



Scientific Committee on Consumer Safety
SCCS

SCIENTIFIC ADVICE ON
the SCCS Opinion on methyl-N-methylantranilate (MNM)
(SCCS/1455/11)



The SCCS adopted this scientific advice
by written procedure on 16 October 2020

Corrigendum of 1 June 2021

ACKNOWLEDGMENTS

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This scientific advice is not subject to a commenting period.

Corrigendum made to align the abstract sentence on page 3 with the conclusion of the SCCS on page 13.

1. ABSTRACT

The SCCS concludes the following:

We would like to request scientific advice on whether the sentence from the SCCS Opinion (SCCS/1455/11) "...the SCCS considers that for the use in sunscreen/sun care products or products (including fragrances) intended for use on areas exposed to light (especially face and neck), a risk cannot be excluded" means that methyl-Nmethylantranilate should not to be used in sunscreen products and products marketed for exposure to natural/artificial UV light, but is considered safe to be used up to 0.1% for leave-on and 0.2% for rinse-off products".

In the SCCS's opinion, Methyl-N-methylantranilate should not be used in sunscreen products and products marketed for exposure to natural/artificial UV light.

It is considered safe to be used up to 0.1% for leave-on and 0.2% for rinse-off products.

Keywords: SCCS, scientific advice, fragrance ingredient, methyl-N-methylantranilate (SCCS/1455/11), Regulation 1223/2009, CAS No. 85-91-6, EC No. 201-642-6, SCCS/1616/20

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SCCS

The Committee shall provide Opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Methyl-N-methylantranilate (CAS No. 85-91-6, EC No. 201-642-6) is a fragrance ingredient used in various cosmetics, including fine fragrances, shampoos, soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents.

Methyl-N-methylantranilate is a restricted substance according the IFRA (International Fragrance Association) standards (concentration restriction of 0.10% in certain product categories)¹. It has also been subject to evaluation by the SCCNFP² in the opinion SCCNFP/0392/00 entitled "*An Initial List of Perfumery Materials which must not form part of Cosmetic Products except subject to the restrictions and conditions laid down*". SCCNFP recommended that the substances mentioned in this opinion may be used as ingredients in cosmetic products only under the conditions and restrictions specified in the table attached in its opinion. In that table, Methyl-N-methylantranilate was mentioned under entry No. 21 with the restriction: '*For applications on areas of the skin exposed to sunlight, excluding bath preparations, soaps and other wash-off products, limit to 10 % in the finished cosmetic product*'.

After the first submission, an updated IFRA recommendation led to submission II for this substance. It led to an SCCP³ opinion (SCCP/1068/06) on photo-toxicity being adopted in 2006 with the following conclusion: '*Methyl-N-methylantranilate is phototoxic as demonstrated by both in vivo and in vitro experiments. Although the action spectrum of the phototoxicity has not been provided, phototoxicity is normally within the UVA spectrum. The NOAEL in humans was at 0.5% with 16 J UVA/cm² (with 0.75 MED UVB) (ref 34768). However, an in vitro test indicated that it was phototoxic at 0.05%, the lowest dilution tested. Phototoxicity is related to the product of dose and UV exposure. Because of the phototoxicity, methyl-N-methylantranilate should not be deliberately added to leave-on cosmetic products, as there is always the potential for light exposure. Until appropriate toxicity data on the substance are available, including information on the possible nitrosamine formation by this secondary amine, up to 0.1% can be used in rinse-off finished cosmetic products. The above opinion applies also to the presence of methyl-N-methylantranilate in essential oils, including Petitgrain Mandarin*'.

In 2008, EFFA⁴ submitted a compilation of studies based on a complete literature search in order to allow the substance to be used in concentration up to 0.1% in leave-on products and up to 0.2% in rinse-off products. In 2011, the SCCS⁵ (SCCS/1455/11) concluded that there are no safety concerns on the use of methyl-N-methylantranilate at up to 0.2% in rinse-off products. Nevertheless, the SCCS stated that '*Methyl-N-methylantranilate is phototoxic and this is the toxicological endpoint of concern. Whilst up to 0.1% methyl-N-methylantranilate may be safe for use in many leave-on cosmetic products, including deodorants and antiperspirants, the SCCS considers that for the use in sunscreen/sun care products or products (including fragrances) intended for use on areas exposed to light (especially face and neck), a risk cannot be excluded*'.

