



Scientific Committee on Consumer Safety

SCCS

**Addendum to the scientific Opinion SCCS/1491/12 on the
hair dye substance 2-methoxy-methyl-p-phenylenediamine
and its sulfate salt**

COLIPA n° A160

Submission II – use on eyelashes



The SCCS adopted this Opinion
by written procedure on 12 March 2019

ACKNOWLEDGMENTS

Members of the Working Group are acknowledged for their valuable contribution to this Opinion. The members of the Working Group are:

For the Preliminary and the final versions

SCCS members:

Dr U. Bernauer

Dr L. Bodin

Prof. Q. Chaudhry (SCCS Chair)

Prof. P.J. Coenraads (SCCS Vice-Chair and Chairperson of the WG)

Prof. M. Dusinska

Dr J. Ezendam (Rapporteur)

Dr E. Gaffet

Prof. C. L. Galli

Dr B. Granum

Prof. E. Panteri

Prof. V. Rogiers (SCCS Vice-Chair)

Dr Ch. Rousselle

Dr M. Stepnik

Prof. T. Vanhaecke

Dr S. Wijnhoven

SCCS external experts:

Dr A. Koutsodimou

Dr A. Simonnard

Dr. W. Uter

All Declarations of Working Group members are available on the following webpage:
http://ec.europa.eu/health/scientific_committees/experts/declarations/sccs_en.htm

This Opinion has been subject to a commenting period of a minimum eight weeks after its initial publication (from 21 December 2018 until 5 March 2019).

Comments received during this time period were considered by the SCCS. For this Opinion, comments received resulted in the following main changes: *the SCCS comment on the batch composition and purity was removed after clarification on the new batch by the Applicant in paragraphs 3.1.1.6 (Purity, composition and batch codes) and 3.5 (Discussion). No change in the conclusion section.*

1. ABSTRACT

The SCCS concludes the following:

In light of the data provided, does the SCCS consider 2-methoxy-methyl-p-phenylenediamine and its sulfate salt (A160) safe when used in oxidative eyelash colour products at maximum in-use concentration of 1.8 %?

Based on all data provided, the SCCS considers that 2-methoxy-methyl-p-phenylenediamine and its sulfate salt (A160) are safe to be used in oxidative eyelash colour products at the proposed maximum in-use concentration of 1.8%.

Keywords: SCCS, addendum, scientific opinion, hair dye, 2-methoxy-methyl-p-phenylenediamine, A160, CAS 337906-36-2, Regulation 1223/2009, SCCS/1603/18

Opinion to be cited as: SCCS (Scientific Committee on Consumer Safety), Addendum to the Opinion SCCS/1491/12 on 2-methoxy-methyl-p-phenylenediamine) – A160 – Submission II, preliminary version of 21 December 2018, final version of 12 March 2019, SCCS/1603/18

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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.).

Scientific Committee members

Bernauer Ulrike, Bodin Laurent, Chaudhry Qasim, Coenraads Pieter-Jan, Dusinska Maria, Ezendam Janine, Gaffet Eric, Galli Corrado Lodovico, Granum Berit, Panteri Eirini, Rogiers Vera, Rousselle Christophe, Stępnik Maciej, Vanhaecke Tamara, Wijnhoven Susan

Contact

European Commission
Health and Food Safety
Directorate C: Public Health, Country Knowledge, Crisis Management
Unit C2 – Country Knowledge and Scientific Committees
L-2920 Luxembourg
SANTE-C2-SCCS@ec.europa.eu

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2. MANDATE FROM THE EUROPEAN COMMISSION

Background

Submission I on the use of 2-methoxy-methyl-p-phenylenediamine (CAS 337906-36-2) in oxidative hair dye formulations was transmitted by Cosmetics Europe in March 2016. In its corresponding opinion, SCCS/1491/12, the SCCS concluded that “the use of 2-methoxy-methyl-p-phenylenediamine and its sulfate salt as oxidative hair dye with a concentration on head of maximum 1.8% does not pose a risk to the health of the consumer, apart from its sensitising potential”.

