

The Directorate General

Maisons-Alfort, 9 February 2016

## **OPINION**

### **of the French Agency for Food, Environmental and Occupational Health & Safety**

#### **on the use of methylisothiazolinone (MIT) in everyday products and the associated risks of dermal and respiratory sensitisation**

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*ANSES undertakes independent and pluralistic scientific expert assessments.*

*ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.*

*It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.*

*It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).*

*Its opinions are made public.*

*This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 9 December 2016 shall prevail.*

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On 11 August 2014, ANSES issued an internal request to undertake the following expert appraisal: review of the use of methylisothiazolinone (MIT) in everyday products and the associated risks of dermal and respiratory sensitisation.

#### **1. BACKGROUND AND PURPOSE OF THE REQUEST**

Methylisothiazolinone (MIT) is a substance used as a preservative in a wide range of water-based commercial mixtures such as detergents, paints and varnishes and in mixtures for professional use (e.g. cutting fluids). It can also be found in rinse-off and leave-on cosmetic products. This use is regulated at European level (Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products): its concentration should not exceed 0.01% (100 ppm)<sup>1</sup> in finished cosmetic products and the presence of this substance should be mentioned on the packaging.

At a toxicological level, MIT is recognised as a skin sensitiser, based on experimental data in animals and humans, but does not have a harmonised European classification under Regulation (EC) No 1272/2008 of 16 December 2008 on classification, labelling and packaging of substances and mixtures, known as the CLP Regulation<sup>2</sup>.

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<sup>1</sup> Percentage by weight (weight of the substance/total weight of the mixture). 1 ppm equals 1 mg.kg<sup>-1</sup> or 0.0001% of the mixture.

<sup>2</sup> An application for harmonised classification has since been submitted, in January 2015 (see p.8).

In the past three years, in France and elsewhere in Europe, many publications have shown an alarming increase in the number of cases of sensitisation to this substance. A French multi-centre study by REVIDAL-GERDA<sup>3</sup> undertaken between 2010 and 2012 in 7,874 subjects irrespective of the exposure circumstances (general population and working population) found that the number of subjects sensitised to MIT more than tripled over a three-year period, increasing from 1.5% in 2010 to 3.3% in 2011 and 5.6% in 2012 ( $p < 0.001$ )<sup>4</sup>. Since the beginning of 2014, other European countries have also observed a steady increase in the number of individuals sensitised to MIT, with the most recent studies showing figures of as much as 5 to 7% (Denmark, Sweden, Belgium, Ireland, Finland and Great Britain).

In light of this increase, several Member States referred the matter to the European Commission. The European Directorate General for Health and Consumers (DG SANCO) asked the European Scientific Committee on Consumer Safety (SCCS) to assess the risks related to the use of this preservative in cosmetic products and to make recommendations. The SCCS issued its opinion in December 2013. It confirmed the significant increase in the number of cases of sensitisation<sup>5</sup> to MIT in various European countries including France since 2010-2011, with on average, 2 to 4% of people with contact dermatitis identified as patch-test positive to MIT (i.e. sensitised to this substance). Allergic reactions were also observed in sensitised individuals exposed to very low concentrations of MIT (<15 ppm). The SCCS thus recommended that MIT no longer be used in leave-on cosmetic products and that concentrations in rinse-off products be limited to levels guaranteeing a lack of elicitation reactions<sup>6</sup> (0.0015%, i.e. 15 ppm). Moreover, the SCCS drew attention to the risks related to exposure through other types of products (household products), in particular in previously sensitised individuals<sup>7</sup>.

Moreover, expert members of the Working Group 'Toxicovigilance of chemical products' of the Toxicovigilance Coordination Committee (CCTV) (in particular dermatologists belonging to the REVIDAL-GERDA network) confirmed these observations and described an upsurge in cases of skin allergies from airborne exposure.

