

Danish Comments to the CLH proposal for 2- methylisothiazol-3(2H)-one (MIT), (CAS no 2682-20-4).

The Danish comments relate only to the proposal with respect of the end-point of sensitisation.

The Danish CA agrees with the proposal to classify for 2- methylisothiazol-3(2H)-one (MIT) (CAS no. 2682-20-4) for skin sensitisation in category 1A (**Skinksens 1A, H317**). However, we propose to amend the proposal with respect to setting of a specific concentration limit (SCL). Based on scientific evidence the Danish CA considers that an **SCL of 0.0015% (15ppm)** is justified. The reasoning is provided in the comments below:

Re point 4.6.1 Skin sensitisation

Comment: The Danish CA disagrees with the proposal of setting a specific concentration limit for MIT at 0.06% (600 ppm) for skin sensitisation.

The classification proposal presents no specific arguments to support the choice of this particular SCL, but refers to the result of animal and human experimental data, whilst epidemiological data from published articles are considered to lack scientific robustness and are therefore dismissed as unsuitable for classification purposes (point 4.6.1.3., last paragraph).

The Danish EPA considers that the wealth of available clinical data on sensitisation from MIT makes it clear that the substance causes sensitisation at much lower levels than the SCL proposed by the Slovenian CA. With reference to the evaluation of available data from the SCCS (SCCS, 2014; SCCS, 2015), the Danish EPA considers that an SCL of 0.0015% is appropriate.

Strong evidence from valid human data:

Comment: The criteria for CLP stipulate that all relevant available information should be taken into account, including i.a. experience on the effects on humans and any new scientific information (CLP, Article 5 point 1). Information published in peer reviewed scientific journals, from medical authorities and dermatological clinics from all over Europe all demonstrate that the use of MIT is responsible for a dramatic increase in incidences of cases of sensitisation by MIT through uses in paints, glues, household products and cosmetics. The information has been reviewed by the Scientific Committee for Consumer Safety in relation with their preparation of their opinions in 2013/14 (SCCS, 2014) and 2015 (SCCS, 2015). The criteria for classification of substances for skin sensitisation include case reports, epidemiological studies, medical surveillance and reporting schemes based on human patch testing as human data to be used for classification (CLP Annex I, point 3.4.2.2.1.1). Thus, the epidemiological data are robust, adequate and their reporting and presentation suitable for being taken into account for classification and labelling purposes.

Exposure levels causing sensitisation in humans:

In the CLH proposal, it is put forward that details of human exposure to MIT are not known.

Comment: Since MIT has been set on the market as a replacement for CMIT: MIT 3:1 in the beginning of the 00's, use of MIT has increased and the substance has a widespread use in water-based paints, glues, cleaning products and in cosmetics. Information of concentrations of MIT in various products is available, and is summarised by the SCCS (SCCS, 2015, SCCS 2014) and by the Danish EPA (Danish EPA, 2015).

The preservative is used extensively in water-based decorative paints for indoor use. Information from the Danish Coatings and Adhesives Association (DFL) reports that 80% of water-based paints from their members contain less than 100 ppm (0.01%) MIT, while 19% of water-based paints contain between 100 and 200 ppm of the substance. DFL member companies are continuously trying to reduce the amounts (Anette Harbo Dahl, DFL, personal communication, 2013).

An article by Michael Lundov and co-workers reports concentrations of 10-300 ppm (0.001-0.03%) MIT in 39 water-based wall paints on the Danish market (Lundov et al., 2014).

A Danish survey of MIT in different types of consumer products demonstrates that the concentration of MIT across the different types of products is generally under 100 ppm (0.01%) and only surpassed 100ppm in very few products (Tordrup et al., 2015). None of the 22 cosmetic products analysed contained more than 100 ppm.

A survey of water based paints across Europe show that MIT was present in all but 5 of the 71 selected paints (7%). Eighteen percent of the paints contained <15 ppm MIT, 45% between 15 and 100 ppm and 30% contained over 100 ppm MIT (Schwensen et al., 2014).

In cosmetics, 100 ppm has been the maximum permitted content for a decade.

Thus, the typical concentration of MIT in products on the market is generally much lower than 600ppm (0.06%), which has been proposed as the specific concentration limit.

