

Whilst Rome Burns: The Epidemic of Contact Allergy to Methylisothiazolinone

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On behalf of the ESCD

Preservatives, essential in our daily life, can sensitize and elicit allergic contact dermatitis (ACD). Before introduction in the market their sensitizing risk is assessed based on *in vivo* studies. However, normal exposures to preservative-containing products in the real world can cause ACD. During recent decades we recall several 'epidemic' outbreaks of ACD from newly introduced preservatives. Methylidibromo glutaronitrile was completely banned from cosmetic products as no safe use limits were determined. For methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), risk management measures were introduced and following 'safe' limits of this preservative in cosmetics in the EU (15 ppm), contact allergy to MCI/MI significantly decreased to around 2% of patch tested patients after the 90's and until recently. The sensitizing properties of MCI/MI were attributed to methylchloroisothiazolinone (MCI) whereas methylisothiazolinone (MI) was considered a weaker sensitizer, unable to sensitize individuals in concentrations below 1000 ppm (1, 2). After the year 2000, MI was introduced in industrial products (e.g., paints, inks, glues, lacquers, varnishes and cooling fluids), and due to its weaker biocide effect, using higher concentrations. Despite the first description of ACD in an occupational setting in 2004 (3), the following year MI was also allowed in cosmetics products at a maximum level of 100 ppm (Cosmetic Directive 2005/42/EC).

Several cases of occupational ACD from MI were then observed from paints (4, 5) followed by non-occupational cases in 2010 (6), mainly due to wet wipes for hygiene (baby wipes, moist tissues, moist toilet paper), hair cosmetics (shampoos), facial cosmetics (7, 8), deodorants (9) and sunscreens (10). Moreover, airborne exposure to MI caused severe cases of airborne and systemic dermatitis particularly from recently painted walls (11, 12) or from toilet cleaners (13), including a case in a 4-year-old child very probably sensitized to MI through baby wipes (11).

Accompanying the increasing number of published cases of ACD from MI, particularly since 2009, in Europe a rise in contact allergy to MCI/MI, the only isothiazolinone patch tested in the baseline series, has been observed.

In Germany, with more than 12 000 patients tested/year, positive patch tests to MCI/MI increased from 2.3% in 2009 to 3.9% in 2011 (14), similar to Leeds, UK

(increase from 0.9% to 4.9%) (15) and London (from < 3% to > 8%) (Orton D & Willis C, *Contact Dermatitis*, submitted). In Coimbra, Portugal, reactivity to MCI/MI rose from 1.5% (in 2006/7) to 2.9% and 3.6%, respectively in 2011 and 2012 (personal data). Similar figures are being observed all over Europe, with alerts particularly during late 2012 in France and Belgium at the REVIDAL, a system to collect alerts in contact dermatitis.

The rise in contact allergy to MCI/MI cannot be explained by a change in exposure to MCI/MI but is due to the increasing exposure to MI, present in concentrations very near 100 ppm both in leave-on and rinse-off cosmetics, as documented in a recent survey from Denmark (8).

MI has only recently been tested as a single allergen in the baseline series in several countries. Reactivity was around 1.5% until 2008 in Denmark (8) but values increased from 0.9% in 2006 to 1.8% in 2008 in Finland (16) and very high values were detected in 2011/12 in Leeds (4.6%) (15), London (6%), Coimbra (4.5%) and Leuven, Belgium (5.8%), with a very high percentage of relevant reactions (personal data). In Germany, although in selected patients with suspected cosmetic or occupational exposure, MI reactivity rose from 1.9% in 2009 to 4.4% in 2011, particularly in female patients (188% increase) and in patients with facial dermatitis (200%), suggesting that increase in reactivity is most probably related to cosmetic exposure (14). In the USA a similar situation seems to occur as MI was considered the allergen of the year 2013 (10).

The increasing rise in contact allergy to MI recalls the outbreak of contact allergy to methylidibromo glutaronitrile but occurring at a faster rate, particularly if we note that MI by itself has been allowed in cosmetics for only 7 years. MI needs to be included in the European baseline patch test series. Testing with MCI/MI, even if at 200 ppm, has too low a concentration of MI (50 ppm) to properly diagnose contact allergy to MI. There is no agreement on the best concentration to test MI, with commercial allergens varying between 0.02% and 0.2% in water (200–2000 ppm). The concentration of 300 ppm fails to detect almost half of the cases. Increasing to 1000 ppm is not irritating and detects more cases, and relevant ones as all patients reacted in the ROAT

with a cream containing 100 ppm, the highest allowed concentration in cosmetics (16).

