EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS

SCCP

Opinion on

Vetiveryl acetate

(sensitisation only)

Adopted by the SCCP
during the 7th plenary meeting of 28 March 2006

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1. BACKGROUND

During the 18th Plenary meeting of 25 September 2001, the Scientific Committee on Cosmetic Products and Non-Food Products intended for the Consumer (SCCNFP) adopted an opinion on an initial list of perfumery materials to be included in Annex III - List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down - to Directive 76/768/EEC (doc. n° SCCNFP/0392/00 final).

The SCCNFP adopted its first update of the "Initial List of Perfumery Materials which must not form part of Cosmetic Products except subject to the restrictions and conditions laid down" during the 26th plenary meeting of 9 December 2003 (doc. N° SCCNFP/0770/03). For further evaluation of fragrance ingredients the SCCNFP asked for additional information.

The European Flavour & Fragrance Association informed the Commission of the recently submitted information on Vetiveryl acetate.

2. TERMS OF REFERENCE

1. *On the basis of currently available information, the SCCP is asked to assess the risk to consumers when vetiveryl acetate is present in cosmetic products, and if necessary, to revise the maximum concentration in fragrances used in cosmetic products considering the concentration limits or other restrictions suggested by industry.*

2. *And/or does the SCCP recommend any further restrictions with regard to the presence of vetiveryl acetate as an ingredient of fragrances used in cosmetic products?*

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

* Vetiveria zizanioides, ext. Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene - free fractions, distillates, residues, etc., obtained from Vetiveria zizanioides, Gramineae
CAS: 84238-29-9
EINECS: 282-490-8

* Vetiveria zizanioides, ext., acetylated *
CAS: 84082-84-8
EINECS: 282-031-1

* Vetiverol
CAS: 68129-81-7
EINECS: 268-578-9

Vetiverol, acetate
CAS: 62563-80-8
EINECS: 263-597-9

3.1.1.1. Primary name and/or INCI name

Vetiveryl acetate results from the acetylation of "*Vetiveria Zizanioides* Root oil" (INCI name)

3.1.1.2. Chemical names

1,2,3,3a,4,5,6,8a-Octahydro-2-isopropylidene-4,8-dimethylazulen-6-yl Acetate

3.1.1.3. Trade names and abbreviations

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3.1.1.4. CAS / EINECS number

CAS number for "*Vetiveria Zizanioides* Root oil": 8016-96-4
RTECS number for "*Vetiveria Zizanioides* Root oil": YY3180000

EINECS number for vetiveryl acetate:	204-225-7	263-597-9
CAS number for vetiveryl acetate:	117-98-6	62563-80-8

3.1.1.5. Structural formula

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3.1.1.6. Empirical formula

/

3.1.2. Physical form

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3.1.3. Molecular weight

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3.1.4. Purity, composition and substance codes

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3.1.5. Impurities / accompanying contaminants

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3.1.6. Solubility

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3.1.7. Partition coefficient (Log P_{ow})

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3.1.8. Additional physical and chemical specifications

Restrictions: Only if acetylated with acetic anhydride either without catalyst (at<120°), or with orthophosphoric acid (at room temperature), or with sodium Acetate in toluene(reflux) followed by distillation

3.2. Function and uses

Vetiver is an important woody note in perfumery. Approximately 40 to 60 tons are used per year (ref parfums Cosmétiques actualité N° 138 décembre 1997).

Vetiveryl acetate, as used, is a mixture of products resulting from direct acetylation of crude vetiver oil with acetic anhydride. The esterification is performed in order to improve the olfactory properties of the oil, because of the higher volatility of the acetate. (ref Chromatographia vol. 28 December 1989). The vetiveryl acetate used in perfumery industry contains a variety of substances including 5-15% of sesquiterpenes. In gas chromatography/

mass spectrometry it produces more than 100 peaks (perfumer & flavorist, vol. 20 January 1995).