In the same period, the prevalence of sensitised male and female consumers and professionals to MIT has increased from around 1-2% to 6%-over 10% in several European countries, as it is illustrated in the below figure from the SCCS opinion (SCCS, 2015). The clinical data available from a large number of dermatological clinics over the past 5-10 years, and including 10.000's of patients, clearly indicate that the current use levels of MIT in mixtures with different applications has caused an increase in the prevalence of contact allergy to an extent that is considered by dermatologists to be an epidemic.

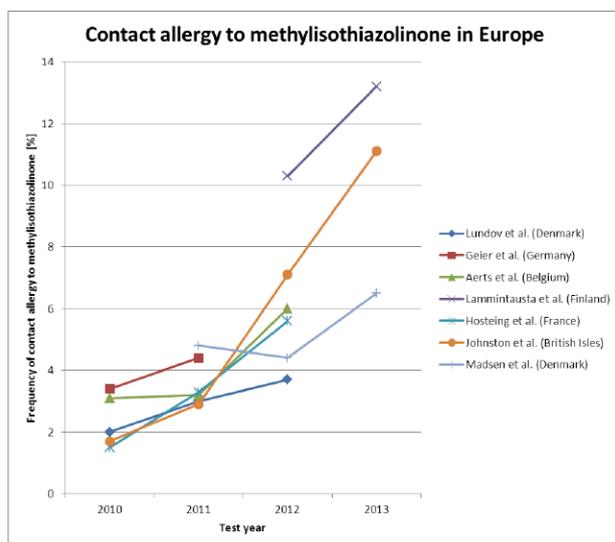


Figure 1. Data from recently published scientific literature concerning changes over time in MI contact allergy among patch-tested patients in different countries, based on refs: 18, 20-23, 29, 30

This development indicates that MIT is a potent sensitiser in humans, as product concentrations of around 100 ppm have resulted in a dramatic increase in the number of sensitised individuals, as reported by dermatological clinics across Europe. These data clearly indicate that the users need information on the hazard from MIT through the label, in order to prevent a further increase in the number of sensitised persons from a level much lower than 600 ppm, which would only apply to very few products on the market.

Experimental data versus clinical data.

The classification proposal includes results from experimental animal studies and from experimental studies in humans. The animal data point at MIT being a potent sensitiser. The experimental studies conducted on MIT in humans are reported to produce a positive (sensitising) reaction at 400 and 500 ppm. No sensitisation reaction occurred at 100, 200, 300 or 600 ppm induction concentrations. Another author reported a positive result at 0.01% (100 ppm) in 1/98 subjects (Shelanski, 2000, Table 11B of the CLP proposal). In point 4.6.1.3 of the proposal, it is discussed that the protocol used exaggerates the exposure, that the use of water as vehicle may affect the sensitisation potential and that the lack of dose-response questions the suitability of the study for defining an SCL. The proposed SCL of 0.06% (600 ppm) appears to be set on the basis of the negative result in the experiment with

600 ppm in spite of the reactions at 400 and 500 ppm. No mention is made of the positive result at 100 ppm from the Shelanski study.

A few clinical data are also mentioned in the classification proposal. However, the data are not included in discussion leading to proposed setting of an SCL.

Comment:

The Scientific Committee for Consumer Safety's opinion on the sensitisation of MIT (SCCS, 2014) referred in the proposal (point 4.6.1.3) has reviewed the available information on sensitisation from MIT. In July 2015, the SCCS published an additional opinion on sensitisation of MIT (SCCS, 2015), following up on their opinion from April 2014 on the same subject.

The opinions conclude recommending that MIT no safe level can be established for leave-on cosmetic products and that 15 ppm is the maximal allowable content in rinse-off cosmetic products. The experts of the committee have included in the opinions a summary and a discussion of the available experimental data from animal and human testing as well as human data from real life situations from the dermatological clinics. The Danish EPA supports that the analysis of available data on sensitisation of MIT from this group of EU scientific experts should be recognised and taken into account in the setting an SCL for classification and labelling of MIT, in order to avoid duplication of work.

