UPDATE ON ISOTHIAZOLINONES

Isothiazolinones, including methylisothiazolinone, methylchloroisothiazolinone, and benzisothiazolinone, are common synthetic biocides/preservatives found in many skin and hair products as well as industrial products.

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Allergic contact dermatitis (ACD) is a socially and economically significant condition. It is estimated to affect more than 72 million Americans each year.[1] In addition to physical morbidity, ACD can have a significant impact on quality of life leading to missed work days and lost income, inability to enjoy leisure activities, and loss of sleep. Often, numerous doctor visits and medications result in significant expenditures for the patient before the underlying cause is discovered. In 2004, the total direct cost (eg, prescription drugs, office visits, etc.) associated with treatment for contact dermatitis was 1.6 billion.[1]

Patch testing is the gold standard for ACD diagnosis.[2] Once the offending allergen is identified, avoidance is critical for sustained remission. However, because ACD has a delayed-onset (time between sensitization or exposure and elicitation of the dermatitis) it may be difficult to make the association. Therefore, when ACD is suspected, a patient-centered educational approach focusing on pathophysiology, risk of recurrence, and avoidance strategies should be initiated to break the ACD cycle.

Experimental design studies indicate that antigenic potency in addition to the concentration of antigen are important factors in the determination of whether an exposure to an antigen will result in sensitization. For weakly sensitizing allergens, exposures can occur over many years before a reaction develops; whereas for strong sensitizers, sensitization can occur more rapidly. If there is skin barrier compromise or exposure to a suprapotent antigen, even a single exposure could induce primary sensitization (eg, poison ivy). Kanerva and colleagues[3] collected clinical cases in which a single exposure had resulted in suspicion for development of ACD. Six patients with accidental occupational exposure and no previous relevant skin symptoms were patch tested to demonstrate sensitization. Methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) were found to have induced both sensitization and subsequent ACD without further exposure following a single accidental exposure.[3] The authors concluded that these allergens described must be considered strong allergens. YYet, MCI and MI are not included in the Consumer Product Safety Commission (CPSC) designated "strong allergens".[4] These designated allergens are paraphenylenediamine, orris root, epoxy resins systems containing any concentration of ethylenediamine, diethylenetriamine, and diglycidyl ethers of molecular weight less than 200, formaldehyde, and oil of bergamot. Notably, neither the FDA nor the CPSC has added any strong sensitizers to this list since 1961.

This article highlights ACD in relation to isothiazolinones, including MCI, MI, and benzisothiazolinone (BIT), which are common synthetic biocides/preservatives found in many skin and hair products as well as industrial products. Also, discussed is the historical use of isothiazolinones and the current epidemic due to the rise in usage among consumer products.

SOURCES OF EXPOSURE

The history of bathing began as a religious or ritual practice of "removing the stains of life."[5] Historically, these "stains" came from childbirth, touching the dead, murder, or contact with persons of inferior caste and disease.[5] Today, the act of bathing is to achieve good hygiene as well as for relaxation, but it also poses a potential risk of allergic reactions via exposure to many preservatives and other allergens from skincare products. MCI/MI (in a fixed 3:1 ratio) were first registered as preservatives in the United States in 1977 under the trade name Kathon CG.[5] During the 1980s, isothiazolinone preservatives became extensively used in consumer personal care and industrial products, because they are compatible with surfactants and emulsifiers and able to maintain biocidal activity over a wide pH range (pH 2-9).[5,6]

A recent search on GoodGuide, a resource for searching more than 250,000 available products on the market, listed MI to be an ingredient in 6725 consumer products,[7] while the Environmental

Table 1. EXPOSURE TO ISOTHIAZOLINONES

Consumer Products	Industrial Products
Dishwashing products	Paints
Shampoos	Inks
Household cleaners	Glues
Hair conditioners	Lacquers
Laundry detergents/softeners	Varnishes
Soaps and cleansers	Cutting oils
Air fresheners	Jet fuels
Hand sanitizers	Pesticides
Baby wipes	Paper manufacturing
Vaginal products	Ultrasound gel
Sanitary napkin adhesives	
Sunscreens	
Moisturizers	
Cosmetics	
Pharmaceuticals	
Children's crafting supplies	

