

Methylisothiazolinone and Isothiazolinone Allergy

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PRACTICE POINTS

- Methylisothiazolinone (MI) is a preservative found in water-based personal care products and is a common allergen in patch-tested populations.
- Methylisothiazolinone also has been identified in household products, industrial chemicals, paint, adhesives, and other unique sources.
- Benzisothiazolinone and octylisothiazolinone are structurally similar to MI, and a subset of MI-allergic patients may need to avoid them.

Methylisothiazolinone (MI) is a preservative commonly used in water-based personal care products. Increases in the allowable concentration of MI alone in these products has led to an epidemic of allergic contact dermatitis (ACD). Although personal care products are the most common source of MI contact allergy, other novel exposures include household products, industrial chemicals, paint, slime, and adhesive agents. Other isothiazolinones such as benzisothiazolinone (BIT) and octylisothiazolinone (OIT) are uncommon in personal care products but have been found in leather products, glue, industrial chemicals, paints, and cleaning products. There may be cross-reactivity between OIT and MI, and a minority of patients who are allergic to MI are cosensitized to BIT. In this article, we review MI and related isothiazolinone chemicals.

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Unless you have been living under a rock, you probably already know that the preservative methylisothiazolinone (MI) has caused an epidemic of allergic contact dermatitis (ACD) and was named the 2013 American Contact Dermatitis Society Allergen of the Year.¹ Methylisothiazolinone is not new on the market, but its solo use as a preservative is relatively new. In this article,

we review the emergence of MI as a common allergen, discuss North American MI patch test results, and describe common and uncommon sources of MI exposure. We also explore the related isothiazolinones, benzisothiazolinone (BIT) and octylisothiazolinone (OIT).

Background

Methylchloroisothiazolinone (MCI) and MI have been utilized as a preservative in a 3:1 ratio since the 1980s. In 2005, MI was first used alone as a preservative in personal care products in concentrations of up to 100 ppm, which represented a 25-fold increase in exposure to MI in personal care products and thus unleashed an epidemic of ACD.¹ In the 2015 to 2016 cycle of the North American Contact Dermatitis Group (NACDG) patch testing results, MI was found to be positive in 13.4% of patch tested patients (N=5597) and also had the highest significance-prevalence index number, a calculation that represents the relevance of positive reactions in relationship to prevalence.² In Europe, MI is banned in leave-on products and is allowed in rinse-off products in concentrations of up to 15 ppm. In the United States, the Cosmetic Ingredient Review panel concluded that MI is safe at a maximum concentration up to 100 ppm in rinse-off products and safe in leave-on products when formulated to be nonsensitizing, which may be determined based on a quantitative risk assessment.³

It is recommended that MI be patch tested at a concentration of 2000 ppm (0.2% aqueous).⁴ Testing at lower concentrations may result in missed positives. In addition, it should be noted that MCI/MI is present in the T.R.U.E. Test (SmartPractice), but MI alone is not.

Sources of MI Exposure

The first few case reports of MI contact allergy were associated with occupational exposures. In 2004, Isaksson et al⁵ reported 2 cases of MI allergy following

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exposure to wallpaper glue and a chemical burn from a biocide, respectively. Soon after, Thyssen et al⁶ reported 4 occupational cases of MI allergy at a paint manufacturing plant.

An early case series of MI contact allergy associated with personal care products was published in 2010 in which the authors described adults with ACD from wet wipes and a makeup remover that contained MI.⁷ A more recent report indicated that MI is now an infrequent ingredient in wet wipes but is still found in a wide variety of household and personal care products.⁸ A 2017 query of the American Contact Dermatitis Society's Contact Allergy Management Program (CAMP) database revealed that 12.9% of all products contained MI. Furthermore, CAMP data revealed that MI was the most commonly found preservative in both hair care and household products.⁹ An additional CAMP database study revealed that 53% of shampoos and 45% of conditioners contained MI, and it also was commonly found in hair dyes, soaps and cleansers, hand cleaners and sanitizers, vaginal hygiene products, sunscreens, and moisturizers.¹⁰

Household products represent an important source of MI exposure. A chemical analysis of water-based paints identified the presence of isothiazolinones. Contact allergy from isothiazolinones in paint can present as either direct or airborne-pattern contact dermatitis.¹¹ Sodium bisulfite has been used to inactivate MCI/MI in wall paint and could be utilized in severe cases of airborne contact dermatitis.¹² Off-gassing may take up to 5.5 weeks before the paint cures and the isothiazolinone level decreases.¹³ A 2016 analysis of household products in the CAMP database revealed that MI commonly was found in dishwashing soap (64%), followed by household cleaners (47%), laundry softeners/additives (30%), surface disinfectants (27%), and laundry detergents (13%).¹⁰ Because certain chemical ingredients are not always listed on household product labels, patients with MI contact allergy may be at higher risk for unanticipated exposure to this allergen.

