Risks of skin sensitization from contact with mixed isothiazolinones (CMI/MI)

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The mixture of 5-chloro-2-methyl-4-isothiazolinone (CMI, 26172-55-4) and 2-methylisothiazolinone (MI, 2682-20-4) in a 3:1 ratio (CMI/MI) is a preservative that frequently induces allergic reactions in users of cosmetics and skin care products. It is also used in art materials: individuals who are sensitive to CMI/MI may react adversely to art materials containing this preservative. Assessments of the relationship between induction or elicitation of allergic responses are quantitatively related to the amount of preservative that comes into contact with the skin per unit area except when the skin contact area is <0.5 cm² where allergic risk is related to the percentage of the allergen in the art material. A detailed discussion of this relationship is found in the accompanying paper, "Quantitative Risk Assessment of Skin Sensitizers and Irritants."

Acceptable content levels of CMI/MI have been set in toys under the EU’s EN71.9 regulations at 15 ppm. Safe levels of CMI/MI in products to limit the risk of induction of an allergic response to this preservative mix have been determined both in humans through use and repeat patch tests and in animal models. Basketter et al (1999) used human repeat insult patch testing (HRIPT) to test the sensitization potential of CMI: none of 175 subjects became sensitized to a 10 ppm aqueous solution, equivalent to an exposure of 1.25 mcg/cm² of CMI. For MI, the HRIPT NOEL was found to be 300 ppm (17 mcg/cm²) in one test round and 500 ppm in a 2nd round (SCCNFP, 2003). Cardin et al (1986) used HRIPT of various prototype skin care products containing CMI/MI to address the sensitization potential of this preservative. No sensitization was seen at concentrations of 5, 6 or 10 ppm CMI/MI but 1/175 subjects exposed to 12.5 ppm was sensitized. Two different application methods were used. In 5 test laboratories, 0.5 ml of product was applied to 3.5 cm² pads while in the remaining laboratories 0.3 ml of product was applied to 3.6 cm² pads such that at the NOEL test concentration one group of subjects did not react to 1.4 mcg/cm² of CMI/MI and the 2nd group did not react to 0.83 mcg/cm² CMI/MI. At the LOEL, exposures were 1.0 and 1.7 mcg/cm². The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP, 2003) has reviewed company generated and published data on CMI/MI induction testing in humans involving 2244 test subjects, as outlined in the following table, and found the NOEL exposure level in a HRIPT protocol to be 10 ppm, equivalent to an exposure to 0.83 mcg/cm²:
In the murine local lymph node assay (LLNA), induction response to an allergen is measured by increases in \([H^3]\) thymidine uptake in local lymph nodes at the application site, a measure of T lymphocyte proliferation. If there is a 3 fold or greater increase in draining lymph node proliferation compared with concurrent untreated controls (the EC3 value), the chemical is considered a sensitizer. The smaller the EC3 value, the greater the potency of the skin sensitizing chemical (ECVAM, 2008). After contact with CMI/MI EC3 values for the LLNA range from 1.2-2.5 mcg/cm\(^2\) (Gerberick et al, 2001; Schneider & Akkan, 2004; Warbrick et al, 1999). Based on LLNA results, the European Centre for the Validation of Alternative Methods (ECVAM, 2008) considers CMI to be a potent sensitizer.

Exposures to CMI/MI in cosmetics and skin care products have been associated with a prevalence of allergy to this preservative of 0.58% in a large EU clinical population of dermatitis patients (Hannuksela, 1986). Prevalence of allergies to CMI/MI in smaller tested EU populations ranged from 0.8 to 4.1% among dermatitis patients. In North America, the prevalence of allergy to CMI/MI averages about 2.5% among dermatitis patients (Thyssen et al, 2012).

When deriving an acceptable exposure level for a sensitizer based on human NOEL data, an uncertainty factor of 10 is usually applied to account for interindividual differences, such as atopic status and skin injury or dermatitis, that might make exposed individuals more likely to have an allergic response then test subjects (Felter et al, 2003). To protect against induction of sensitization to CMI/MI, the exposure level would then be limited to 0.08 mcg/cm\(^2\).

Hannuksela (1986) tested patients with documented allergies to CMI/MI on patch testing with a repeat open application test (ROAT) protocol. He found that that some patients reacted to test concentrations of CMI/MI as low as 10 ppm. He noted that use testing in patients with allergies to CMI/MI were negative when concentrations were 7 ppm (0.8 mcg/cm\(^2\)) or less except in one subject. With a use test Weaver et al (1985) found that CMI/MI-sensitized individuals could tolerate using a liquid soap, shampoo, hair conditioner and fabric softener containing 4-6 ppm CMI/MI for 6 weeks without any reactions. When individuals previously sensitized to CMI/MI were patch tested against CMI/MI, the level of exposure necessary to elicit a reaction in 10% of the population (the ED\(_{10}\)) was found to be 1.05 mcg/cm\(^2\) (Fischer et al, 2011). To protect against elicitation
of reactions to CMI/MI in sensitized individuals, it is reasonable to include a 10 fold uncertainty factor to account for individual variability on their likelihood of reacting to low level exposure to CMI/MI. Acceptable levels of CMI/MI to prevent elicitation of an allergic reaction would then be 0.08 mcg/cm², the same level needed to prevent induction of an allergy to CMI/MI.

References