Working Group's skin deep database has 3234 cosmetic skincare products listed to contain MI as an ingredient.[8] This is a substantial increase from previous reports estimating that the use of MI nearly doubled between 2007 (1125 products) and 2010 (2408 products).[9]

In 2016, Scheman and Severson[10] analyzed 2013 data from the American Contact Dermatitis Society's (ACDS) Contact Allergen Management Program (CAMP). For the study, 4660 consumer products were evaluated by category and MI was found in dishwashing products (64%), shampoos (53%), household cleaners (47%), hair conditioners (45%), hair dyes (43%), laundry additives/softeners (30%), soaps/cleansers (29%), and surface disinfectants (27%).[10] Nearly 100% (except 1 product) contained MI (without MCI) in household cleaning, dishwashing, and laundry products. Although a small overall percentage of makeup products (<5%) did contain MI, when it did, it was always without MCI. Other product categories that contained MI (without MCI) in high percentage included moisturizers (82%), shaving products (78%), sunscreens (71%), anti-aging products (67%), hairstyling products (56%), soaps and cleansers (30%), and hair dyes (20%).[10] It is important to note that products that are marketed as "hypoallergenic," "gentle," "sensitive," "organic," "100% natural," and "dermatologist-recommended," can contain MI. One study surveyed 2 major retail stores of pediatric skincare products and found that 30 of 152 products (19.7%) contained MI.[11] Significant allergic reactions to MI found in baby wipes has been documented.[11,12] One pediatric review of ACD ranked MCI/MI No. 8 (2.61%) among its top 10 allergens found in personal hygiene products across 5 studies.[13]

The industrial and occupational settings are another source of isothiazolinone exposure. (**Table 1**). These preservatives can be found in a wide range of products such as hand care and surface-wipes, children's craft paints, beauty products, water-based paints, latex paints, lacquers, printer ink, cutting fluid, coolants, pesticides, and ultrasound gel.[14] Airborne contact dermatitis has been recognized in people using water-based paint which may contain MCI, MI, or BIT and has been associated with dyspnea, as well as facial dermatitis.[14] Unlike MCI/MI, BIT has not been deemed safe to use as a preservative in cosmetic products.[15] Notably, a multicenter study of paints from 5 European countries reported that BIT was found in 95.8%, MI in 93.0%, and MCI in 23.9% of paints, and the use of isothiazolinones in paints is less regulated.[15]

The Environmental Protection Agency's Reregistration Eligibility Decision (R.E.D)[16] (containing the evaluation of chemicals, conclusions of potential human health and environmental risks, and decisions and conditions under which the use of products are eligible) on MI states that "the agency determined that methylisothiazolinone is highly to very highly toxic" in mammalian studies, yet the agency also concluded that "the risks to workers in most situations are not of concern and short-term risks of corrosivity can be adequately managed, as necessary. The agency further believes risks from secondary occupational exposures, residential exposures, and postapplication exposures are comparatively less and also not of concern."[16] To mitigate the potential inhalation and dermal toxicity risk to workers, the agency requires the use of personal protective equipment.[16] In certain instances, it has been necessary for painted walls to be treated with inorganic sulfur salt to inactivate the isothiazolinone component.[5] Additionally, the R.E.D. environmental assessment states that MI is also "highly toxic to freshwater and estuarine/marine organism" and that "quantitative risk assessment has not been conducted."[16]