With the current submission II, received in July 2018, the applicant requests to extend the use of this ingredient to oxidative eyelash colour products at 1.8% use concentration. The submission includes in particular additional data and considerations on eye irritation.

Terms of reference

In light of the data provided, does the SCCS consider 2-methoxy-methyl-p-phenylenediamine and its sulfate salt (A160) safe when used in oxidative eyelash colour products at maximum in-use concentration of 1.8 %?

3. OPINION

3.1 Chemical and Physical Specifications

The chemical and physical specifications are described in detail in SCCS/1491/12.

3.1.1 Chemical identity

2-methoxy-methyl-p-phenylenediamine is used in hair dyes and eyelash products as either free base or its sulfate salt.

3.1.1.1 Primary name and/or INCI name

2-methoxy-methyl-p-phenylenediamine (INCI name)
2-methoxy-methyl-p-phenylenediamine sulfate (INCI name)

3.1.1.2 Chemical names

Free base

1,4-Benzenediamine, 2-(methoxymethyl) (CA INDEX NAME, 9CI)
2-(methoxymethyl)benzene-1,4-diamine (IUPAC)
1,4-Diamino-2-methyl-benzene

Sulfate salt

1,4-Benzenediamine, 2-(methoxymethyl)-, sulfate (CA INDEX NAME, 9CI)
2-(methoxymethyl)benzene-1,4-diamine sulfate (IUPAC)
1,4-Diamino-2-methoxymethyl-benzene sulfate

3.1.1.3 Trade names and abbreviations

Free base

MBB (Dragon)
COLIPA A160

Sulfate salt

1,4-Diamino-2-methoxymethyl-benzene sulfate (DMMBS)
COLIPA A160

3.1.1.4 CAS / EC number

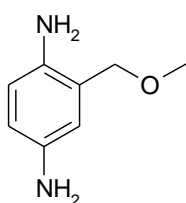
Free base

CAS: 337906-36-2
EC: 679-526-3

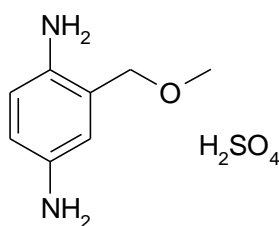
Sulfate

337906-37-3
638-749-6

3.1.1.5



Free base



Sulfate

3.1.1.6 Purity, composition and batch codes

Additional data provided in submission II

The purity composition and specification of 2-methoxy-methyl-p-phenylenediamine are conform to those indicated in the SCCS Opinion (SCCS/1491/12). The composition of the new batch 7215614652 used in the new study reported in this submission is given and compared to previous used batches in the table below. Batch 7215614652 is also identified by batch code XXMBB161102W, i.e., both batch codes refer to one identical raw material quality of 2-methoxy-methyl-p-phenylenediamine. The purity of 2-methoxy-methyl-p-phenylenediamine batch XXMBB161102W was 99.8 ± 0.1 (area-%).

Table 1: Purity and impurities in various batches of 2-methoxy-methyl-p-phenylenediamine

	Batch 20080201	Batch093-09/178-01*	Batch 721561465 (also identified by XMBB161102W)
Purity HPLC	≥ 99.0 area%	≥ 99.0 area%	≥ 99.8 area%
Potential Impurities			
-2-(Hydroxymethyl)benzene-1,4- diamine	130 ppm	130 ppm	102.2 ppm
- 4-Amino-2-(methoxymethyl)-phenol	< 34 ppm**	< 34 ppm**	49.9 ppm**
- 1,4-Diamino-2-methylbenzene	50 ppm	50 ppm	<56.4 ppm
- Toluene	≤ 2100ppm	≤ 2100ppm	< 39.5 ppm

*batches used in toxicological studies reported in submission 1

** LOD = 30ppm

The purity composition and specification of 2-methoxy-methyl-p-phenylenediamine sulfate conform to those indicated in the SCCS opinion (SCCS/1491/12) (Table 2).

