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SCCS ADDENDUM TO THE OPINION ON Climbazole (P64) ref. SCCS/1506/13

Ulrike Bernauer, Laurent Bodin, Leonardo Celleno, Qasim Chaudhry, Pieter Jan Coenraads, Maria Dusinska, Janine Ezendam, Eric Gaffet, Corrado Lodovico Galli, Berit Granum, et al.

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Scientific Committee on Consumer Safety

SCCS

ADDENDUM TO THE OPINION ON

Climbazole (P64) ref. SCCS/1506/13

The SCCS adopted this final addendum to the opinion
during the plenary meeting of 24-25 October 2017

About the Scientific Committees

Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.
They are: the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and are made up of independent experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

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

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

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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

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This Addendum to the Opinion is final and has not been subject to a commenting period as requested by the mandating DG because it was about revision of calculation only.

Keywords: SCCS, addendum, scientific opinion, Climbazole, preservative, P64, Regulation 1223/2009, CAS 38083-17-9, EC 253-775-4

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

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1. BACKGROUND

The cosmetic ingredient Climbazole (CAS 38083-17-9), with the chemical name 1-(4-chlorophenoxy)-1-imidazol-1-yl-3,3-dimethyl-2-butanone, is currently regulated in the Cosmetics Regulation (EC) 1223/2009 as a preservative in Annex V, entry 32, up to a maximum authorized concentration of 0.5%.

Climbazole has been subject to different safety evaluations by the SCCP in 2005 (SCCP/0918/05[1]) and 2009 (SCCP/1204/08[2]) and by the SCCS in 2013 (SCCS/1506/13[3] and SCCS/1500/13[4]).

In particular, in the opinions of 2009 and later in 2013, the experts assessed the combined use of Climbazole in different cosmetic product categories as preservative at concentration up to 0.5% in leave-on cosmetics and as anti-dandruff agent in rinse-off hair products up to a maximum concentration of 2%. Margin of Safety (MoS) values were calculated for each product type and then combined to assess the safety of Climbazole for use in different product types (i.e. shampoo, hair lotion, face cream, foot care).

The SCCS concluded in 2013 that the separate use or combined use of 2 of the above products, all containing Climbazole at the maximum requested concentration, does not pose a risk to the health of consumers.

However, the two combinations of 3 products that include both hair lotion as well as foot care (i.e. foot care/hair lotion/face care or foot care/hair lotion/shampoo) result in too high overall exposure. As a consequence, also the combined use of the 4 types of products (shampoo, hair lotion, foot care and face care cosmetic), all containing Climbazole at the maximum allowed concentration, results in too high consumer exposure.

Furthermore, in view of the on-going debate on the decreasing palette of authorised preservatives as well as the fact that less than 1% of products launched in the EU between 2010- 2015, as per specific product categories, contained Climbazole[5], in April 2017, Cosmetics Europe submitted to the Commission services new margin of safety data including a proposal for reduced concentrations of Climbazole for use in different product types.

[1] http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_027.pdf
[2] http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_164.pdf
[3] http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_120.pdf
[4] http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_121.pdf
[5] Cosmetics Europe document

2. TERMS OF REFERENCE

(1) In light of the new margin of safety data provided, does the SCCS consider safe the use of Climbazole (CAS 38083-17-9) as a cosmetic preservative in hair lotion and foot care with a maximum concentration of 0.31 % and in face cream with a maximum concentration of 0.5% and as anti-dandruff agent in shampoo with a maximum concentration of 2.0% under an aggregate exposure scenario for cosmetics?

(2) If not, what is according to the SCCS, the maximum concentration considered safe for use of Climbazole (CAS 38083-17-9) as a cosmetic preservative in hair lotion, foot care and face cream as well as anti-dandruff agent in rinse-off shampoos under an aggregate exposure scenario for cosmetics?

