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**Facial dermatitis from undeclared methylisothiazolinone in a gel mask: is the preservation of raw materials in cosmetics a cause of concern ?**

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**Running title:** Undeclared methylisothiazolinone in a facial mask.

**Key words:** allergic contact dermatitis, case report, chemical analysis, cosmetics, facial mask, raw materials, labelling, methylisothiazolinone, sodium hyaluronate, spot test.

## Introduction

Certain ingredients added to cosmetic raw materials might theoretically still be present in finished cosmetic products without being labeled. Here, we report about a case of facial dermatitis due to a gel mask containing methylisothiazolinone (MI), which was not mentioned on the packaging. However, its presence could be confirmed and quantified by chemical analysis.

## Case report

An otherwise healthy 56-year-old female patient, who had been suffering from rosacea, consulted because of an acute, itching dermatitis of the face, i.e. erythematous, slightly swollen eyelids, and erythematous papules and infiltrated patches on both her cheeks and forehead. The dermatitis had occurred a few days following a facial treatment by a beautician who had applied Bio Balance intensive algoherbal essence gel “camomille”® (Alpaya Dermaceuticals, Istanbul, Turkey), a “moisturizing and relaxing natural facial mask”. The product had remained on her face for 15 minutes and was then washed off, and a moisturizing cream was applied.

She was patch tested with our extended Belgian standard series, a cosmetic series and with her own cosmetics, as well as those applied by the beautician. The culprit facial mask, together with 2 related facial masks (“rose” and “lavender”) from the same manufacturer, were tested semi-open. Patch tests were performed with IQ Ultra™ chambers (Chemotechnique, Vellinge, Sweden) and read according to the European Society of Contact Dermatitis recommendations (1). Readings on day (D)2 showed a reaction to MCI/MI 0.02% aq. (+), to MI 0.2% aq. (+), as well as to all three masks (++) (**Figure 1**). On D3, all tests had turned into ++ reactions. No later reactions were reported. The ingredients on the label of the mask did not mention MCI/MI nor MI, and both the distributor (Districos, Belgium) and the manufacturer denied their presence.

A first qualitative chemical analysis of the mask was performed at the department in Antwerp, using an experimental isothiazolinone test kit (Tintometer® Group, Amesbury, UK; <http://www.lovibondwater.com>), originally designed for the detection of isothiazolinones in industrial water systems, which showed the potential presence of isothiazolinones (**Figure 2; supplemental file 1**). The detailed description of the analytical method of this test is company proprietary information, but according to the manufacturer, it concerns a colorimetric determination of isothiazoline-derivatives based on a rather aspecific

blue color formation produced by reducing agents and the Folin and Ciocalteu's reagent. Briefly, 5 mL of the gel mask was dissolved in 20 mL of physiological saline and this aqueous solution was subsequently used for the spot test. Four other cosmetics, i.e. three positive controls containing MI, and one negative control free from MI that had been previously investigated by high performance liquid chromatography with ultraviolet detection (HPLC-UV)(2) were all correctly identified with regard to their MI content using this experimental detection method.

Meanwhile the manufacturer had agreed to provide us with samples of the individual ingredients of the mask (**Table 1**), which were additionally patch tested in the concentrations as present in the finished product. Only the patch test with sodium hyaluronate 0.1% aq. was clearly positive (++) on D2 and D4(**Figure 3**).

Thereupon, (more time-consuming) chemical analyses, i.e. high performance liquid chromatography with ultraviolet detection (HPLC-UV) were performed, both of the mask and the sodium hyaluronate ingredient. These investigations were performed at the Laboratory NatuRA of the University of Antwerp, using a validated method as previously described (2). The presence of MI in the facial mask (147 ppm), as well as and in the sodium hyaluronate solution (326,5 ppm) was thus confirmed. No other isothiazolinone derivatives could be detected.

## **Discussion and Conclusion**

According to the European Cosmetics Regulation all ingredients should be clearly labeled on the packaging, with some of them adhering to specific concentration limits (EU directive 1223/2009). Cosmetic products have largely contributed to the recent epidemic of MI (3), with several of them being mislabeled (2, 4), and/or were shown to contain MI in a concentration higher than previously permitted (i.e. > 100 ppm)(2, 5). The preservation of individual cosmetic ingredients with MI has previously been suggested as a possible explanation for the current observation (2), in which a qualitative test detected the presence of isothiazolinones in the mask, and further extensive chemical analyses enabled us to confirm the presence of, and to quantify MI in the mask and in the individual sodium hyaluronate raw material. This case highlights two particularities: (i) a rinse-off cosmetic (i.e. a facial mask) caused severe allergic contact dermatitis due to MI that was shown to be present in a concentration > 100 ppm, though not labeled on the packaging, and (ii) MI was

detected in a very high concentration (326.5 ppm) in one of the individual cosmetic raw materials, i.e. in the 0.1% sodium hyaluronate solution, which probably explains the presence of the high final concentration of MI (147 ppm) in the finished product.

Hidden exposure to preservatives in cosmetic and non-cosmetic products, both in occupational and non-occupational settings, has been studied before (6-9).

Despite recent changes in the EU Cosmetics Regulation, with MI being forbidden in leave-on cosmetics and its presence limited to 15 ppm in rinse-off cosmetics, this case shows that vigilance is still required. Moreover, a cosmetic manufacturer should verify the exact nature (including the preservation system or other additions) of all raw materials incorporated.

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### **Acknowledgements:**

We are grateful to the manufacturer, Alpaya Dermaceuticals, Istanbul, Turkey, for their willingness to provide us the individual ingredients of the gel mask.

### **Tables**

**Table 1: Ingredients of the facial gel mask (as provided by the cosmetic manufacturer)**

<b>Ingredient (INCI)</b>	<b>%</b>
Aqua	70,1498
Glycerin	10
Butylene glycol	6
Aloe barbadensis leaf extract	5
Anthemis nobilis flower extract	4
Hydrolyzed collagen	2
Carbomer	0.7
Triethanolamine	0.7
Phenoxyethanol	0.5
Panthenol	0.3
Allantoin	0.2
PEG-40 hydrogenated castor oil	0.2
Parfum	0.1
Sodium hyaluronate	0.1
Disodium EDTA	0.05
CI 19140	0.0002

**Figure legends**

**Fig. 1** Strong reactions (++) to semi-open tests with three facial masks on day 3.



**Fig. 2** Experimental spot test indicating the potential presence of isothiazolinones in the facial gel mask.





**Fig. 3** Strong reaction (++) to a patch test with sodium hyaluronate 0.1% aq. on D2.



**Supplemental file: The working mechanism of the experimental test for isothiazolinone derivatives in industrial water systems (as provided by its manufacturer, Tintometer® Group, Amesbury, UK; <http://www.lovibondwater.com>).**

The method is a colorimetric determination of isothiazoline (0-7.5 ppm), based on the quantitative blue color formation produced by reducing agents and the Folin and Ciocalteu's reagent.

1. In the first step of the test CDTA is added to remove copper, this has the effect of preventing interference from methylenebisthiocyanate that may be dosed into the water with isothiazolinone.
2. The second step combines two issues – a salt of molybdic acid is added in order to mask the presence of thiocyanate ion that may be present, and pentasodium phosphate is also added to remove hardness.
3. Two set of hydroxide reagents are added in the next two steps, this splits the isothiazolinone ring to form an oxidizable group.
4. Folin and Ciocalteu's reagent is added. This produces a blue color for measurement. Folin and Ciocalteu's measures reducing power.

A calibration is provided either in the form of a comparator disc or color chart.

