization to MI and MCI/MI from 2007 to 2014–2015, when the peak of maximum prevalence is reached (6%–15% for MI and 7%–13% for MCI/MI). From then on, a slower decline is observed until now. On the contrary, the most recent study of the North American Contact Dermatitis Group (NACDG)[20] recorded the highest prevalence to date, analysing a 2017–2018 population in which 15.3% of patients were sensitized to MI and 11% to MCI/MI. This is probably due to the absence of regulation regarding the use of isothiazolinones in cosmetics in the United States. In Europe, the 2015 recommendation of the Scientific Committee on Consumer Safety,[21] according to which for leave-on cosmetics no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated, whereas for rinse-off cosmetics a concentration of 15 ppm is considered safe, and the following measures adopted by the European Parliament and of the Council on cosmetic products,[22–24] have resulted in a slowly progressive decline in sensitization. However, the pre-epidemic epidemiological situation has not yet been reached, as corroborated by our work.

With regard to the factors associated with sensitization to MI and MCI/MI, we identified being occupationally active, hand dermatitis and the use of detergents as significant risk factors; age over 40 years was also a risk factor for sensitization to MCI/MI. On the other hand, female sex, facial dermatitis and being retired were significant protective factors.

Several studies have studied the risk factors linked to sensitization to MI and MCI/MI.[4–6,15,17,25] The reports in Danish consecutive patients by Schwensen et al.[5] who studied a 2009–2013 multi-centre sensitized population, and Havmose et al.,[4] who studied a 2005–2019 uni-centre sensitized group, identified female sex, being occupationally active, facial dermatitis, hand dermatitis and age over 40 years as risk factors. Havmose's study indicates that leave-on cosmetics have been losing importance as a source of exposure to MI, in favour of rinse-off cosmetics. The authors also observed a lower frequency of current relevance, work-related ACD, hand dermatitis and facial dermatitis. Uter et al. identified the same variables, as well as atopic and anogenital dermatitis, as risk factors in a 2009–2012 MI patch-tested population of the Information Network of Departments of Dermatology (IVDK).[6] In these studies, occupations at risk of sensitization were housekeeper, cleaning worker, beautician/cosmetology, painter, tile setter/terrazzo worker, industrial operator and welding—blacksmith.

These data are partially consistent with ours. In line with previous findings, we identified being occupationally active, hand dermatitis, age over 40 and the use of detergents as risk factors. Both leave-on and rinse-off cosmetics were the most frequent sources of sensitization to every isothiazolinone, but association was not significant. It should be noted that, despite European regulations, leave-on cosmetics still are a possible source of sensitization to MI and MCI/MI in Spain, differing from the experience in others countries, such as Belgium.[12] In addition, opposite to previous studies, female sex and facial dermatitis were protective factors. This indicates that, at present, maintenance of sensitization to MI and MCI/MI in Spain is probably work-related, while cosmetics have seemingly lost importance as a source of sensitization in favour of hidden sources. Although we did

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not identify a significant risk association with any specific occupation, we found a higher frequency of sensitization in health workers, whereas being retired significantly protected against it. Surprisingly, contrary to aforementioned studies, working as cleaning worker/housekeeper was not a risk factor in our research, even though the use of detergents was linked to sensitization. Probably, the wide range of occupations made it difficult to identify specific occupations at risk for sensitization. A list of occupations and sources of allergen exposure can be found in Tables S1 and S2, respectively.

4.2 | Benzisothiazolinone and octylisothiazolinone

The frequency of sensitization and relevance of the BIT and OIT in Europe has been less studied.[3,10,13,26] We documented similar results in a previous study analysing a partial 2019–2020 sample of the present population, supporting the inclusion of the BIT in the extended Spanish series.[10] Uter et al. have conducted a multi-centre study in a 2019–2020 European group, which showed a frequency of sensitization to BIT of 4.7%, so that the authors conclude that its inclusion in the European standard series appears suitable.[26] Also noteworthy is the study of Soriano et al. in a 2019 UK sample, which observed frequencies of sensitization to BIT and OIT of 4% and 1%, respectively,[3] similar to ours. King et al. reported a gradual increase in the prevalence of contact allergy to BIT in another UK group, from 0.3% in 2014 to 3.4% in 2019, probably as a consequence of increased use in household products.[13]