3. OPINION

In the current mandate, the SCCS is being asked to re-evaluate the safety levels of Climbazole in different cosmetic formulations under an aggregate exposure scenario.
In the process of reviewing the existing data, the Committee decided to make a new risk assessment according to the latest revision of the SCCS Notes of Guidance (SCCS/1564/15).
In consequence, the standard deviation values were added to the mean dermal absorption values and the application frequency F= 2.14/day for face creams was considered as a more realistic in-use scenario (replacing the frequency F= 1). For the sake of correctness, an application frequency (F= 2.28/day) has also been added to leave-on body lotion, although this application was already considered as unsafe in SCCP/1204/08.

3.1 Relevant Information taken from the previous opinions

3.1.1 General toxicological profile of Climbazole

Irritation / sensitisation

The previous results of an old Draize eye test and a combination of two newly carried out *in vitro* screening tests for eye irritation (HET-CAM and CEET) suggest that Climbazole is not an eye irritant. Its potential to cause skin irritation is assessed through a human single patch test and shows only mild to no skin irritation. Considering the results of the above studies and considering the dilution of the compound in its intended use, there appears to be no reason to suspect any irritation problems with the use of Climbazole in cosmetic products.
As far as sensitising potential is concerned, a well-performed LLNA shows Climbazole to be non-sensitising in the performed mice assay.

Ref. 5, 6

Dermal absorption

A well-performed dermal absorption study for Climbazole (2% in a shampoo formulation) is available and reveals a dermal absorption value of 0.297 ± 0.209 µg/cm² (0.506 µg/cm²) or 0.150 ± 0.106 % (0.256%). As far as application under leave-on conditions at a concentration of 0.5% is concerned, a recent *in vitro* dermal absorption study reveals absorption levels of 1.10± 0.619 µg/cm² (1.719) or 2.23± 1.12% (3.35%) and 1.25 ± 0.469 µg/cm² (1.719) or 3.46±1.25% (4.71%) for an aqueous hair lotion and a water-in-oil skin preparation, respectively.

Ref. 6

General toxicity

Several subacute and subchronic studies with rodents and non-rodents were available, although they were performed before the introduction of GLP. Based upon the available test descriptions and raw data, the SCCP deduced a **conservative NOEL** value of **5 mg/kg bw/day** from the presented 90-day oral rat study.

Ref. 5

Mutagenicity / genotoxicity

Climbazole showed to be negative in an Ames test, in an *in vitro* micronucleus test and in an *in vitro* mammalian cell gene mutation test (with the exception of the prolonged exposure scheme, where some mutagenic potential became apparent).
An *in vivo* micronucleus test and an *in vivo* UDS assay with Climbazole showed the substance to be negative, meaning that no mutagenic/genotoxic effects are to be expected.

Ref. 6

Reproduction toxicity

Climbazole was tested in a 1-generation reproductive toxicity test which was considered questionable as far as its overall scientific validity is concerned. Also, a well-performed teratogenicity study was present, leading to a NOAEL (embryotoxicity) of 30 mg/kg bw/day and a NOAEL (maternal toxicity) of 15 mg/kg bw/day.

Ref. 5

Toxicokinetics

An oral bioavailability assay of ^{14}C Climbazole in mice confirmed the results that were described earlier, namely that Climbazole is rapidly absorbed and excreted and that its maximum concentration in plasma is reached after approximately 8 hours. These data were published by Pérez-Rivera et al.(2009).

Ref. 4, 6

SCCS comments
SCCS is aware of the current assessment of Climbazole under REACH. Climbazole has been put on the Community rolling action plan (CoRAP) by the competent Authority of the United Kingdom (evaluating MSCA), due to initial grounds for concern relating to human health/suspected CMR (reproductive toxicity, with unusual and severe general toxicity noted). Following the assessment made by the evaluating MSCA and on behalf of ECHA, the decision from 30 June 2016 was published on the ECHA website (ECHA Decision on substance evaluation pursuant to Article 46(1) of Regulation (EC) No 1907/2006 (REACH) for Climbazole, 30 June 2016;
https://echa.europa.eu/documents/10162/5640e75e-2bcc-45ad-8468-3decf06b9ea8
(in appeal: case A-009-2016;
https://echa.europa.eu/documents/10162/13574/a-009-2016_announcment_en.pdf)