The SCCS consider that 15 ppm (0.0015%) is considered safe with respect of induction of contact allergy from MIT for rinse-off cosmetic products (SCCS, 2014). The Danish EPA considers that this level is an appropriate level for the SCL for classification and labelling of MIT as a skin sensitiser.

The dossier submitter argues that the higher exposure from cosmetic products supports that the "safe" level in rinse-off cosmetic products should be lower in these products (point 6.4.1.3, after the citation from SCCS opinion) than the concentration limit for classification and labelling of other mixtures containing MIT.

Comment: Differences in exposure pattern between use of cosmetic products and use of other chemical mixtures will obviously affect the risk from MIT. However, scientific data on sensitisation from MIT include many different types of products (mixtures) as paints, lacquers, glues, detergents, metal working fluids etc.. Both consumer and occupational exposure has been reported. (Uter et al, 2013; Schweensen et al., 2014) demonstrating that MIT causes sensitisation from many types of products.

Occupational exposure may have a longer duration or be repeated several times during the day, and gloves are often only used when the hazard from the chemical is known. The pattern of exposure, including dose/area and frequency of exposure is important for the development of skin sensitisation, as reflected in section 3.4.2.2.3.1, around table 3.4.2-c, of the Guidance on the Application of the CLP Criteria (ECHA, 2015). However, the guidance stresses that as such data are often unavailable, and that concentration may be use as a surrogate indicator of exposure. Classification is the sole parameter that is regulated by setting an SCL. The Danish EPA is of the opinion that the concentration of MIT inducing skin sensitisation is similar whether the substance is used in a cosmetic product or e.g. a detergent.

In conclusion the Danish EPA supports that a specific concentration limit 15 ppm should trigger classification of a mixture containing MIT as a skin sensitiser. This would ensure a more appropriate protection level for both consumers and workers and will user to take the relevant precautions in the handling of MIT containing mixtures.

Re point 4.6.2 Respiratory sensitisation

Comment: The Danish EPA agrees with the conclusion from the proposal that no classification should be proposed for respiratory sensitisation. However, the proposal for classification includes data under this heading that relate to airborne, **contact** dermatitis. These data should be taken into account in the evaluation of skin sensitisation.

References:

Danish EPA, 2015: Risk management option analysis - conclusion document for Methylisothiazolinone: <http://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/pact/-/substance-rev/1941/term?viewsubstances WAR echarevsubstanceportlet SEARCH CRITERIA NAME=2-methyl-2H-isothiazol-3-one&viewsubstances WAR echarevsubstanceportlet SEARCH CRITERIA EC NUMBER=220-239-6>.

Lundov et al. (2014): Lundov MD, Kolarik B, Bossi R, Gunnarsen L and Johansen, JD. Emission of isothiazolinones from water-based paints. Environ.Sci.Technol. 2014, 48, 6989-6994.

SCCS, 2014: (SCCS (Scientific Committee on Consumer Safety), Opinion on Methylisothiazolinone (P94) – Submission II, 12 December 2013, SCCS/1521/13. http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm

SCCS, 2015: (SCCS (Scientific Committee on Consumer Safety), Opinion on Methylisothiazolinone (MI) (P94) sensitisation only, 25 June 2015, SCCS/1557/15. http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm

Schwensen et al. (2014): Schwense, JF, Lundov MD, Bossi R, Banerjee P, Gimenez-Arnau, E, Lepoittevin JP, Lidén C, Uter W, Yazar K, White, I and Johansen, JD:: Methylisothiazolinone is widely used in paint: A multicentre study of paints from five European countries. Contact Dermatitis, 72, 127–138.

Tordrup, S W; Kryzowkowski, K; Tønning, K; Schweensen J F and Johansen J D (2015): Survey and Exposure Assessment of Methylisothiazolinone in Consumer Products. Danish EPA, <http://mst.dk/service/publikationer/publikationsarkiv/2015/apr/survey-and-exposure-assessment-of-methylisothiazolinone-in-consumer-products/>

Uter W, Geier J, Bauer A, et al. Risk factors associated with methylisothiazolinone contact sensitization. Contact Dermatitis 2013; 69: 231-8.

ECHA, 2015: Guidance on the application of the CLP criteria: http://echa.europa.eu/en/view-article/-/journal_content/title/guidance-on-clp-application-criteria-panel