Very few studies have investigated risk factors related to BIT and OIT sensitization. The report of Schwensen et al. did not identify any significant risk factors associated with sensitization to BIT.[5] In our study, we identified leg dermatitis and age over 40 years, while female sex, atopic dermatitis, facial dermatitis and student occupation were significant protective factors. Although we have not been able to identify the origin of sensitization, our data indicate that sensitization to BIT is possibly a consequence of continued exposure to the allergen and appears in more advanced stages of adulthood. While most cases of contact allergy to BIT are unknown, it is worth stressing that cosmetics were identified as a possible sensitization source in 22/89 (25%) of the cases (Table 1), despite the European regulations forbidding the use of BIT in cosmetics.[27] Since these data is based on clinical signs, not labelling, these cases may be related to MI and BIT concomitant sensitization. On the other hand, OIT sensitization was not associated with any of the variables studied, probably due to the low sample size of OIT-positives. In fact, exposure to OIT in Spain may be lower than in other countries.[28]

It should be noted that the proportion of weak positives (+) was high in the group of patients patch-tested with BIT (58.4%), and to a lesser extent in that of patch-tested with OIT (38.5%). In the BIT group, 69.2% (36/52) of weak positives were not considered currently relevant (data not given in Table 1). Similarly, the proportion of doubtful reactions (−/+) was high in both groups, affecting almost one in every four patients, albeit we did not find irritant reactions. Although several authors have recommended patching both allergens at 0.1% in petrolatum,[1,8,18] we found a high proportion of weak positives, most of which were not currently relevant, and doubtful reactions, which indicate the need for further research on the optimal concentration and vehicle for patching BIT and OIT.

4.3 | Simultaneous sensitization

In our study, approximately only one in nine (11.6%) MI-positive patients were also positive to BIT and one in five (22.5%) BIT-positive patients were also positive to MI. On the other hand, only 3% of MI-positive patients were also positive to OIT and almost two in five (38.5%) OIT-positive patients were also positive to MI. Concerning MCI/MI and simultaneous sensitization to BIT and OIT, our findings are comparable to those of MI (Figure 1).

Concomitant sensitization between MI, BIT and OIT has been reported,[3,12,29–34] with findings similar to ours. In general, in MI-sensitized patients, concomitant sensitization to BIT or OIT is uncommon, less than 10%–20% of cases. In BIT-sensitized patients, simultaneous sensitization to MI is also low, standing at around 20%–25%, while in OIT-positive patients, simultaneous sensitization to MI is much higher and occurs in 60%–80%. In addition, these reports have studied the presence of BIT and OIT in the products that act as source of sensitization to MI in MI-sensitized patients, which is high and low, respectively. Taking into account the lower structural similarity between MI and BIT, all these data indicate that the most likely mechanism of concomitant sensitization between MI and BIT is simultaneous exposure. The report of Schwensen et al.[33] is the only one that defends the potential cross-reactivity between MI and BIT, as long as exposure to sufficient concentration of the allergen is reached. Our data are scarce to determine whether concomitant sensitization between MI and OIT is due to simultaneous exposure or cross-reactivity.

4.4 | Strengths and limitations

This research is a multi-centre REIDAC study with a large and recent sample of consecutive patients, which can be considered representative of the Spanish population attending hospitals for ACD. The main limitation of the study is the low number of patients sensitized to OIT, which may explain why we have not identified any factor associated with sensitization.

4.5 | Conclusions

At present, there is a high frequency of sensitization to MI, MCI/MI and BIT in Spain, while sensitization to OIT is rare. Sensitization to MI and MCI/MI is associated with being occupationally active, hand dermatitis, the use of detergents and the age over 40 years, so it seems to be occupationally related. We have not found the origin of sensitization to BIT, although it is associated

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with leg dermatitis and age over 40 years. Simultaneous sensitization between MI and BIT is rare.

AUTHOR CONTRIBUTIONS

Carlos Pelayo Hernández Fernández: Conceptualization; investigation; writing – original draft; methodology; validation; supervision; data curation; project administration; formal analysis; software; visualization; resources. **Leopoldo Borrego:** Conceptualization; investigation; funding acquisition; writing – original draft; methodology; validation; visualization; resources; supervision; data curation; project administration; formal analysis; software. **Pedro Mercader García:** Methodology; investigation. **Ana María Giménez Arnau:** Investigation; methodology. **Javier Sánchez Pérez:** Investigation; methodology. **Juan Francisco Silvestre Salvador:** Methodology; investigation. **Ricardo González Pérez:** Investigation; methodology. **Tatiana Sanz Sánchez:** Methodology; investigation. **Araceli Sánchez Gilo:** Investigation; methodology; resources. **Gemma Melé Ninot:** Methodology; investigation; resources. **Violeta Zaragoza Ninet:** Investigation; methodology. **Francisco Javier Miquel Miquel:** Investigation; methodology. **José Manuel Carrascosa Carrillo:** Investigation; methodology. **Susana Córdoba Guijarro:** Methodology; investigation. **María Elena Gatica Ortega:** Methodology; investigation. **Inmaculada Ruiz González:** Investigation; methodology. **Esther Serra Baldrich:** Methodology; investigation. **Fátima Tous Romero:** Methodology; investigation. **Mercedes Rodríguez Serna:** Methodology; investigation. **María Antonia Pastor Nieto:** Investigation; methodology. **Patricia Pérez Feal:** Methodology; investigation. **Marcos Hervella Garcés:** Investigation; methodology. **Marina de Vega Martínez:** Investigation; funding acquisition; methodology; resources; project administration; software; formal analysis; data curation. **Ignacio García Doval:** Investigation; funding acquisition; resources; supervision; data curation; project administration; formal analysis; software; methodology; conceptualization; validation; visualization.