The evaluating MSCA considered that further information was required to clarify the above-mentioned concerns and asked for:

- An extended one-generation reproductive toxicity study (OECD 443) in rats, by oral route
- *In vitro* endocrine disruption screening studies such as an H295R Steroidogenesis Assay (OECD 456) and either a Stably Transfected Human Androgen Receptor Transcriptional Activation Assay for Detection of Androgenic Agonist and Antagonist Activity of Chemicals (OECD 458) or an Androgen Receptor Binding Assay.

The evaluating MSCA considered that there was some evidence that Climbazole had a specific effect on reproduction (sexual function and fertility; specifically, parturition and pregnancy outcomes) in the rat, although this interpretation was associated with a considerable number of uncertainties in terms of the information available in the study reports.

Based on these considerations, the SCCS will closely follow up the outcome of further studies to be conducted in the context of the REACH legislation and, if necessary, reassessment of the safety of Climbazole will be carried out.
In this risk assessment the previously used conservative NOEL of 5 mg/kg bw/day, derived from a 90-day oral repeated dose toxicity study in rat, will be used. No correction is made for oral bioavailability as an earlier study, carried out in male mice, showed rapid absorption and high bioavailability in plasma using radiolabelled Climbazole (Ref 4).

Calculation for the use of Climbazole at 2% as an anti-dandruff agent in shampoo

Dermal absorption through human skin	A (µg/cm²)	=	0.506 µg/cm²
Skin Area surface (area hand + ½ area head)	SAS (cm²)	=	1440 cm²
Frequency of application of the finished product	F (day^{-1})	=	1.00
Typical human body weight		=	60 kg
Systemic exposure dose (SED)	A x (10^{-3}mg/µg) x SAS / 60 kg	=	0.0121 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day
Margin of Safety	NOEL/ SED	=	413

Calculation for the use of Climbazole as preservative at 0.31% in aqueous hair lotions

Dermal absorption through human skin*	A (µg/cm²)	=	1.065 µg/cm²
Skin area surface (area hand + ½ area head)	SAS (cm²)	=	1440 cm²
Frequency of application of the finished product	F (day-1)	=	1.00
Typical human body weight		=	60 kg
Systemic exposure dose (SED)	A x (10^{-3}mg/µg) x SAS / 60 kg	=	0.0255 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day
Margin of Safety	NOEL / SED	=	196

Calculation for the use of Climbazole as preservative at 0.5% in a cosmetic face cream: application 2.14 times/day according to frequency of application per product type by Bremmer et al. (2006a, 2006b) and SCCS/1564/15

Dermal absorption through human skin	A (µg/cm²)	=	1.719 µg/cm²
Skin area surface (1/2 area head female)	SAS (cm²)	=	565 cm²

Frequency of application of the finished product	F (day^{-1})	=	2.14
Typical human body weight		=	60 kg
Systemic exposure dose (SED)			
A x (10^{-3}mg/µg) x SAS x F (day-1) / 60 kg		=	0.0346 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day

Margin of Safety	NOEL / SED	=	144

Calculation for the use of Climbazole as preservative at 0.5% in leave-on body lotion application 2.28 times/day (according to frequency of application per product type by Bremmer et al. (2006a, 2006b) and SCCS/1564/15

Dermal absorption through human skin	A (µg/cm²)	=	1.719 µg/cm²
Skin area surface (whole body)	SAS (cm²)	=	18,000 cm²
Frequency of application of the finished product	F (day^{-1})	=	2.28
Typical human body weight		=	60 kg
Systemic exposure dose (SED)	A x (10^{-3}mg/µg) x SAS / 60 kg	=	1.175 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day

Margin of Safety	NOEL/ SED	=	4

Calculation for the use of Climbazole as preservative up to 0.31% in foot care products