In our view, the health risk of methyl-N-methylantranilate is linked to its photosensitivity. In particular, such risk could be envisaged when body parts are exposed to intensive sunlight

¹ Amendment 49, published in 2020

² Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers

³ Scientific Committee on Consumer Products

⁴ European Flavour & Fragrance Association

⁵ Scientific Committee on Consumer Safety

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(natural UV light) or any artificial sources of UV light, after the application of cosmetics containing methyl-N-methylantranilate. In our understanding, products which pose risks of such exposure are sunscreens, as well as other products marketed for exposure to natural or artificial UV light (i.e. products marketed for sunbeds). Therefore, we would like to search advice from the SCCS on how these elements can be more precisely reflected in the conclusions. Notably, we would like to ask for a scientific advice on whether the clarification suggested below would be scientifically valid.

Provided that our suggested clarification is valid, we would consider that for leave-on products containing methyl-N-methylantranilate other than sunscreens and products marketed for exposure to natural or artificial UV light, this substance should be restricted to 0.1%.

Terms of reference

We would like to request scientific advice on whether the sentence from the SCCS opinion (SCCS/1455/11) "...the SCCS considers that for the use in sunscreen/sun care products or products (including fragrances) intended for use on areas exposed to light (especially face and neck), a risk cannot be excluded" would mean that methyl-N-methylantranilate should not to be used in sunscreen products and products marketed for exposure to natural/artificial UV light, but is considered safe to be used up to 0.1% for leave on and 0.2% for rinse off products".

3. SCIENTIFIC ADVICE

3.1 FUNCTION AND USES

From Opinion SCCS/1455/11

Methyl N-methylantranilate is a fragrance ingredient used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. Its use worldwide is in the region of 10 to 100 metric tonnes per annum.

In a use level survey, the ten highest concentrations used in fragrance compounds were from 1.285 - 4.8%. A total of 4065 fragrance compounds contained the ingredient (IFRA 2004).

Methyl-N-methylantranilate has an IFRA Standard restricting its use to 0.1% for leave-on products. There are no restrictions for its use in non skin-contact products or on rinse-off products including household cleaning products. The Standard is set due to the phototoxic effects of the material.

It is reported to occur in orange peel oil (200 ppm); mandarin peel oil (3800-8500 ppm); tangerine peel oil (720 ppm); shima-mikan peel oil (6700 ppm) and in grapefruit juice, bergamot oil, honey and starfruit (TNO, 2008).

It is also found in Petitgrain Mandarinier (*Citrus reticulata blanco*): range 4-55% (ISO 8898) Mandarin oil Italian (*Citrus reticulata blanco*): range 0.3-0.6% (ISO 3528) and there are traces of it in Petitgrain bigaradier (*Citrus aurantium amara*).

The main natural food occurrence is in Mandarin oil (6500 mg/kg). (Council of Europe 2000). The daily oral intake in humans was stated as 10.1 mg per day (Bar; 29590). In Europe, daily oral intake is estimated at 60µg/day (1 µg/Kg bw/day). An ADI of up to 0.2 mg/kg bw was established (JECFA 2005)

3.2 TOXICOLOGICAL EVALUATION

The toxicological evaluation of Methyl N-methylantranilate is covered under SCCS/1455/11.

3.2.1 Photo-induced toxicity

3.2.1.1 Phototoxicity / photo-irritation and photosensitisation

From Opinion SCCS/1455/11

Methyl-N-methylantranilate has an established phototoxic potential.

- 1.0% dimethyl anthranilate (w/v in 25% v/v diethyl phthalate / ethanol) was considered to be phototoxic and produced reactions in 14/35 humans.
- 0.5% dimethyl anthranilate (w/v in 25% v/v diethyl phthalate / ethanol) produced reactions in 0/26 humans.

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- 3T3 Neutral Red phototoxicity test (used for hazard identification) indicated that methyl-N-methylantranilate is non-phototoxic at 0.1% under the experimental conditions used.
- In an in vitro yeast toxicity study (*Saccharomyces cerevisiae*), 0.05% dimethyl anthranilate was phototoxic.

In the above experiments in humans, the test substance was applied under occlusion for 24 hours before irradiation. It is unknown what the retention and metabolism of the test substance is under these conditions.

- The experiment with 1% dimethyl anthranilate (w/v in 25% v/v diethyl phthalate / ethanol) indicates that the test substance was present in sufficient quantity to cause a phototoxic reaction.
- There is no information on the scenario of applying $\leq 0.5\%$ methyl-N-methylantranilate and then exposing to UV irradiation soon afterwards.
- There is also no information on repeated low-dose exposures to methyl-N-methylantranilate with irradiation.

Essential oils containing methyl-N-methylantranilate may be phototoxic.

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The SCCP Opinion SCCP/1068/06 was updated in the SCCS Opinion SCCS/1455/11. In these Opinions, several studies (in vitro, in vivo, in humans) were presented, showing that Methyl-N-methylantranilate (M-N-MA) has a hazard for phototoxicity on the human skin. Phototoxic reactions are elicited by UV-A (wavelength 315 – 400 nm).