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approval of the manuscript, or decision to submit the manuscript for publication.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Herman A, Aerts O, de Montjoye L, Tromme I, Goossens A, Baeck M. Isothiazolinone derivatives and allergic contact dermatitis: a review and update. *J Eur Acad Dermatol Venereol*. 2019;33(2):267-276. doi:10.1111/jdv.15267
2. Uter W, Aalto-Korte K, Agner T, et al. The epidemic of methylisothiazolinone contact allergy in Europe: follow-up on changing exposures. *J Eur Acad Dermatol Venereol*. 2020;34(2):333-339. doi:10.1111/jdv.15875
3. Soriano LF, Chowdhury MMU, Cooper SM, et al. Current prevalence and relevance of positive patch test reactions to cosmetic and non-cosmetic isothiazolinones in the UK. *Br J Dermatol*. 2021;185(1):223-225. doi:10.1111/bjd.19898
4. Havmose M, Thyssen JP, Zachariae C, Menné T, Johansen JD. The epidemic of contact allergy to methylisothiazolinone-an analysis of Danish consecutive patients patch tested between 2005 and 2019. *Contact Dermatitis*. 2021;84(4):254-262. doi:10.1111/cod.13717
5. Schwensen JF, Menné T, Andersen KE, Sommerlund M, Johansen JD. Occupations at risk of developing contact allergy to isothiazolinones in Danish contact dermatitis patients: results from a Danish multicentre study (2009-2012). *Contact Dermatitis*. 2014;71(5):295-302. doi:10.1111/cod.12286
6. Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis*. 2013;69(4):231-238. doi:10.1111/cod.12123
7. Wilkinson M, Gallo R, Goossens A, et al. A proposal to create an extension to the European baseline series. *Contact Dermatitis*. 2018;78(2):101-108. doi:10.1111/cod.12918
8. Wilkinson M, Goncalo M, Aerts O, et al. The European baseline series and recommended additions: 2019. *Contact Dermatitis*. 2019;80(1):1-4. doi:10.1111/cod.13155
9. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. *Contact Dermatitis*. 2015;73(4):195-221. doi:10.1111/cod.12432
10. Hernández-Fernández CP, Mercader-García P, Silvestre Salvador JF, et al. Candidate allergens for inclusion in the Spanish standard series based on data from the Spanish Contact Dermatitis Registry. *Actas Dermosifiliogr*. 2021;112(9):798-805. doi:10.1016/j.adengl.2021.07.013
11. Magdaleno-Tapial J, Valenzuela-Oñate C, Ortiz-Salvador JM, et al. Contact allergy to isothiazolinones epidemic: current situation. *Contact Dermatitis*. 2020;82(2):83-86. doi:10.1111/cod.13396
12. Herman A, Aerts O, Jacobs MC, et al. Evolution of methylisothiazolinone sensitization: a Belgian multicentric study from 2014 to 2019. *Contact Dermatitis*. 2021;85(6):643-649. doi:10.1111/cod.13956
13. King N, Latheef F, Wilkinson M. Trends in preservative allergy: benzisothiazolinone emerges from the pack. *Contact Dermatitis*. 2021;85(6):637-642. doi:10.1111/cod.13968
14. Uter W, Amario-Hita JC, Balato A, et al. European surveillance system on contact allergies (ESSCA): results with the European baseline series, 2013/14. *J Eur Acad Dermatol Venereol*. 2017;31(9):1516-1525. doi:10.1111/jdv.14423
15. Isaksson M, Ale I, Andersen KE, et al. Multicenter patch testing with methylisothiazolinone and methylchloroisothiazolinone/-methylisothiazolinone within the International Contact Dermatitis Research Group. *Dermatitis*. 2017;28(3):210-214. doi:10.1097/der.0000000000000272
16. Schwensen JF, Uter W, Bruze M, et al. The epidemic of methylisothiazolinone: a European prospective study. *Contact Dermatitis*. 2017;76(5):272-279. doi:10.1111/cod.12733
17. Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy–growing epidemic. *Contact Dermatitis*. 2013;69(5):271-275. doi:10.1111/cod.12149
18. Holden C, Sabroe R. The frequency of contact allergy to four isothiazolinones in a general patch-test population, including a pilot study to determine the optimum patch-test concentrations of benzisothiazolinone and octylisothiazolinone. ESCD abstracts: free communications. *Contact Dermatitis*. 2016;75(1):37-59. doi:10.1111/cod.12636
19. Urwin R, Craig S, Latheef F, Wilkinson M. Methylisothiazolinone: the epidemic is declining - but not gone. *Contact Dermatitis*. 2017;76(5):301-302. doi:10.1111/cod.12750
20. DeKoven JG, Silverberg JI, Warshaw EM, et al. North American contact dermatitis group patch test results: 2017–2018. *Dermatitis*. 2021;32(2):111-123. doi:10.1097/der.0000000000000729
21. Scientific Committee on Consumer Safety (SCCS), European Commission. Opinion on methylisothiazolinone (P94) submission III (sensitization only), 2013. Accessed March 26, 2022. https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_178.pdf.