Dermal absorption through human skin*	A (µg/cm^2)	=	1.065 µg/cm²
Skin area surface (feet, Ref. 2)	SAS (cm^2)	=	1170 cm^2
Frequency of application of the finished product	F (day-1)	=	1.00
Typical human body weight		=	60 kg
Systemic exposure dose (SED)			
A x (10^{-3}mg/µg) x SAS x F (day-1)/ 60 kg		=	0.0207 mg/kg bw
No observed effect level (90 day, oral, rat)	NOEL	=	5 mg/kg bw/day

Margin of Safety	NOEL / SED	=	241

* dermal absorption A (µg/cm^2) has been proportionally adjusted for the requested, lowered concentration of Climbazole from 0.5 to 0.31%

The individual uses of Climbazole, except its use as preservative up to 0.5% for whole body applications (MoS= 4), are considered safe:

- as an anti-dandruff compound up to 2% in cosmetic shampoos (MoS= 413),
- as preservative up to 0.31% in an aqueous hair lotion (MoS= 196),
- as preservative up to 0.5% in a face cream (MoS= 144),
- as preservative up to 0.31% in foot care (MoS= 241).

However, combinations of products that include both hair lotion as well as foot care and another product (i.e. foot care/hair lotion/face cream or foot care/hair lotion/shampoo) result in a too high overall exposure (MoS lower than 100) and cannot be considered as safe (Tab.1).

	Inclusion %	A* (ug/cm$^{2)}$	SAS (cm^2)	F (day^{-1})	bw (kg)	SED	NOEL (mg/kg/day)	MoS
shampoo	2	0.506	1440	1	60	0.0121	5	413
hair lotion	0.31	1.065	1440	1	60	0.0255	5	196
face cream	0.5	1.719	565	2.14	60	0.0346	5	144
foot care	0.31	1.065	1170	1	60	0.0207	5	241
shampoo + hair lotion						0.0376	5	132
shampoo + face cream						0.0467	5	107
shampoo + foot care						0.0328	5	152
hair lotion + face cream						0.0601	5	83
hair lotion + foot care						0.0462	5	108
face cream + foot care						0.0553	5	90
shampoo + hair lotion + face cream						0.0722	5	69
shampoo + hair lotion + foot care						0.0583	5	85
shampoo + face cream + foot care						0.0674	5	74
hair lotion + face cream + foot care						0.0808	5	61
shampoo + hair lotion + face cream + foot care						0.0929	5	53

Tab. 1 Combined use of Climbazole at maximum concentration as preservative (0.31% and 0.5%) in leave-on and rinse-off cosmetic products and as an anti-dandruff agent in shampoo (2%), respectively; realistic frequency of use values and conservative absorption values +1SD were taken into consideration; *Dermal absorption values were proportionally adjusted for the requested, lowered concentration of Climbazole (from 0.5 to 0.31%).
NOTE: only cosmetic products with MoS ≥ 100 were included in combined-use calculations.

In Table 1, the SED and MOS for all possible combinations of 2, 3 and 4 cosmetic products containing Climbazole at the requested maximum concentration are shown. Note, however, that only the products that are individually safe for the consumer have been included. When 1 SD was added to the dermal absorption values and a realistic frequency factor for face creams was taken into consideration, some of 2- and all of 3- and 4-product combinations provide a MOS < 100.

Since no experimental data were present for the dermal absorption study of the lowered concentration (0.31%) of Climbazole, the earlier accepted dermal absorption values for 0.5% were proportionally adjusted for the lower concentration of Climbazole.