Further to the conclusions of the SCCS opinion of December 2013 and the observations reported by dermatologists, ANSES decided to issue an internal request in order to review the uses of MIT in consumer products and describe the associated risks of dermal and respiratory sensitisation. The aim was to identify classes of products entailing the highest exposures in order to issue recommendations, if necessary, to limit exposure in previously sensitised and non-sensitised individuals.

This internal request relied on a national sector survey and on a review of the scientific data in the literature. The study was undertaken in conjunction with the appraisal of regulatory dossiers on MIT, within the framework of the CLP Regulation and Regulation (EU) No 528/2012 of the

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<sup>3</sup> Dermatology-Allergology Monitoring Network reporting to the Dermatology-Allergology Research and Study Group made up of approximately 160 allergists

<sup>4</sup> Hosteing S, Meyer N, Waton J, Barbaud A, Bourrain JL, Raison-Peyron N, Felix B, Milpied-Homsy B, Ferrier Le Bouedec MC, Castelain M, Vital-Durand D, Debons M, Collet E, Avenel-Audran M, Mathelier-Fusade P, Vermeulen C, Assier H, Gener G, Lartigau-Sezary I, Catelain-Lamy A, Giordano-Labadie F; REVIDAL-GERDA network, 2014. Outbreak of contact sensitization to methylisothiazolinone: an analysis of French data from the REVIDAL-GERDA network. *Contact Derm.* 70(5):262-9.

<sup>5</sup> Sensitisation: primary exposure to an allergen, triggering the induction of an allergic reaction.

<sup>6</sup> Elicitation: occurrence of an allergic reaction in a previously sensitised individual, following new exposure to the same allergen.

<sup>7</sup> On 5 January 2015, the SCCS received another request from the European Commission to assess the safety of MIT in rinse-off cosmetic products and leave-on hair products (see p.8).

European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. With regard to cosmetic products, the study was undertaken in collaboration with the French National Agency for Medicines and Health Products Safety (ANSM).

## **2. ORGANISATION OF THE EXPERT APPRAISAL**

This expert appraisal was carried out in accordance with the French standard NF X 50-110 "Quality in Expertise – General Requirements of Competence for Expert Appraisals (May 2003)".

The collective expert assessment was undertaken by the Expert Committee (CES) 'Assessment of chemical risks of consumer articles and products', between 22 May 2014 and 25 September 2015. One of the committee's experts was appointed rapporteur in order to critically review the summary of toxicity data.

ANSES analyses interests declared by experts from this CES before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in this expert appraisal. The experts' declarations of interests are made public on ANSES's website ([www.anses.fr](http://www.anses.fr)). Two experts from the Expert Committee 'Assessment of chemical risks of consumer articles and products' were identified as having conflicts of interest. They therefore did not take part in the committee's discussions and decisions.

A national sector survey was undertaken, based on several hearings held between April and June 2014. The following were consulted: the French Association of Manufacturers of Detergents (AFISE), the European Council of Paint, Printing Ink and Artists' Colours Industry (CEPE), the Dow Chemical Company, the French Federation of Paint, Inks, Colours, Glues, Adhesives, and Wood Preservation Industries (FIPEC), the French Chemical Trade Association (UFCC), the Chemical Industries Union (UIC), and the company Thor. Data were extracted from the national database on products and compositions (BNPC) of the Poison Control and Monitoring Centres (CAPTV) in order to obtain information on mixtures containing MIT (categories of use, concentrations of MIT).

## **3. ANALYSIS AND CONCLUSIONS OF THE CES**

Methylisothiazolinone (MIT) has been used instead of the chloromethylisothiazolinone (CMIT)/MIT mixture (in a 3:1 ratio) since the early 2000s. Up until then, it had not been possible to synthesise MIT separately from CMIT without generating excessive additional costs to remove CMIT from the mixture. Since the synthesis of MIT individually became possible, the substance has largely replaced the CMIT/MIT mixture.

From a regulatory standpoint, only the CMIT/MIT mixture has a harmonised classification under the CLP Regulation; in particular, it is classified as a Category 1 skin sensitiser with a specific concentration limit of 0.0015% (15 ppm).