Table 2: Purity and impurities in various batches of 2-methoxy-methyl-p-phenylenediamine sulfate

	Batch GST070-05/24-01*	Batch RD- CRU093-09/02-07*
Purity HPLC (qualitative (254 nm))	≥ 96.0 area%	≥ 96.0 area%
Purity NMR (quantitative (salt))	≥ 95.0 %, w/w	≥ 95.0 %, w/w
Potential Impurities		
-2-(Hydroxymethyl)benzene-1,4- diamine	≤ 4100 ppm	≤ 4100 ppm
- 4-Amino-2-(methoxymethyl)-phenol	≤ 35 ppm**	≤ 35 ppm**
- 1,4-Diamino-2-methylbenzene	< 0.38 – 1.15 %, w/w	< 0.38 – 1.15 %, w/w

*batches used in toxicological studies reported in submission I

** LOD = 30 ppm

3.2 Function and uses

2-methoxy-methyl p-phenylenediamine is used as an oxidative hair colouring agent (precursor). The intended maximum in-use concentration is 1.82% in oxidative eyelash formulations. The oxidative colouring agent and the developer are mixed at a ratio of 1+1 (0.5 g dye formulation + 0.5 g developer formulation).

Like conventional dyes for scalp hair, oxidative hair dyes for use on the eyelashes consist of two components: a hydrogen peroxide preparation is used as a developer containing maximally up to 4% hydrogen peroxide (versus conventional hair dyes containing up to 12%), corresponding to a concentration applied on the eyelashes (in the mixture to be used) of up to 2%.

The procedure of application of the dye mixture to eyelashes: immediately prior to application, the dye and hydrogen peroxide are mixed using an application stick in the proportions prescribed by the producer. Once the customer has closed the eyes, and a special sticker is fixed around eyelids to protect it from contamination of the skin below, ~1g of the mixture is applied to the eyelashes with the application stick until they are entirely covered. The application time is up to 10 minutes, At the end of the application time, the dye formulation is removed with wet cotton buds.

3.3 Toxicological evaluation

The toxicological evaluation of 2-methoxy-methyl-p-phenylenediamine (referred to as 1,4-diamino-2-methoxymethyl-benzene in the toxicological studies) is described in detail in SCCS/1491/12. In this Addendum the use of 2-methoxy-methyl-p-phenylenediamine in oxidative eyelash formulations is evaluated. The critical toxicological endpoints considered of relevance to the use of oxidative dyes on eyelashes are skin and eye irritation and skin sensitisation, either by the dye substance or hydrogen peroxide used as oxidant (SCCS/1553/15).

3.3.1 Irritation and corrosivity

3.3.1.1 Skin irritation

From SCCS/1491/12

2-methoxy-methyl-p-phenylenediamine was tested in an *in vitro* skin corrosion assay (Transcutaneous Electrical Resistance (TER) Test Method). Based on the results of this study, 2-methoxy-methyl-p-phenylenediamine as neat substance is classified as “non-corrosive”.

2-methoxy-methyl-p-phenylenediamine was tested in an *in vitro* skin irritation assay (Episkin™ Reconstructed Human Epidermis (RHE) Test). Based on this test, 2-methoxymethyl-p-phenylenediamine is classified as non-irritant (MTT viability > 50%), when applied as neat test item, at 1.83 and 6.1% (w/v) in sterile water. The histological examinations confirmed the absence of cytotoxicity for 2-methoxy-methyl-p-phenylenediamine tested neat, and at 1.83 and 6.1% (w/v) in sterile water.

SCCS comment

The available histological data suggests that 2-methoxy-methyl-p-phenylenediamine is not irritant to skin at anticipated use exposure.

Additional data provided in submission II

No new data provided.