Dear reader, we know that you know all of this. We know that you have been watching the MI epidemic and have followed its every turn. But something that may be new to you are the unique MI exposures identified over the last several years.

In 2017, MI was identified in the glue used to affix 3 layers of the upper portion of a shoe.¹⁴ In addition, a recent chemical analysis of US consumer adhesives confirmed the presence of isothiazolinones in 50% (19/38) of products; 44.7% (17/38) specifically contained MI.¹⁵ Slime, the sticky play substance that children concoct out of household materials, has caused ACD, and not surprisingly, MI has been identified as a culprit allergen. In one case report, contact allergy was caused by MI present in a slime mixture made up of laundry detergent, dish soap, shampoo, and hand cream.¹⁶ In another case series, 3 children with MI contact allergy had played with slime that included dishwashing liquid, which contained MI,

along with polyvinyl acetate glue and liquid soap components.¹⁷ Another case report documented slime made from MI-containing school glue as the source of ACD.¹⁸ Isothiazolinones also have been identified as causative allergens in "noise putty," another homemade play item.¹⁹

Additionally, there has been a report of contact allergy to MI in a designer eyeglass frame.²⁰ There also have been several documented cases of ACD to MCI/MI aerosolized from water used during ironing.^{21,22}

There also have been several reports of photoaggravated ACD and possible photoallergic contact dermatitis from MI.^{23,24} In such cases, patients also may have transient photosensitivity even when MI exposure is discontinued; therefore, MI should be considered for inclusion in photopatch test panels when relevant.

Methylisothiazolinone contact allergy also should be considered for products that do not list MI on the label, which presents another potential exposure. In products that do not list MI as an ingredient on the label, its presence may be due to inclusion of the preservative in raw materials used in production. For example, a patient who reacted to a facial mask gel had a positive patch test reaction to MI, the facial mask gel, and sodium hyaluronate, the raw ingredient in the gel. Further analysis revealed that MI was unexpectedly present in the sodium hyaluronate.²⁵ Similar scenarios have been reported in association with facial wet wipes,²⁶ an exfoliating facial sponge,²⁷ and a polyurethane sponge from a wound vacuum pump,²⁸ among others.

Other Isothiazolinones

Other isothiazolinones also are known to cause ACD, albeit less commonly than MI. Benzisothiazolinone has been identified in glues, cleaning agents, paints, and industrial chemicals; unlike MI, the presence of BIT is infrequent in personal care products.^{15,29} This chemical is not commonly included in patch test screening series in the United States but is currently present in the NACDG screening series as BIT 0.1% in petrolatum.

Octylisothiazolinone (OIT) has been reported in leather furniture, belts, shoes, and watchbands, as well as industrial chemicals.^{30,31} Similar to BIT, OIT is not commonly tested in screening series in the United States; the NACDG tests this chemical as OIT 0.025% in petrolatum.

The cross-reaction patterns between the isothiazolinones remain uncertain. A study in mice supported cross-reactivity between MI, OIT, and BIT³²; however, several clinical epidemiologic studies suggested that although there is evidence that there may be cross-reactivity between OIT and MI, concomitant positive BIT and MI reactions more likely represent cosensitization.³³⁻³⁵

Final Interpretation

Methylisothiazolinone continues to have high positive patch test rates in North American patch test populations and should be tested at a concentration of 2000 ppm (0.2% aqueous). Methylisothiazolinone may now be rare

in wet wipes, but it is still present in numerous personal care products including hair care products, liquid soaps, and cleaning products. Novel exposures to MI include paint, slime, and glues. It also is important to remember that MI can cause photoaggravated or photoallergic contact dermatitis and might be a worthy addition to photopatch test trays. Finally, keep a look out for BIT and OIT, which may be present in industrial chemicals, glues, paints, cleaning products, and leather items.

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