### **■ Regulatory data**

- CLP and REACH Regulations

Within the framework of the CLP Regulation and Regulation (EC) No 1907/2006 of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Denmark published its Risk Management Option Analysis (RMOA) conclusion document indicating the various actions that could be taken in relation to MIT:

- A harmonised classification of MIT with a low specific concentration limit,
- A proposed restriction for the use of MIT in toys intended to be put into the mouth for children under the age of three,

- A proposed restriction to reduce airborne exposure to MIT from painted surfaces,
- The implementation of the Biocides Regulation and the Cosmetics Regulation.

In January 2015, Slovenia submitted an application dossier for a CLP harmonised classification, suggesting that MIT be classified as a Category 1 skin sensitiser with a specific concentration limit of 0.06% (600 ppm). This proposed classification is to be discussed shortly with all of the EU Member States.

- Biocides Regulation

Considering Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products, MIT is used as a preservative. A finalised assessment on the use of MIT as a biocide will be issued in 2016 by Slovenia, the Rapporteur Member State.

- Toys Directive

Directive 2009/48/EC of the European Parliament and of the Council of 18 June 2009 on the safety of toys refers to the NF EN 71-7 test standard for finger paint. In this standard, MIT is authorised as a preservative with a maximum authorised concentration of 0.01% (100 ppm).

- Cosmetics Regulation

Annex V of Regulation (EC) No 1223/2009 authorises MIT as a preservative in cosmetic products with a maximum concentration of 0.01% (100 ppm) in ready-for-use mixtures.

#### ■ **National sector survey/uses of MIT**

MIT is primarily used for its preservation properties in particular in paints and coatings, detergents, industrial processes, cosmetic products and cutting fluids. A recent study (Schwensen *et al.*, 2015) detected MIT in 93% of tested paints. MIT can also be used for its fungicidal, bactericidal and disinfecting properties in a wide variety of sectors, including varnishes, glues, detergents and textiles.

According to the national sector survey and the review of the literature, MIT concentrations vary depending on the category of consumer product, from below 15 ppm to over 600 ppm. Cosmetic products and consumer products, in particular paints, generally contain less than 100 ppm MIT. However, since mixtures are included in commercial mixtures, it is not possible to ensure actual concentrations of MIT in final mixtures with certainty, when comprehensive information is not provided on the packaging.

Identification of these primary uses suggests that dermal exposure is significant. Few data are available on respiratory exposure.

#### ■ **Summary of toxicity data**

Many studies have been published on the skin sensitising potential of MIT. As summarised by the SCCS in its opinion of December 2013, an "epidemic" of skin sensitisation related to increasing use of this substance in various products (cosmetics and consumer products) is currently being observed in Europe. Moreover, as has been seen with other isothiazolinones such as the CMIT/MIT mixture, cases of airborne exposure causing allergic skin reactions have been identified in recent years. However, the role of MIT remains difficult to determine due to exposure co-factors and difficulty detecting and quantifying MIT in suspected products.

Regarding dose-response relationships and the elicitation potential of MIT, the data currently available deal with the cosmetic use of MIT. The study by Lundov *et al.* (2011) on the elicitation capacity of MIT showed that 18% of individuals developed an allergic reaction at 5 ppm. According

to the authors, these results reinforce the need to revise the threshold below 100 ppm MIT in cosmetic products as this threshold does not provide sufficient protection for previously sensitised subjects. In addition, the study by Yazar *et al.* (2015) concluded that the threshold of 50 ppm in rinse-off cosmetic products is not safe for sensitised individuals. This study does not define a concentration protecting against elicitation.

The SCCS, in its opinion of 2013, could not determine a concentration threshold guaranteeing a lack of skin sensitisation for leave-on cosmetic products. Nor could it determine a concentration threshold guaranteeing a lack of elicitation. The scientific data tend to conclude that the elicitation threshold for previously sensitised individuals varies from one individual to another, in particular depending on age, with in some cases, elicitation concentrations below 15 ppm in leave-on products and 50 ppm in rinse-off products.