3.3.1.2 Mucous membrane irritation / eye irritation

From SCCS/1491/12

2-methoxy-methyl-p-phenylenediamine and its sulfate salt were tested in three Isolated Chicken Eye Tests (ICE).

In study 1, 2-methoxy-methyl-p-phenylenediamine was tested neat. On the basis of the results obtained in this ICE study, 2-methoxy-methyl-p-phenylenediamine tested neat is identified as irritating to eyes (classification Category 2 according to the EU-CLP classification scheme).

In study 2, 2-methoxy-methyl-p-phenylenediamine was tested at aqueous concentrations of 1.83% and 6.1% (w/w). On the basis of the results obtained in this ICE study, 2-methoxy-methyl-p-phenylenediamine is identified as not irritating to eyes (Not Classified according to the EU-CLP classification scheme).

In study 3, 2-methoxy-methyl-p-phenylenediamine sulfate was tested at aqueous concentrations of 3% and 10% (w/w). On the basis of the results obtained in this ICE study, 2-methoxy-methyl-p-phenylenediamine sulfate is identified as not irritating to eyes (Not Classified according to the EU-CLP classification scheme).

SCCS comment

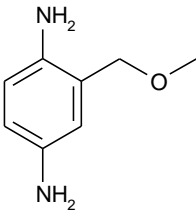
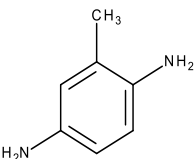
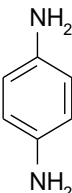
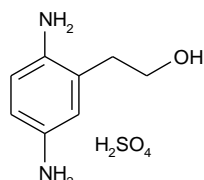
The available data suggests that 2-methoxy-methyl-p-phenylenediamine and its sulfate salt are not expected to be irritant to the eye at anticipated use exposures.

The CEET (ICE) is a screening method for hazard identification and not for risk assessment. The method has now been adopted as OECD guideline 438 (2009) for eye corrosivity and severe irritancy. No fully validated alternative methods for eye irritation exist.

Additional data provided in submission II

The mucous membrane (eye) irritation potential of 2-methoxy-methyl-p-phenylenediamine was evaluated using a Weight of Evidence (WoE) approach provided by the Applicant. This approach uses primarily read-across information available for structurally-related dyes of known *in vivo* irritation potential from the same chemical family. This information is combined with supporting data from *in vitro* assays for eye irritation. The read-across approach and information that is used are provided in Submission I. An overview on chemicals and studies used for the read across approach are given in Table 3 below. Details of the *in vitro* test method for eye irritation and the results are provided in Submission I ICE tests. Furthermore, the hair color p-phenylenediamine is accepted for eyelash use by the SCCS (SCCS/1475/12).

Addendum on the Opinion SCCS/1491/12 on hair dye 2-methoxy-methyl-*p*-phenylenediamine and its sulfate salt - A160 - Submission II – use on eyelashes**Table 3:** Overview of chemical structures and *in vivo* eye irritation data for 3 members of the *p*-phenylenediamine family structure and structurally related to 2-methoxy-methyl-*p*-phenylenediamine