ISOTHIAZOLINONES SENSITIZATION CAUSES AN EPIDEMIC

The first cases of ACD to MCI/MI were reported in 1985 from cosmetic use, marking the beginning of the first epidemic to isothiazolinones.[17] In 1988, de Groot and colleagues[18] reported on the significant ingredients responsible for allergy to cosmetics. In the 119 patients with cosmetic-related contact dermatitis, 56.3% were associated with skincare products. They also found that preservatives were most frequently implicated (32.0%), followed by fragrances (26.5%) and emulsifiers (14.3%). The most significant cosmetic allergen was Kathon CG, (a preservative system containing, as active ingredients, a mixture of MCI and MI) reacting in 33 patients (27.7%).[18] Within 6 months de Groot and Herxheimer[19] published another study on a significant number of the cases of Kathon CG (MCI/MI) allergy caused by products of the "leave-on" variety (eg, moisturizing creams) and stated that an epidemic had begun. Furthermore, they asserted that the use of isothiazolinone preservative in these types of products should be abandoned. They emphasized that this continuing epidemic of ACD due to this preservative might have been prevented if a more critical evaluation of

its sensitizing potential before marketing was done. The researchers concluded, "New chemicals should undergo extensive toxicological evaluation before their use in cosmetics is allowed. Ingredient labeling should be made a legal requirement."[19]

Furthermore, in 1996, Connor and colleagues[20] reported MCI/MI to be a potent sensitizer and bacterial mutagen. Three of the 5 evaluated products that had listed MCI/MI were found to be direct acting mutagens, while the remaining 2 products were considerably more toxic than the other products and could not be evaluated for mutagenicity. Based on these findings and the reported skin sensitization by Kathon CG, the researchers recommended that additional testing be done to assure the safety of products containing Kathon CG.[20]

Year after year, new associations and risks have been revealed related to isothiazolinone exposure: from airborne associated contact dermatitis, first reported in 1997, to MCI/MI to skin exposure leading to severe chemical burns.[21,22] More than 250 articles to date in PubMed have spoken to the health risks associated with MCI/MI in shampoos, conditioners, skincare lotions, and other cosmetic products.

THE SECOND ISOTHIAZOLINONE EPIDEMIC

"We are in the midst of an outbreak of allergy to a preservative [methylisothiazolinone] which we have not seen before in terms of scale in our lifetime…. I would ask the cosmetic industry not to wait for legislation but to…address the problem before the situation gets worse," stated John McFadden, FRCP, consultant dermatologist at St. John's Institution of Dermatology in London, in a 2013 article in *The Telegraph*.[23]

Because MCI was believed to be a more potent allergen than MI,[24] MI was approved for use as an individual preservative in industrial products in 2000 and in cosmetics in 2005.[15,25] Comparing pooled prevalence rates from the previous decade (2001-2010) to the 2011-2012 data, the North American Contact Dermatitis Group (NACDG), a self-elected research group based in Canada and the United States, reported statistically higher positive reaction rates to MCI/MI (doubling to 5.0%) (**Figure**). The Significance-Prevalence Index Number (SPIN) number is a rated positivity score weighted by relevance. For MCI/MI, the SPIN number was 273 (rank No.4) for 2011-2012. This is a substantial jump in ranking from the No. 16 allergen (SPIN 128) in 2009-2010.[26,27] In their most recent data, the NACDG suggested that this increase in SPIN number for MCI/MI was likely due to the impact of MI sensitization and that their data points to the "beginning of an epidemic" in North America.[27,28] Of note, the 2013-2014 NACDG screening series now includes methylisothiazolinone alone, at a concentration of 0.2% (2000 parts per million [ppm]).