Table 1: Phototoxicity studies in humans, presented in SCCS/1455/11

Concentration of M-N-MA	Positive reactions / nr tested	Ref
'As is'	8/10	Kaidbey 1978
'As is'	18/25	Kaidbey 1978
5% in hydrophilic ointment	14/18	RIFM 1978a
0.5% in 75% EtOH/25% DEP	0/29	RIFM 1998
0.3% in 75% EtOH/25% DEP	0/29	RIFM 1998
0.1% in 75% EtOH/25% DEP	0/29	RIFM 1998
1% in 75% EtOH/25% DEP	14/35	RIFM 1999
0.5% in 75% EtOH/25% DEP (phototoxicity evaluated during the induction phase of a photoallergy test)	0/26	RIFM 2001

However, the risk is dependent on the UV (in particular UV-A) dose and M-N-MA concentration. The overview in the Table above shows that no phototoxic reactions occurred upon UV-irradiation at concentrations of M-N-MA varying from 0.1% to 0.5%.

Taken and expanded from SCCS/1455/11

Guideline: /

Species: human

Group: 34 (of which 29 (24 females and 5 males) completed the study)

Substance: dimethyl anthranilate

Vehicle: 75% ethanol and 25% diethylphthalate

Batch: /

Purity: /

Doses: Sample A: 0.5% dimethyl anthranilate w/v in 25% v/v diethyl phthalate in ethanol.
Sample B: 0.3% dimethyl anthranilate w/v in 25% v/v diethyl phthalate in ethanol.

Sample C: 0.1% dimethyl anthranilate w/v in 25% v/v diethyl phthalate in ethanol.

Administration: Patches on skin with 0.3 ml of test article, during 24 hours

Light Source: 1000W Xenon arc solar simulator

UV dose: 16J/cm² UV-A, followed by 0.75 MED UV-B

Irradiation: UV-A within 10 minutes upon removal of patches, followed by UV-B

GCP: in compliance

0.3 ml of the test substances (with vehicle and blank controls) were applied in duplicate in 25 mm Hill Top Chambers under occlusive conditions for 24 hours. 10 minutes after patch removal, 16 J/cm² UVA was given then 0.75 MED UVB to the sites for irradiation. Observations were made at 1, 24, 48 and 72 hours.

Under the conditions of the study, the test articles did not induce a phototoxic reaction.

Ref.: Berger *et al.*, 1998; RIFM, 1998

Interpretation of the results of testing with 0.1% M-N-MA

In order to evaluate the risk of phototoxic reactions from a product containing 0.1% M-N-MA, the RIFM 1998 report can be regarded as the key study. The study was performed correctly in 30 human volunteers. The choice of the vehicle was appropriate and the study used a realistic irradiation dose of 16 J/cm² UV-A.

The key results are presented on pages 25 – 29 of the RIFM 1998 report. The results do not consistently point towards phototoxicity from the concentrations tested. While a few people displayed patchy or mild erythema after irradiated areas of their skin were exposed to the test concentrations 0.5%, 0.3% and 0.1% M-N-MA, such reactions were also seen on other areas of the skin that were exposed (and irradiated) to the vehicle and a blank patch.

One participant showed a reaction to 0.1%, but did not react to the higher (0.3% and 0.5%) test concentrations.

In one participant, a reaction was observed at approximately 1 hour after irradiation, but this occurred also with the vehicle and the blank patch. This could be the result of occlusion or be the result of a reaction to the concomitant UV-B (which is obligatory erythematous at sufficient UV-dose, as opposed to the UV-A which does not easily cause erythema at such UV-doses).

At the lowest test concentration of 0.1%, two subjects reacted with mild erythema, but they did not show increased reactions at higher test concentrations; one of them did not show any reaction at the higher 0.3% and 0.5% concentrations. Moreover, the other subject also reacted to the vehicle and the blank patch.

Exposure to ambient UV-A in relation to the phototoxicity test with M-N-MA.

Maximum daily ambient (unweighted) UV flat on the ground, under a completely cloudless summer sky in Europe, can add up to of 130 – 150 J/cm², but it is extremely unlikely that anybody would receive such a daily dose on the skin, even on a day spent deliberately sunbathing at the beach (Diffey 2015). There is a considerable reduction of this dose by variables such as posture, moving around and clothing; therefore a skin exposure fraction has to be applied to these values (Diffey 2008). Sunbathing while remaining horizontal for 6-8 hours on a clear summer's day would give a maximum daily UV exposure of about 50 J/cm² (Diffey 2015). Most Europeans would not sustain this because the UV-B fraction of this exposure would result in a severe sunburn; this occurs when the unacclimatised skin has received an unweighted sunlight UV (290–400 nm) dose of 15 J/cm² (Harrison 2002, Diffey 2003).