COLIPA Number	Chemical Structure	Chemical Name	CAS Number	<i>In vivo</i> Eye Irritation
A160		2-methoxy-methyl- <i>p</i> -phenylenediamine	337906-36-2	No <i>in vivo</i> data available * <i>In vitro</i> data available: ICE Tests <u>Conclusion:</u> Not irritating to the eyes when applied at 1.83% and 6.1% (w/w) aqueous; irritating to eyes when applied neat
A005		<i>p</i> -Toluenediamine	95-70-5(free base)	Study I: 50.6% aqueous: Draize, 100 µl, no rinse, 1 rabbit. Slight to moderate corneal opacity, slight iritis and marked conjunctival irritation with redness/ chemosis. All effects fully reversed within 7-8 days. <u>Conclusion:</u> Irritating to the eyes Study II: 2.5% (w/v) aqueous: Draize, 100 µl, rinse after 10 seconds, 3 rabbits. Mild conjunctival irritation was observed in 2 animals on days 1 and 3 respectively. <u>Conclusion:</u> Practically non-irritating to eyes <i>Ref.: SCCS/1390/10 (2011)</i>
A007		<i>p</i> -Phenylenediamine	106-50-3 (free base)	2.5% aqueous; Draize, 100 µl, rinse after 10 seconds, 3 rabbits. Minimal conjunctival irritation in one animal only. <u>Conclusion:</u> Not irritating to the eyes <i>Ref.: SCCNFP/0129/99 (2002)</i>
A080		Hydroxyethyl- <i>p</i> -phenylenediamine sulfate	93841-25-9	Neat; Draize, 60mg (100 µl), no rinse; 3 rabbits. No corneal opacity, slight iritis at 24h and conjunctival redness/chemosis and discharge that resolved in 2/3 animals by day 7 and in the remaining animal by day 14. <u>Conclusion:</u> Irritating to the eyes <i>Ref.: SCCS/1310/10 revision of 12.07.10 (2010)</i>

**In vitro* data for 2-methoxymethyl-*p*-phenylenediamine have been added to Table 1 since they are used in the overall WoE approach as detailed in the text below

Using this read-across approach for dyes of the *p*-phenylenediamine family for which *in vivo* eye irritation data are available for neat and in the range of intended use concentrations, it is possible to conclude that:

- Members of the *p*-phenylenediamine family of dye materials tested neat are typically irritant to eyes. They are non-irritant to practically non-irritating to eyes when tested at the intended use concentrations *in vivo*.
- 2-methoxy-methyl-*p*-phenylenediamine as a member of the *p*-phenylenediamine family of dyes is predicted to be non-irritating to eyes when used at the intended use concentration of 1.82%.

As identified earlier, this read-across approach is the primary element in a Weight of Evidence (WoE) approach to identification of 2-methoxy-methyl-p-phenylenediamine as non-irritating to eyes at in-use concentrations. Other supporting data that are derived from *in vitro* studies are also included in the Weight of Evidence approach. The *in vitro* data support the primary conclusion that 2-methoxy-methyl-p-phenylenediamine will be not irritating to eyes at the in-use concentration (1.82%) since they demonstrate that 2-methoxymethyl-p-phenylenediamine is not irritating to eyes at 1.83% (w/w) aqueous and at the higher concentration of 6.1% (w/w) aqueous.

The neat 2-methoxy-methyl-p-phenylenediamine was tested to be irritating to eyes by *in vitro* RhCE test and the *in vitro* ICE test. Results from the *in vitro* ICE test demonstrate that 2-methoxy-methyl-p-phenylenediamine tested at 1.83 and 6.1% (w/w) is not irritating to eyes and does not require classification according to the EU-CLP classification scheme. Statements of test validity described in the text below justify that it is appropriate to use this *in vitro* assay. This is based on ICE being an ECVAM validated method (April 2007) for identification of severe eye irritants with subsequent establishment of an OECD test guideline (OECD 438) for this purpose in combination with publications from the peer-reviewed scientific literature (see *Reference 6, 7, 8 and 9*) on the use of ICE for identification of eye irritation lower than severe for chemicals and different product categories.

As such, these ICE studies are considered as sufficiently reliable to evaluate the eye irritation potential of 2-methoxy-methyl-p-phenylenediamine neat and at the intended use concentration of 1.82% in hair dye formulations.

The test results for eye irritation from the ICE tests were already reviewed and accepted by the SCCS, and documented in the "Opinion on 2-methoxy-methyl-p-phenylenediamine and its sulfate salt" (SCCS/1491/12). Details of the new *in vitro* RhCE study for eye irritation is provided below.