3.3. Toxicological Evaluation

3.3.1.	Acute toxicity

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3.3.2.	Irritation and corrosivity

3.3.2.1.	Skin irritation

Guideline: /
Species: human volunteers
Group: 231
Substance: vetiveryl acetate
Purity: 76%
Batch: /
Dose: /
GLP: /

Primary irritation was studied by Takenaka (ref document n° 11652, 1986?).
Closed patch testing on the back or forearm was applier for 24 or 48 hours and the results read 30 minutes after removal. It was a part of a global survey of intolerance to perfumes carried out over several years. Vetiveryl acetate was considered irritating to 6 subjects with an erythema (+) and 8 with a slight erythema (±) in a population of 231 subject tested, while vetiverone and vetiverol did not induce any reaction on 35 subjects.

3.3.2.2.	Mucous membrane irritation

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3.3.3.	Skin sensitisation

Maguire hypersensitivity tests in guinea pig

Guideline: /
Species: Hartley female Guinea pig
Group: 8 per treatment group
Substance: vetiveryl acetate
Batch: /
Purity: /
Dose: 4 x 0.2 ml test substance (day 0, 2, 4 and 7)
2 x 0.1 ml Freund's complete adjuvant (i.d.) on day 4
GLP: /

This test, similar to a Buehler test (with a maximisation process of 4 sensitising doses on abraded skin covered with Blenderm followed by 2 challenges), was performed on 8 animals with vetiveryl acetate specially purified (72-20-236); 4 weak positive and one positive were observed.

Ref.: (document 5745 year 1973)

Guideline: /
Species: Hartley albino Guinea pig
Group: 10 (males and females) for each test
Substance: vetiveryl acetate
Batch: /
Purity: /
Dose: 0.1 ml, 20 % (sensitisation), solvent not stated
0.1 ml, 0.25 % (challenge), solvent not stated
GLP: /

A modified Draize procedure was used (10 guinea pigs; four simultaneous sensitising injections; one topical and one intradermal challenge 14 days later). Vetiveryl acetate was used at a concentration of 20% for sensitization and 0.25% as a challenge concentration. It was considered a sensitiser (number of positive animals not given) after two sensitisation treatments. The author notes the discordance with the human sensitisation tests performed by Kligman which were negative.

Ref.: Sharp Toxicology 9 (1978) 261-271

Guideline: /
Species: Guinea pig
Group: not stated
Substance: vetiver acetate
Batch: /
Purity: /
Dose: not stated (test concentration: 20 %)
GLP: /

An open epicutaneous test was performed on groups of six to eight guinea pigs on 194 substances including vetiveryl acetate at a concentration of 20%. No reaction was observed. The author noted a good correlation between his test and the human maximisation test performed by Kligman on the same substances.

Ref.: document (4154 year 1979)

Marzulli and Maguire compared the results obtained by various guinea pig sensitizing methods. The superiority of the guinea pig maximisation test (GMPT) over Draize, Buehler, split-adjuvant, and cyclophosmamide – complete Freund's adjuvant techniques was shown and the comparison with Marzulli & Maibach test in human given. For each guinea pig test three round using each time 10 animals were performed. Vetivert acetate was used at a concentration of 20%. The results were as follow:

	Round 1	Round 2	Round 3	Cumulative

Draize	0	0	0	0
Buehler	0	0	0	0
Cy/CFA	1	2	0	3
GPMT	2	5	4	11
Spilt adjuvant	6	2	2	10

The results of the human test using a 20% concentration showed one sensitisation in 62 subjects tested. After having used several other guinea pig tests using DMSO the authors concluded that the GMPT was the best with less false negative tests when compared to human tests.