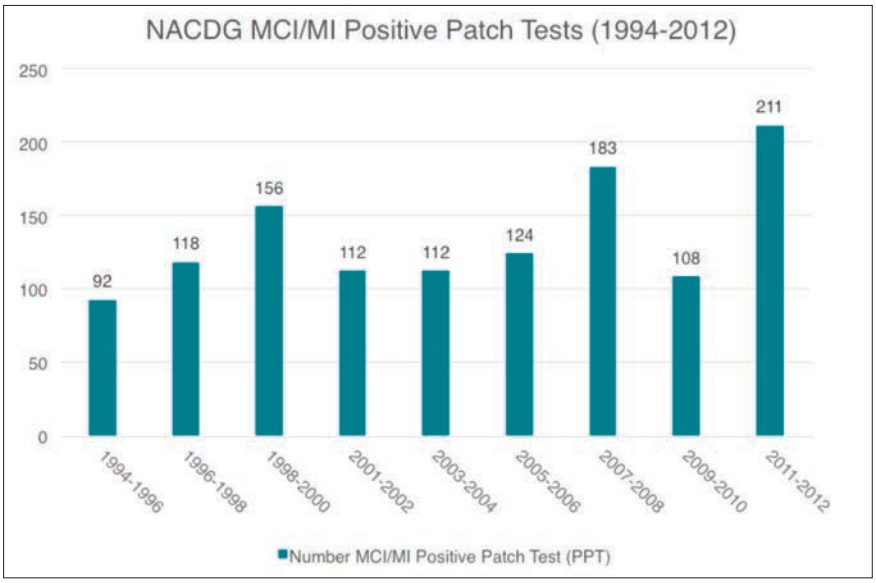

Figure. North American Contact Dermatitis Group methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) positive patch tests results 1994-2012. Doubling (1994 vs 2012) of positive reactions to MCI/MI is consistent with the epidemic of allergy to this preservative seen in Europe and does not account for those reactions to MI alone that may be missed by testing with this allergen combination and the likely culprit for this increase.[27]

A 2012-2014 retrospective review by the Cleveland Clinic for patients suspected of ACD reported a patch test sensitivity in 2014 to MI only (6.8%), MCI/MI only (0.9%), and both MCI/MI and MI (4.7%). They also reported that MI sensitivity increased from 2.5% in 2012 to 6.8% in 2014. Notably, the investigators increased their MI patch test concentration from 200 ppm to 2000 ppm in 2013, attributing their rise in prevalence rates to increased detection.[29] Gameiro and colleagues[28] reported in their retrospective review from the university hospital at Coimbra, Portugal, that their prevalence rate of MCI/MI rose from <1% in 2005 to 3.28% in 2008. After additional testing to isolated MI was added in 2012, sensitization rates doubled from 5.15% to 10.9% by the next year.

The current and unprecedented increase in contact allergy to MI in Europe led Schwensen and colleagues[30] to evaluate temporal trends of preservative contact allergy used in cosmetic products to address failures in risk assessment and risk management. The researchers concluded that the rapidly increased overall burden of skin diseases caused by preservatives was attributed to the introduction of new preservatives in Europe with inadequate premarket risk assessment.

REGULATORY ISSUES

In the 1980s, in response to the newly recognized isothiazolinone allergens, expert panels from the United States and European Union recommended more strict concentrations in cosmetic products. The Scientific Committee on Consumer Safety (SCCS) recommended to the Cosmetic Directive of the European Union to limit the concentration of MCI/MI to 15 ppm in leave-on and rinse-off products, while the US Cosmetic Ingredient Review recommend a lower concentration limit of 7.5 ppm in leave-on cosmetic products.[31,32] Despite these restrictions made on MCI/MI concentrations in cosmetics, by the 2000s MCI/MI sensitization was reported to be as high as 4% by the European

Table 2. COMMON PATCH TESTING SCREENING SERIES OF ISOTHIAZOLINONES SUBSTRATES

Type of Patch Test	MCI/MI Concentration	MI Concentration
T.R.U.E test	4 mcg/cm^2 in Povidone MCI 2.4 mcg/MI 0.8 mcg	Not included
NACDG series	100 ppm (MCI 75 ppm/MI 25 ppm)	2000 ppm
ACDS core allergen series	100 ppm (MCI 75 ppm/MI 25 ppm)	2000 ppm
European baseline series S-1000	200 ppm MCI 150 ppm/MI 50 ppm	2000 ppm

Abbreviations: ACDS, American Contact Dermatitis Society; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; ppm, parts per million; NACDG, North American Contact Dermatitis Group.