The maximum ambient UV-A flat on the ground, under a completely cloudless summer sky in Europe for 1 hour at noon is up to 20 J/cm². For latitude 30 (approx. Canary Islands) it is 20 J/cm², for latitude 40 (approx. Madrid) this is 19 J/cm², for latitude 50 (approx. Berlin) 17 J/cm² and for latitude 60 (approx. Stockholm) it is 14 J/cm² (Elwood 1993, Diffey 1994). Also in these circumstances, a skin exposure fraction of 5 % to 25% should be applied, unless there is deliberate continuous sunbathing (with a risk of sunburn), which would increase the exposure fraction up to 50% (Diffey 2015).

Based on the abovementioned maximum ambient UV-A exposures, while applying an exposure fraction of 25%, two hours around noon would result in a maximum UV-A skin exposure dose of $0.25 \times 2 \times 20 \text{ J/cm}^2 = \text{about } 10 \text{ J/cm}^2$.

The phototoxicity testing in the key study (RIFM 1998) was performed with a UV-A dose of 16 J/cm². This dose amply reflects more than 2 hours of non-sunbathing exposure, and can therefore be assumed to be sufficient for the use in the testing with M-N-MA.

SCCS conclusion

M-N-MA has phototoxic properties. However, the data provided show that exposing human skin with concentrations from 0.1% to 0.5% with a UV dose that realistically represents skin exposure during outdoor activities (excluding sunbathing) does not elicit phototoxic reactions. Nevertheless, it is not advised to use it as ingredient for sunscreen products or products that are specifically marketed for exposure to natural/artificial UV light, because these products imply prolonged and intense sunlight exposure to UV doses that may be above the doses that were used in the tests. Moreover, it is not an essential ingredient for the purpose of such products.

For other products intended for use on areas exposed to sunlight, a maximum concentration of 0.1% M-N-MA can be considered safe, based on the data provided.

Methyl-N-methylantranilate should not to be used in sunscreen products and products marketed for exposure to natural/artificial UV light.

3.3.9.2 Photomutagenicity / photoclastogenicity

/

3.2.2 Human data

See SCCS/1455/11

3.2.3 Special investigations

See SCCS/1455/11.

3.3 EXPOSURE ASSESSMENT

See SCCS/1455/11.

3.4 SAFETY EVALUATION (INCLUDING CALCULATION OF THE MOS)

See SCCS/1455/11.

3.5 DISCUSSION

M-N-MA has phototoxic properties. However, the data provided show that exposing human skin with concentrations from 0.1% to 0.5% with a UV dose that realistically represents skin exposure during outdoor activities (excluding sunbathing) does not elicit phototoxic reactions. Nevertheless, it is not advised to use it as ingredient for sunscreen products or products that are specifically marketed for exposure to natural/artificial UV light, because these products imply prolonged and intense sunlight exposure to UV doses that may be above the doses that were used in the tests.

Therefore, the use of Methyl-N-methylantranilate (M-N-MA) in sunscreen products and products marketed for exposure to natural/artificial UV light is not advisable. For other leave-on products intended for use on areas exposed to sunlight, a maximum concentration of 0.1% M-N-MA can be considered safe, based on the data provided.

4. CONCLUSION

We would like to request scientific advice on whether the sentence from the SCCS opinion (SCCS/1455/11) "...the SCCS considers that for the use in sunscreen/sun care products or products (including fragrances) intended for use on areas exposed to light (especially face and neck), a risk cannot be excluded" would mean that methyl-Nmethylantranilate should not to be used in sunscreen products and products marketed for exposure to natural/artificial UV light, but is considered safe to be used up to 0.1% for leave on and 0.2% for rinse off products".

In the SCCS's opinion, Methyl-N-methylantranilate should not be used in sunscreen products and products marketed for exposure to natural/artificial UV light.

It is considered safe to be used up to 0.1% for leave-on and 0.2% for rinse-off products.

5. MINORITY OPINION

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6. REFERENCES

See SCCS/1455/11.

References used for this scientific advice

Berger (1998)

Berger, R.S., Chaconas, C. Evaluation of phototoxicity in humans. HTR project n° 101649. Hill Top Research, New Jersey. 1998. Also cited as: RIFM - Research Institute for Fragrance Materials Inc 1998. Evaluation of the phototoxicity of dimethyl anthranilate. RIFM report number 34768, December 8, RIFM, Woodcliff Lake, NJ, USA.

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7. GLOSSARY OF TERMS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141

8. LIST OF ABBREVIATIONS

See SCCS/1602/18, 10th Revision of the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation – from page 141.

And the following additional Abbreviation:

M-N-MA: Methyl-N-Methylantranilate

UV-A : Ultraviolet A

UV-B : Ultraviolet B