In conclusion, the CES considers that it is not possible to define with certainty a threshold below which there would be no skin reaction (sensitisation or elicitation), irrespective of the type of product containing MIT.

Regarding the respiratory toxicity of MIT, the data are extremely limited and do not indicate whether or not observed toxic effects are due to MIT.

#### ■ **Occupational exposure**

In France, the National Network for Monitoring and Prevention of Occupational Diseases (RNV3P) is currently analysing occupational allergic contact dermatitis. The aim is to describe their prevalence according to pollution type and identify at-risk sectors and professions. On this topic, Bensefa-Colas *et al.* (2015) indicated that the number of cases of occupational allergic contact dermatitis related to isothiazolinones increased by approximately 38% between 2001 and 2010. The authors concluded that it is necessary to guide preventive actions against isothiazolinones and regulate, in particular, the use of MIT in products for professional use in order to halt this increase.

Since MIT has been included in the RNV3P thesaurus of chemical substances since 2013, another appraisal is in progress, specifically on MIT and the data of the RNV3P. It is expected to shed light on the characterisation of at-risk professional sectors and the prevalence of contact dermatitis in these sectors following exposure to MIT.

#### ■ **Conclusions**

This expert appraisal confirmed that MIT is widely used in consumer products to replace the CMIT/MIT mixture. It found that the number of cases of skin sensitisation to this substance has increased all across Europe. The issue of airborne dermatitis, raised by the dermato-allergists of REVIDAL-GERDA, was confirmed by the analysed scientific publications.

Within the framework of the European Cosmetics Regulation, MIT is still being discussed with the aim of limiting its use. These discussions will be need to be monitored, since reducing the threshold from 100 to 15 ppm in rinse-off products would help limit the risk of sensitisation and, to a lesser extent, elicitation. The CES confirms that no studies have been able to define a concentration guaranteeing a lack of elicitation with MIT.

Thus, for individuals previously sensitised to MIT, avoidance is the only way to keep contact dermatitis from continuing or recurring, by direct dermal or airborne exposure, regardless of the type of product. It is therefore essential for patients to be informed of the various sources to which they could be exposed. This could be further improved by providing information about the presence of MIT in consumer (and professional) products.

Within the framework of the CLP Regulation, the 2<sup>nd</sup> Adaptation to Technical Progress (ATP), published in June 2015 requires that any mixture containing a skin sensitizer, such as MIT, shall be

labelled 'Contains methylisothiazolinone'. May produce an 'allergic reaction' over 100 ppm. In light of the toxicity data, the threshold of 100 ppm appears too high to protect against sensitisation and elicitation, although it is a first regulatory step forward pending a harmonised classification. It should be noted that, in order to improve information for consumers, European manufacturers of decorative paints (through their European council of paint and ink - CEPE) have agreed to mention, on a voluntary, proactive basis, "contains methylisothiazolinone" on the packaging of their decorative paints from 15 ppm MIT and even from 1 ppm for some manufacturers.

In January 2015, Slovenia submitted a proposal for a harmonised classification of MIT, suggesting that MIT be classified as a Category 1 skin sensitiser with a specific concentration limit of 0.06%, i.e. 600 ppm. This proposal has not yet been adopted and is to be discussed at European level. Even so, the CES considers that this limit is too high in light of the toxicity data.

A finalised assessment on the use of MIT as a biocide will be issued in 2016 by Slovenia, the Rapporteur Member State.

Moreover, this expert appraisal identified some uncertainties, in particular regarding the respiratory toxicity of MIT, the possible presence of MIT in goods (e.g. sofas, clothing), and their concentration levels.