16000536, 2023, 3, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/cod.14251 by Universidad del Pais Vasco, Wiley Online Library on [04/05/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

22. European Commission. Regulation (EC) no. 1003/2014 of 18 September 2014. *Off J Eur Union*. 2014;L282:1-4. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R1003&from=FR
23. European Commission. Regulation (EC) no. 2016/1198 of 22 July 2016 amending Annex V to regulations (EC) No. 1223/2009 of the European parliament and of the Council on cosmetic products. *Off J Eur Union*. 2016;L198:10 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016R1198&qid=1627208847259
24. European Commission. Regulation (EC) no. 2017/1124 of 6 July 2017 amending Annex V to regulations (EC.) No. 1223/2009 of the European parliament and of the Council on cosmetic products. *Off J Eur Union*. 2017;L174:16 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R1224&qid=1627208847259
25. Marrero-Alemán G, Saavedra Santana P, Liuti F, Hernández N, López-Jiménez E, Borrego L. The role of cleaning products in epidemic allergic contact dermatitis to methylchloroisothiazolinone/methylisothiazolinone. *Dermatitis*. 2018;29(2):77-80. doi:10.1097/der.0000000000000352
26. Uter W, Wilkinson SM, Aerts O, et al. European patch test results with audit allergens as candidates for inclusion in the European baseline series, 2019/20: joint results of the ESSCA(a) and the EBS(B) working groups of the ESCD, and the GEIDAC(C). *Contact Dermatitis*. 2022;86:379-389. doi:10.1111/cod.14059
27. European Commission. Regulation (EC) no. 1223/2009 of 30 November 2009 on cosmetic products. *Off J Eur Union*. 2009;L342:59 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32009R1223&qid=1627208847259
28. Marrero-Alemán G, Borrego L, Antuña AG, Macías Montes A, Pérez LO. Isothiazolinones in cleaning products: analysis with liquid chromatography tandem mass spectrometry of samples from sensitized patients and market. *Contact Dermatitis*. 2020;82(2):94-100. doi:10.1111/cod.13430
29. Isaksson M, Gruvberger B, Bruze M. Patch testing with serial dilutions of various isothiazolinones in patients hypersensitive to methylchloroisothiazolinone/methylisothiazolinone. *Contact Dermatitis*. 2014;70(5):270-275. doi:10.1111/cod.12184
30. Geier J, Lessmann H, Schnuch A, Uter W. Concomitant reactivity to methylisothiazolinone, benzisothiazolinone, and octylisothiazolinone. International network of departments of dermatology data, 2009-2013. *Contact Dermatitis*. 2015;72(5):337-339. doi:10.1111/cod.12347
31. Aalto-Korte K, Suuronen K. Patterns of concomitant allergic reactions in patients suggest cross-sensitization between octylisothiazolinone and methylisothiazolinone. *Contact Dermatitis*. 2017;77(6):385-389. doi:10.1111/cod.12855
32. Craig S, Urwin R, Latheef F, Wilkinson M. Patch test clinic experience of potential cross-reactivity of isothiazolinones. *Contact Dermatitis*. 2017;76(5):299-300. doi:10.1111/cod.12741
33. Schwensen JF, Menné Bonefeld C, Zachariae C, et al. Cross-reactivity between methylisothiazolinone, octylisothiazolinone and benzisothiazolinone using a modified local lymph node assay. *Br J Dermatol*. 2017;176(1):176-183. doi:10.1111/bjd.14825
34. Russo JP, Aerts O. In vivo demonstration of immunologic cross-reactivity to octylisothiazolinone in patients primarily and strongly sensitized to methylisothiazolinone. *Contact Dermatitis*. 2020;83(5):391-397. doi:10.1111/cod.13661

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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