***In vitro* Eye Irritation Test: EpiOcular™ Eye Irritation Test (EIT)**

Guideline:	OECD 492 (2017)
Test system:	Reconstructed human Cornea-like Epithelium (EpiOcular™)
Replicates:	2 tissues per condition
Test Substance:	2-methoxy-methyl-p-phenylenediamine
Test Batch:	XXMBB161102W
Purity:	99.8 ± 0.1 area %
Test item:	Neat
Exposure dose:	50 mg (83.3 mg/cm ²) test item or 50 µL (83.3 µl/cm ²) controls
Treatment period:	6 hours ± 15 minutes
Positive control:	Methyl acetate
Negative control:	Deionised water
GLP:	In compliance
Study period:	6 February – 2 October 2018

Preliminary tests were performed to detect the ability of the test item formulation to directly reduce MTT as well as its colouring potential. Following the preliminary tests, the eye irritation potential of the test item formulation was assessed in the main test. The 50 mg 2-methoxy-methyl-p-phenylenediamine and both negative (deionised water) and positive (methyl acetate) controls were applied topically on duplicate tissues and incubated at 37°C for 6 hours. At the end of the treatment period, each tissue was rinsed with D-PBS, incubated for 25 minutes at room temperature to remove any remaining test item formulation absorbed into the tissue, blotted on absorbent material, and then incubated for another 18 hours at 37°C, 5% CO₂ in a humidified incubator. The cell viability was then

assessed by means of the colorimetric MTT reduction assay. Mean viability values were calculated for each tissue and expressed as a percentage of the mean viability of the negative control tissues which was set at 100% (reference viability).

Results

In the preliminary tests, the test item formulation was found to have direct MTT reducing properties and colouring potential. Therefore, additional tests with freeze-killed tissues and viable tissues (without MTT addition) had to be performed.

Main test

After treatment with the negative control, the absorbance values were well within the required acceptability criterion of $OD > 0.8$ and < 2.5 , thus showing the quality of the tissues. Treatment with the positive control induced a decrease below 50% viability compared with the negative control value in the relative absorbance, thus ensuring the validity of the test system. The difference of viability between the two relating tissues was $< 20\%$ in the same run (for test item tissues, positive and negative control tissues). The study was therefore considered to be valid.

Irritating effects were observed following incubation with neat 2-methoxy-methyl-p-phenylenediamine. Compared with the value of the negative control, the relative mean absorption value corresponding to the viability of the tissues decreased below 60% (-4.0% (threshold for irritancy: $\leq 60\%$) respectively to 4.1% without any data correction procedure), consequently the test item was irritant to eye.

Conclusion

In conclusion, neat 2-methoxy-methyl-p-phenylenediamine possesses an eye-irritating potential.

Ref.: Spohr, 2018

SCCS comment

The process used for read-across has not been explained in terms of whether it was based on a rule/principle/algorithm based system or random selection of analogues. It is not clear on what basis the structural analogues shown were selected, and whether any other analogues were omitted from the comparison.

The newly submitted study showed that neat 2-methoxy-methyl-p-phenylenediamine has to be considered as an eye irritant. However, based on all submitted data, 2-methoxy-methyl-p-phenylenediamine and its salt form are not expected to be irritant to the eye at the anticipated maximum in-use concentration of 1.8%.

3.3.2 Skin sensitisation

From SCCS/1491/12

1,4-Diamino-2-methoxy-methyl-benzene sulfate was a moderate skin sensitiser in the local lymph node assay (LLNA), with a calculated EC3 value of 7.11%.

SCCS Comment

For the free base of 1,4-diamino-2-methoxymethyl-benzene:
The EC3 value of the free base may be calculated from the sulfate salt by using the conversion factor to account for the different molecular weight.

- EC3 value SO₄-salt: 7.11%
- $7.11\% = 7.11 \text{ g/100 ml} \times 0.61$ (conversion factor) = 4.3 g/100 ml = 4.3%
- EC3 value free base: 4.3%

Therefore, the calculated EC3 value for the free base of 1,4-diamino-2-methoxy-methyl-benzene is 4.3%, which is a moderate skin sensitiser.