Surveillance System on Contact Allergy Network and 3.6% by the NACDG.[33,34]

In 2005, the SCCS in the European Union and the Cosmetic Ingredient Review in the United States reported that 100 ppm of MI alone was a safe concentration for its use in cosmetic products.[31,32] This resulted in a more than 25 time increase in allowable concentration of MI in rinse-off products (formerly 3.75 ppm) and a more than 50 time increase for leave-on products (formerly 1.875 ppm). Of note, no regulatory amount limitations were set on industrial products.

In 2013, MI was named allergen of the year by the ACDS due to its growing recognition as a sensitizer and its increased use in cosmetics as a preservative.[9] Margarida Goncalo, president of the European Society of Contact Dermatitis, stated in a letter to the European Commission, "This new epidemic of allergic contact dermatitis from isothiazolinones is causing harm to European citizens….Urgent action is required."[23] In 2013, the SCCS recommended to the European Commission to ban MI in all leave-on body products as they found that "for leave-on cosmetic products (including 'wet wipes'), no safe concentrations of MI for induction of contact allergy or elicitation have been adequately demonstrated."[31] Following this recommendation, the European cosmetic industry voluntarily agreed to remove MI from leave-on skin products (including wet-wipes). The SCCS also concluded that concentrations of up to 15 ppm were safe for use in rinse-off products.

Regulation in the United States has yet to follow. In 2013, The Cosmetic Ingredient Review expert panel re-examined their 100 ppm concentration limit placed on MI in leave-on and rinse-off products. They have maintained their opinion that "MI is safe for use in rinse-off cosmetic products at concentrations up to 100 ppm and safe in leave-on cosmetic products when they are formulated to be nonsensitizing, which may be determined based on a quantitative risk assessment."[32]

Currently, FDA regulations mandate cosmetic products to label only the net quantity of all items—such as the weight of the whole moisturizer bottle. Although a list of ingredients from the most frequent to the least frequent appears on the product label, declaring actual amounts of each ingredient is not required. Moreover, products used solely at professional establishments not sold for retail use, as well as free samples do not require ingredient declarations as these do not fall under the Fair Packaging and Labeling Act. These sample products are not required to list any ingredient declarations at all.[35]

On April 20, 2015, Sen Dianne Feinstein (D, California) introduced a bill that aims to address the lack of cosmetic product regulation. Specifically, S 1014 focuses on amending the FDA labeling policies to ensure cosmetic labels "include the amounts of a cosmetic's ingredients."[36] The bill also attempts to address safety by limiting the sales of cosmetics with any "ingredient that is not safe, not safe under the recommended conditions of use, or not safe in the amount present in the cosmetic." Moreover, it would require cosmetic companies to "report to the FDA any serious adverse health event associated with their cosmetics."

Bill S 1014 was referred to the committee on Health, Education, Labor and Pensions and will need to be passed by the Senate, House and President to be implemented. MedWatch is the FDA's program for reporting serious reactions, product quality problems, therapeutic inequivalence/failure, and product use errors with human medical products, including cosmetics.[37] The MedWatch online reporting form can be accessed at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home. Consumers may also submit voluntary adverse event reports by calling 800-FDA-1088.

These consumer filed reports generate a Manufacturer and User Facility Device Experience (MAUDE). The MAUDE database houses medical device reports submitted to the FDA by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as health care professionals, patients, and consumers.[38] A review of available MAUDE data on April 14, 2016 revealed that only 10 reports had been filed to date: 3 on methylisothiazolinone, 4 on methylchloroisothiazolinone, and 3 on isothiazolinone. The Dermatitis Academy is tracking these MAUDE reports on the FDA website on http://dermatitisacademy.com/methylisothiazolinone-page/.