#### ■ Recommendations

The CES recommends the implementation of a strategy for the prevention of MIT exposure through consumer products, in anticipation of or in addition to upcoming regulatory actions:

- Providing systematic information for consumers, on the packaging of mixtures containing MIT, regardless of the concentration level in the mixture, apart from cosmetic products and detergents for which this information is already mandatory. This approach has already been proposed by European manufacturers of decorative paints, from 1 ppm for some manufacturers and from 15 ppm for all manufacturers. Providing systematic information even at the lowest concentration applicable to the finished product as placed on the market will enable sensitised individuals to avoid exposure to the allergen;
- Proposing management measures for occupants of a home renovated with paint containing MIT: improve information regarding the need to ventilate after application and to limit access for a few days thereafter;
- Including MIT in the labelling of construction products in order to inform consumers of volatile pollutant emission levels. In the procedure for the qualification of volatile organic compound emissions, proposed by AFSSET in 2009, a lowest concentration of interest (LCI) of 100  $\mu\text{g}\cdot\text{m}^{-3}$  is available for this substance. This French LCI was adopted by the European working group for the harmonisation of protocols and LCIs<sup>8</sup>;
- Within the framework of expected feedback on the specific concentration limit proposed by Slovenia, developing arguments to defend a threshold below 600 ppm, based on the available data.

The CES also recommends the implementation of monitoring and research actions in order to acquire additional data:

- Regarding dose-response relationships: the literature should be monitored in order that an elicitation threshold can be defined;

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<sup>8</sup> [http://www.eu-lci.org/EU-LCI\\_Website/Home.html](http://www.eu-lci.org/EU-LCI_Website/Home.html)

- Regarding respiratory toxicity: research should be undertaken in order to document the possible relationship between MIT exposure and the occurrence of respiratory symptoms;
- Regarding occupational exposure: the RNV3P data should be analysed in order to better characterise occupational sectors at risk and the types of induced diseases. The literature on this topic should be monitored;
- Regarding the search for alternative preservatives: other substances could be considered as substitutes for MIT, in particular the substances authorised within Product-Type 6 (PT6) of the Biocides Regulation and other isothiazolinones. With regard to isothiazolinones, the MIT/BIT (benzisothiazolinone) mixture is increasingly being used as a preservative. OIT (octylisothiazolinone) is primarily used as a fungicide, in particular within PT7 (film preservatives), and is also used as a preservative in detergents in mixtures with MIT or with CMIT/MIT mixtures. Regarding substances in PT6, they are not perfect candidates for MIT substitution due to their human and environmental toxicity and their physico-chemical properties. Use of these substances could give rise to other risks. New research should be undertaken into innovative preservatives or systems.

#### **4. AGENCY CONCLUSIONS AND RECOMMENDATIONS**

The French Agency for Food, Environmental and Occupational Health & Safety agrees with the conclusions of the Expert Committee (CES) "Assessment of chemical risks of consumer articles and products". In commercial mixtures, the growing use of MIT instead of the CMIT/MIT mixture, has caused an increase in the number of skin sensitisation cases to this substance all across Europe, through direct or airborne contact. High concentrations of MIT in various products for professional use have induced severe contact dermatitis in several professional categories.

Recent studies have confirmed this finding, in particular the study by Basketter *et al.* (2015)<sup>9</sup>. In the study by Friis *et al.* (2014)<sup>10</sup>, according to the Danish PROBAS database<sup>11</sup> of mixtures for occupational use, MIT was the second most commonly substance found in the class of isothiazolinones after BIT, with 884 products surveyed including 471 paints-varnishes, 87 cleaning products and 60 polishing agents. MIT concentrations ranged from 0.01 ppm to 100,000 ppm (concentration in a biocidal product).

In its opinion of July 2015, the SCCS confirmed the conclusions issued in 2013: in order to protect against sensitisation, the SCCS recommends that the concentration of 15 ppm MIT not be exceeded in rinse-off cosmetic products. For previously sensitised individuals, the SCCS considers that no elicitation threshold can be defined in the current state of knowledge. This position is supported by recent surveillance data confirming an increase in the number of cases of contact dermatitis from MIT in Europe, and by the results of Yazar *et al.* (2015). The SCCS considers that the concentrations that prevent elicitation also protect against sensitisation. For example, the results of Yazar *et al.* (2015), indicating the occurrence of contact dermatitis from 50 ppm in individuals previously sensitised to MIT, support the assumption that such concentrations in rinse-off cosmetic products do not protect against the risk of elicitation.