Ref.: Marzulli and Maguire; Fd.chem.toxic.vol 20 p67-74, 1982

In conclusion, these guinea pig tests suggest that vetiveryl acetate is a weak allergen**.**

3.3.4. Dermal / percutaneous absorption

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3.3.5. Repeated dose toxicity

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3.3.6. Mutagenicity / Genotoxicity

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3.3.7. Carcinogenicity

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3.3.8. Reproductive toxicity

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3.3.9. Toxicokinetics

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3.3.10. Photo-induced toxicity

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3.3.11. Human data

The materials were pretested on five subjects in order to determine whether SLS pre treatment was required; no subject had any irritation from vetiveryl acetate (VA) and so SLS pre treatment was used.
Maximisation test was performed according to its description in Journal of Investigative Dermatology vol. 47 N°5; pp 393-409; 1966: application under occlusion to the same sites on volar forearms for five alternate day 48 hours periods. Following a ten days rest period, challenge was applied under occlusion on a fresh site, preceded by one hour application of 10% SLS under occlusion. The challenge sites were read on removal of the patch and 24 hours thereafter. Various batches of vetiveryl acetate were tested which are listed below with their RIFM number and specification (VA type) when available. In none of these papers is the concentration given. Data from the article of Marzulli & Maibach (J. Environmental Pathology and Toxicology3:235-245; 1980) suggested that the sensitisation and challenge concentrations were 20%.

Kligman 1972

RIFM N°	VA type	N° Subjects	N° positive	conclusion
71-20-90	VA	25	3	mild sensitiser
71-20-90	VA	25	2	weak
72-20-236	VA special	25	0	not sensitiser

Kligman 1976

SM- 20-676	VA redist.	25	6 (4+)	mild
SM-20-676CaR(6)	VA over $CaCO_3$	25	14	strong
76-20-vaa	VA A	25	7	mild
78-20-VAB-D	VA dist B	25	0	not sensitiser
RIFM 72-8-74	VA R	25	0	not sensitiser
SM 20-676 RES	VA RESIDUE	25	0	not sensitiser

Epstein 1977

RIFM N°				
76-20-VAB	VA B	25	1	
76-20-VAV	VA C	30	3 (1 irritation)	
76-20-VAD	VA D	28	1 (1 irritation)	
76-20-VAB	VA B	21	1	
76-20-VAC	VA C	26	5	
79-20-J-SL	VA-J-SL	32	0	
79-20-H-SL	VA-H-SL	32	0	
76-20-VAAR (7)	VA A	24	0	
78-20-VAAD	VA dist A	32	6	
78-20-VA-33A	VA	32	2(2 irritation)	
79-20-IF	VA-IF	26	0	
79-20-IIF	VA-IIF	29	0	
79-20-I-TESS	VA-I-TESS	29	0(3 irritation+)	
79-20-IV-F	VA IV F	26	2	

79-20-V TESS	VA V TESS	27	0
79-20-VI TESS	VA VI TESS	26	0
79-20IV-TESS	VA IV TESS	24	0

A comparison of the results of maximisation test (RIFM) and modified Draize test (FDA) in human was done by Marzulli & Maibach showing an "intermediate sensitising potential" of vetiveryl acetate. The fact that the preparations used were not stable and that the purity of the preparation had to be improved was exemplified.

Comment
The SCCP does not consider these studies as ethical.

3.3.12. Special investigations

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3.3.13. Safety evaluation (including calculation of the MoS)

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3.3.14. Discussion

The submitted information is old with studies being largely performed during the 1970s. The methods used to assess the sensitising potential of vetiveryl acetate are unacceptable; human maximisation testing is considered unethical.

Batches of vetiveryl acetate tested were of unknown purity.

4. CONCLUSION

The SCCP is of the opinion that the information submitted is inadequate to assess the safe use of the substance.

Before any further consideration, the following information is required:

- Characterisation of the test substance; clarification on purity and impurities;
- Data on sensitisation conforming to modern standards and guidelines;
- Appropriate information on all relevant toxicological endpoints as required to assess the safe use of the substance when used in cosmetic products.

5. MINORITY OPINION

Not applicable

6. REFERENCES

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