The rising 'epidemic' of contact allergy to MI must be dealt as a priority by dermatologists, who need to be alert to this new allergen. A recommendation paper from the ESCD and EECDRG on the best concentration to test MI will soon be available. Of greater importance is urgent intervention by DG Sanco (Consumer Safety & Health Protection) of the European Commission. A speedy re-evaluation of the dermatological safety of MI is necessary followed by rapid risk management. The ESCD raised an alert with DG Sanco in February 2013 (although the matter had been repeatedly raised internally at DG

Sanco for over a year but not considered a priority by the risk managers) and has sent all current information to DG Sanco urging them to undertake action and assess what level(s) of MI may be safe in cosmetics, other consumer products and, as a horizontal approach, assess the need for occupational exposure control. Regrettably, the slow process of risk assessment, risk management and intervention will result in continuing harm. Urgent action is essential to control this new epidemic of allergic contact dermatitis from methylisothiazolinone in Europe.

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References

- 1 Basketter D A, Gilmour N J, Wright Z, Walters T, Boman A, Lidén C. Biocides: characterization of the allergenic hazard of methylisothiazolinone. *Cutaneous Ocul Toxicol* 2003; **22**: 187–199.
- 2 Burnett C L, Bergfeld W F, Belsito D V *et al.* Final report of the safety assessment of methylisothiazolinone. *Int J Toxicol* 2010; **29**: 187S–213S.
- 3 Isaksson M, Gruvberger B, Bruze M. Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. *Dermatitis* 2004; **15**: 201–205.
- 4 Thyssen J P, Sederberg-Olsen N, Thomsen J F, Menné T. Contact dermatitis from methylisothiazolinone in a paint factory. *Contact Dermatitis* 2006; **54**: 322–324.
- 5 Mose A P, Lundov M D, Zachariae C *et al.* Occupational contact dermatitis in painters: an analysis of patch test data from the Danish Contact Dermatitis Group. *Contact Dermatitis* 2012; **67**: 293–297.
- 6 García-Gavín J, Vansina S, Kerre S, Naert A, Goossens A. Methylisothiazolinone, an emerging allergen in cosmetics? *Contact Dermatitis* 2010; **63**: 96–101.
- 7 Lundov M D, Thyssen J P, Zachariae C, Johansen J D. Prevalence and cause of methylisothiazolinone contact allergy. *Contact Dermatitis* 2010; **63**: 164–167.
- 8 Lundov M D, Krongaard T, Menné T L, Johansen J D. Methylisothiazolinone contact allergy: a review. *Br J Dermatol* 2011; **165**: 1178–1182.
- 9 Amaro C, Santos R, Cardoso J. Contact allergy to methylisothiazolinone in a deodorant. *Contact Dermatitis* 2011; **64**: 298–299.
- 10 Castaneda-Tardana M, Zug K. Methylisothiazolinone. *Dermatitis* 2013; **24**: 2–6.
- 11 Aerts O, Cattaert N, Lambert J, Goossens A. Airborne and systemic dermatitis, mimicking atopic dermatitis, caused by methylisothiazolinone in a young child. *Contact Dermatitis* 2013; **68**: 250–251.
- 12 Lundov M D, Zachariae C, Menné T, Johansen J D. Airborne exposure to preservative methylisothiazolinone causes severe allergic reactions. *BMJ* 2012; **345**: e8221.
- 13 Lundov M D, Menné T. Airborne exposure to methylchloroisothiazolinone and methylisothiazolinone from a toilet cleaner. *Contact Dermatitis* 2013; **68**: 252–253.
- 14 Geier J, Lessmann H, Schnuch A, Uter W. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis* 2012; **67**: 334–341.
- 15 Urwin R, Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new "epidemic". *Contact Dermatitis* 2013; **68**: 253–255.
- 16 Ackermann L, Aalto-Korte K, Alanko K *et al.* Contact sensitization to methylisothiazolinone in Finland—a multicentre study. *Contact Dermatitis* 2011; **64**: 49–53.