Given the current medical evidence of an epidemic being reported from US patch test tertiary care centers, this marks a significant underreporting by consumers.

PATCH TESTING AND AVOIDANCE

Critical work by the NACDG has been performed in patch testing.[39] From 1985 to 1987, members of the NACDG tested more than 1100 patients with MCI/MI at a concentration of 100 ppm, and noted 13 reactions to the aqueous and 10 to the petrolatum-based materials, deeming around half the reactions as clinically relevant. This work supported testing MCI/MI mix at a 100 ppm concentration.[39]

Diagnostic accuracy and technique were further evaluated by Stejskal and colleagues[40] utilizing a lymphocyte transformation (proliferation) test (LTT) for isothiazolinones. The researchers detected memory cells in the patients' blood confirming immunologic reaction (activa-

tion) to the inducing agent. Furthermore, to establish clinical relevance of the LTT results, the investigators had 12 patients who had been positive to MCI on patch testing undergo "use test" (self-application of a lotion containing 15 ppm MCI in the same test site) for at least 7 days or until skin reaction occurred. Four of 5 (80%) of LTT-positive patients were use-test-positive suggesting a value of use test and the LTT in detecting patient's allergens.[40]

Patch testing remains the gold standard to confirm ACD. However, some studies have shown that 33% to 60% of patients that are MI sensitive may be missed when testing using only the combined MCI/MI preparation.[9] The lower concentrations of MCI/MI or by failure to test MI alone may lead to a potential false negative result. Subsequent testing at a higher concentration (ie, 2000 ppm of MI), may be needed if still suspected to be the underlying cause. Additionally, some reviews have suggested that more studies are needed to optimize patch test concentrations of MI to effectively detect a true positive patch test without inducing sensitization.[9] **Table 2** shows a list of common patch test screening series available for use.

PEARLS OF TREATMENT: EVERY DOSE COUNTS

In refractory cases of dermatitis involving the hands, facial, and perianal regions, ACD to isothiozolinones should be considered. Patch testing may be the only way to elicit the underlying cause. A thorough history of personal and household products is essential to eliminate products containing isothiazolinones. Exposure can also come just as easily from public environments and should also be considered. For example, air fresheners in public bathrooms can induce a systematized response in a sensitized person.

Education about preservatives as a potential cause of ACD is vital in order for consumers to make informed decisions about the products they buy, and to break the cycle of ACD. Additionally, it is important for consumers to be aware that products labeled as hypoallergenic or dermatologist-recommended may still contain common allergens.

Exposure to a contact allergen can be for days to years before subsequent sensitization occurs and ACD is clinically apparent. With every exposure, there is the possibility that the immune system reaches a threshold and subsequent exposure results in eliciting a cutaneous response.[41] Repeated avoidance is required to stay in remission. Avoiding specific allergens in personal care products can be a difficult task, however, there are programs available that make it easier. The American Contact Dermatitis Society's (ACDS) CAMP provides a guideline for products devoid of known allergens. The database contains a comprehensive ingredient list of thousands of common consumer products in most major product categories and is updated every 18 months.[10,42] The Contact Allergen Replacement Database[43] will also produce a list of products free of specific allergens that a provider can give to a patient for their use. These programs can also exclude cross-reactors. Education for patients can also be accessed through online programs via the Dermatitis Academy and the ACDS (**Table 3**). ■

Table 3. RESOURCE GUIDE

American Contact Dermatitis Society Contact Allergen Management Program www.contactderm.org
Contact Allergen Replacement Database www.allergyfreeskin.com
Consumer Support Groups Allergy to Isothiazolinones www.facebook.com/Allergy-to-Isothiazolinone-Methylisothiazolinone-and-Benzisothiazolinone-307128722674171/ Methylisothiazolinone Victims Public Group www.facebook.com/groups/527024000762338/
Dermatitis Academy www.dermatitisacademy.com
Environmental Working Group www.ewg.org/skindeep
GoodGuide www.goodguide.com

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