New data from Applicant's submission II dossier

No new data provided.

3.4 Safety evaluation

The MoS calculated previously for 2-methoxy-methyl-p-phenylenediamine as oxidative hair dye with a concentration on-head of maximum 1.8% was 800 (SCCS/1491/12). The SCCS concluded that this use does not pose a risk to the health of the consumer, but highlighted its sensitising potential (SCCS/1491/12). In comparison, the use of 2-methoxy-methyl-p-phenylenediamine and its sulfate salt in eyelash dye is expected to give hardly any systemic exposure, since the product is not applied to the skin and skin contact is likely minimal under foreseeable use conditions. The impact of this use on the exposure is therefore likely to be only marginal, even if consumers use both the hair dye as well as the eye lash on the same day. Therefore, SCCS concluded that it is not relevant to calculate the MoS for this specific use.

3.5 Discussion

The critical toxicological endpoints considered of relevance to the use of 2-methoxy-methyl-p-phenylenediamine and its sulfate salt on eyelashes are skin and eye irritation and skin sensitisation, either by the dye substance or hydrogen peroxide used as oxidant.

2-methoxy-methyl-p-phenylenediamine is not irritant to skin at anticipated use exposure.

The new eye irritation study showed that neat 2-methoxy-methyl-p-phenylenediamine has to be considered as an eye irritant. However, based on data provided in Submission I, 2-methoxy-methyl-p-phenylenediamine and its salt form are not expected to be irritant to the eye at the anticipated maximum in-use concentration of 1.8%.

2-methoxy-methyl-p-phenylenediamine is a moderate skin sensitiser. The use of this compound in eye lash dye is not expected to pose any risks for consumers when skin contamination is avoided by using a sticker around the eyes.

In cases where there is unintentional exposure to the skin surrounding the eyes, sensitisation may be induced if exposure is sufficiently high. Subsequent skin exposure may elicit allergic contact dermatitis in such cases. Individuals who are already sensitised to 2-methoxy-methyl-p-phenylenediamine are at the highest risk, since elicitation of allergic reactions occurs at lower exposure concentrations than induction.

The SCCS has previously raised some general concerns regarding the use of oxidative hair dyes in products used to dye the eyelashes (SCCS/1475/12, SCCS/1553/15), which are relevant for this Opinion as well. Transient exposure to 2% hydrogen peroxide may be slightly irritant to the skin and the eye.

4. CONCLUSION

In light of the data provided, does the SCCS consider 2-methoxy-methyl-p-phenylenediamine and its sulfate salt (A160) safe when used in oxidative eyelash colour products at maximum in-use concentration of 1.8 %?

Based on all data provided, the SCCS considers that 2-methoxy-methyl-p-phenylenediamine and its sulfate salt (A160) are safe to be used in oxidative eyelash colour products at the proposed maximum in-use concentration of 1.8%.

5. MINORITY OPINION

None.

6. REFERENCES

1. **Scientific Committee on Consumer Safety**, SCCS OPINION on oxidative hair dye substances and hydrogen peroxide used in products to colour eyelashes, SCCS/1475/12. Revision of 11 December 2012
2. **Scientific Committee on Consumer Safety**, SCCS OPINION on 2-methoxy-methyl-p-phenylenediamine and its sulfate salt, COLIPA n° A160, SCCS/1491/12, 18th plenary meeting of 26 February 2013
3. **Scientific Committee on Consumer Safety**, ADDENDUM to the scientific Opinion on the safety of oxidative hair dye substances and hydrogen peroxide in products to colour eyelashes, SCCS/1553/15, 9th plenary meeting on 25 March 2015
4. **Spohr, C.**; 2-METHOXY-METHYL-PPHENYLENEDIAMINE: In vitro Eye Irritation Test: Human Cornea Model Test – OECD 492. ENVIGO; 1-44, 2018

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