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<sup>9</sup> Basketter DA, White IR, McFadden JP and Kimber I (2015). Skin sensitization: Implications for integration of clinical data into hazard identification and risk assessment. *Human and Experimental Toxicology*, Vol. 34(12), 1222-1230.

<sup>10</sup> Friis UF, Menné T, Flyvholm MA *et al.* (2014). Isothiazolinones in commercial products at Danish workplaces. *Contact Dermatitis*, 71, 65-74.

<sup>11</sup> Danish Product Register Database

Moreover, in July 2015 at European level, Slovenia submitted a final application dossier for the harmonised classification of MIT, proposing in particular a "Category 1A skin sensitiser" classification with a specific concentration limit of 0.06%, i.e. 600 ppm, and a "Category 1B skin corrosive" classification. During the public consultation, France commented on this proposal and disagreed with the specific concentration limit of 600 ppm, much too high in light of the available data. ANSES thus suggested following the SCCS opinions of December 2013 and June 2015 in which a concentration of 15 ppm is proposed. Other comments from European public institutions and Member States have also supported a more conservative concentration limit.

Lastly, in Directive (EU) 2015/2117 amending Directive 2009/48/EC on the safety of toys<sup>12</sup>, a limit value applicable to MIT was set at 0.25 mg/kg (content limit) in aqueous toy materials (i.e. 0.25 ppm). This threshold corresponds to the routine limit of quantification for MIT indicated by the German Federal Institute for Risk Assessment (BfR<sup>13</sup>). It was determined in accordance with the limitation method for allergens adopted by the BfR, stipulating that a sensitised individual can have an allergic reaction even to the lowest concentration of an allergen, and with the opinion of the Scientific Committee on Health and Environmental Risks (SCHER) of the European Commission, concluding that MIT should not be used in toys due to its sensitising and eliciting potential.

In light of the above, the French Agency for Food, Environmental and Occupational Health & Safety recommends the implementation of the following actions:

- In the short term
  - Involving France as a Member State in efforts to monitor the appraisal of MIT under the Biocides Regulation. Sweden mentioned the possibility of using a MIT substitute in cutting fluids (PT13). The discussions arising from this proposal could provide valuable insight into possible replacements for MIT;
  - Through the ANSM, monitoring discussions aiming to modify or maintain concentrations of MIT as a preservative in cosmetic products. If the restriction proposed by the SCCS is applied in the regulations, the risk of dermal sensitisation to MIT through cosmetic products will be significantly reduced;
- In the medium term
  - In order to limit the risk of dermal sensitisation to MIT from airborne exposure, in particular from paint, adding MIT to the list of labelled substances for construction products. Based on the LCI adopted by the European working group, the qualification of MIT emissions with information on packaging would improve avoidance for sensitised individuals and reduce the risk of dermal sensitisation from airborne exposure. On this topic, in December 2015, Sweden published a report recommending a labelling scheme for construction products based on emissions of chemical substances, including MIT;
  - Monitoring work in progress for the identification and characterisation of occupational exposure to MIT, in the framework of the RNV3P. Identification of the sectors and jobs entailing the highest exposures would enable the implementation

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<sup>12</sup> Commission Directive (EU) 2015/2117 of 23 November 2015 amending, for the purpose of adopting specific limit values for chemicals used in toys, Appendix C to Annex II to Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys, as regards chloromethylisothiazolinone and methylisothiazolinone, both individually and in a ratio of 3:1

<sup>13</sup> Bundesinstitut für Risikobewertung



of preventive actions targeting the affected sectors (information, protective measures).

**The Directorate General**

**KEYWORDS**

Methylisothiazolinone, uses, regulations, sensitisation