The maximum concentrations of Climbazole, considered as safe for human health under an aggregate exposure scenario, are calculated as follows:

	Inclusion %	A* (ug/cm2)	SAS (cm2)	F (day-1)	bw (kg)	SED	NOEL (mg/kg/day)	MoS
shampoo	2	0.506	1440	1	60	0.0121	5	413
hair lotion	0.2	0.687	1440	1	60	0.0164	5	304
face cream	0.2	0.687	565	2.14	60	0.0138	5	362
foot care	0.2	0.687	1170	1	60	0.0133	5	375
shampoo + hair lotion						0.0285	5	175
shampoo + face cream						0.0259	5	193
shampoo + foot care						0.0254	5	196
hair lotion + face cream						0.0302	5	165
hair lotion + foot care						0.0297	5	168
face cream + foot care						0.0271	5	184
shampoo + hair lotion + face cream						0.0423	5	118
shampoo + hair lotion + foot care						0.0418	5	119
shampoo + face cream + foot care						0.0392	5	127
hair lotion + face cream + foot care						0.0435	5	114
shampoo + hair lotion + face cream + foot care						0.0556	5	89

Tab. 2 Combined use of Climbazole at maximum concentration as preservative at 0.2% in leave-on and rinse-off cosmetic products and as an anti-dandruff agent in shampoo at 2%; realistic frequency of use values and conservative absorption values +1SD were taken into consideration; *Dermal absorption values were proportionally adjusted.
NOTE: only cosmetic products with MoS ≥ 100 were included in combined-use calculations.

3.3 Discussion

As it is possible that different cosmetic products containing Climbazole at the highest requested concentration (safe for the consumer when used individually) are applied simultaneously, the safety of their combination should also be considered. As such, in the Addendum to Opinion SCCS/1506/13, revision of 18 June 2013, the combination of 3 products (foot care product, face cream and hair lotion) was not considered safe for the consumer.
After lowering the concentration of Climbazole in hair lotion and foot care products from 0.5 to 0.31%, the applicant requested a re-evaluation of the safety of combining several products containing Climbazole.
The Committee recalculated the SED and MoS values according to the principles of the Notes of Guidance [SCCS/1564/15]. However, in a cumulative exposure scenario, the resultant MoS calculations do not support the safe use of Climbazole in 'hair lotion and face cream' and 'face cream and foot care',or in any of 3- and 4- cosmetic products combinations.
As recently some concern was raised by ECHA (see under SCCS comments), individual MoS calculations were interpreted in a conservative way (values close to 100, but lower than 100, were not considered to be safe).

4. CONCLUSION

1. In light of the new margin of safety data provided, does the SCCS consider safe the use of Climbazole (CAS 38083-17-9) as a cosmetic preservative in hair lotion and foot care with a maximum concentration of 0.31 % and in face cream with a maximum concentration of 0.5% and as anti-dandruff agent in shampoo with a maximum concentration of 2.0% under an aggregate exposure scenario for cosmetics?

The use of Climbazole (CAS 38083-17-9) as a cosmetic preservative in hair lotion and foot care with a maximum concentration of 0.31 % and in face cream with a maximum concentration of 0.5% and as anti-dandruff agent in shampoo with a maximum concentration of 2.0% are, when individually used, safe for human health. Combinations of 3- or 4- products, however, cannot be considered as safe. Most combinations of 2 products can be considered as safe, the combinations of 'hair lotion and face cream' and 'face cream and foot care' give, using the conservative "adding on calculation", a MoS below 100 (83 and 90, respectively).

2. If not, what is, according to the SCCS, the maximum concentration considered safe for use of Climbazole (CAS 38083-17-9) as a cosmetic preservative in hair lotion, foot care and face cream as well as anti-dandruff agent in rinse-off shampoos under an aggregate exposure scenario for cosmetics?

The maximum concentrations of Climbazole considered as safe for human health under an aggregate exposure scenario are as follows:
2% as anti-dandruff agent in rinse-off shampoos and 0.2 % as cosmetic preservative in leave - on formulations (face cream, hair lotion, foot care) with the exception of cosmetics applied on a full body area (body lotion).

Based on the considerations by ECHA, the SCCS will closely follow up the outcome of further studies to be conducted in the context of the REACH legislation and, if necessary, will reassess the safety of Climbazole.

5. MINORITY OPINION

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6. REFERENCES

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