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

Cresylpropionaldehyde *(p-Methyldihydrocinnamaldehyde)*

(sensitisation only)

Adopted by the SCCP during the 3rd plenary meeting
of 15 March 2005

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1. BACKGROUND

During the 18th Plenary meeting of 25 September 2001, the SCCNFP[1] adopted an opinion (SCCNFP/0392/00 final) on an initial list of perfumery materials to be included in Annex III to Directive 76/768/EEC.

Following a review of the list, the SCCNFP adopted an updated opinion (SCCNFP/0770/03) during the 26th plenary meeting of 9 December 2003. The SCCNFP asked for additional information to allow further evaluation of fragrance ingredients.

For further evaluation of fragrance ingredients the SCCNFP asked for additional information.

In June 2004, the European Flavour & Fragrance Association submitted additiona1 information on the following fragrances:

- Methylhydrocinnamic aldehyde
- Tagetes absolute, Tagetes minuta absolute and Tagetes oil
- Opoponax
- Storax

2. TERMS OF REFERENCE

- *On the basis of currently available information, the SCCP is asked to assess the risk to consumers when Methylhydrocinnamic aldehyde 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.*

- *Does the SCCP recommend any further restrictions with regard to the presence of Methylhydrocinnamic aldehyde as an ingredient of fragrances used in cosmetic products?*

[1] SCCNFP - Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumer

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Cresylpropionaldehyde (EU Inventory Name)

3.1.1.2. Chemical names

3-p-Cresylpropionaldeyde (IUPAC)
3-p-Cresylpropanal (IUPAC)
3-(4-Methylphenyl)propanal (IUPAC)
3-(p-Methylphenyl)propanal (IUPAC)
3-p-Tolylpropionaldeyde (IUPAC)
Benzopropanal, 4-methyl (CAS)
p-Methyldihydrocinnamaldehyde
p-Methylhydrocinnamaldehyde (IFRA synonym)

3.1.1.3. Trade names and abbreviations

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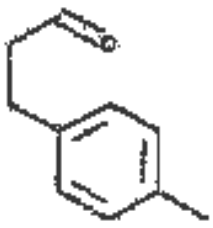
3.1.1.4. CAS / EINECS number

CAS : 5406-12-2
EINECS : 226-460-4

3.1.1.5. Structural formula



3.1.1.6. Empirical formula

Formula : $C_{10}H_{12}O$

3.1.2. Physical form

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3.1.3. Molecular weight

Molecular weight : 148.18

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

/

3.1.7. Partition coefficient (Log P_{ow})

Log P_{ow} : /

3.1.8. Additional physical and chemical specifications

Organoleptic properties	:	/
Melting point	:	/
Boiling point	:	/
Flash point	:	/
Vapour pressure	:	/
Density	:	/
Viscosity	:	/
pKa	:	/
Refractive index	:	/

3.2. Function and uses

Cresylpropionaldehyde is a fragrance ingredient of many fragrance compounds used in perfumery, mainly in hydroalcoholic products. Because of industry assessment that the substance has the potential to cause sensitisation, the IFRA standard recommends:

“p-Methylhydrocinnamic aldehyde should not be used such that the level in consumer products exceeds 0.2%. This is equivalent to 1% in a fragrance compound used at 20% in the consumer product. For use in consumer products for which no skin contact is foreseeable under normal conditions of use, e.g. closed system air fresheners, toilet blocks but not rinse off products and household cleaning products, the level in the consumer product should not exceed 0.4%.

This recommendation is based on test results of RIFM showing sensitization reaction at 20% and no sensitization reaction when tested at 2% (private communication to IFRA)."

In the updated EU Inventory, Section II: Perfume and Aromatic Raw Materials (doc. SCCNFP/0389/00), the above restriction (previously flagged with one asterisk) is summarized as follows:

"Maximum level 0.2 % in the finished product."

3.3. Toxicological Evaluation

3.3.1. Acute toxicity

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3.3.2 Irritation and corrosivity

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3.3.3. Skin sensitisation

Human Predictive (induction) Studies

A maximization test (8, 9) was carried out with 20% test substance in petrolatum (equivalent to a dose/unit area of 13,793 μg/cm^2) on 24 male and female volunteers. Application was under occlusion to the same site for five alternate-day 48-hour periods. Following a 10-14-days rest period, a challenge patch was applied to a fresh site for hours under occlusion. Positive reactions were observed in seven patients (7/24).

Ref.: 4

A second maximization test was carried out with 2% in diethyl phthalate (equivalent to a dose/unit area of 1379 μg/cm^2) on 23 male and female volunteers. Application was under occlusion to the same site for five alternate-day 48-hour periods. Following a 10-14-days rest period, a challenge patch was applied to a fresh site for 48 hours under occlusion. No reactions were observed (0/23).

Ref.: 6

Animal Studies

A Buehler delayed hypersensitivity test was conducted on 3 groups of Hartley albino guinea pigs (20 animals each). Each animal received three 6-hour occluded induction applications (once a week for 3 weeks) with 100% Cresylpropionaldehyde. Approximately two weeks later, it was followed by a six-hour occluded challenge application to a distant site. Reactions were read at 24 and 48 hours with 1%, 3% and 10% Cresylpropionaldehyde in diethyl phthalate.

Results
No reactions at 1 % (0/20)
1/20 reactions at 3%
5/20 reactions at 10%

Ref.: 5

Sensitization was evaluated in a Local lymph node assay (LLNA). Female CBA/J mice (n= 54) were tested with Cresylpropionaldehyde at dose levels of 25% and 50% in acetone / olive oil (4:1) and 100%. Each animal treated by a daily topical application of 25 µL on the dorsal surface of each ear for 3 consecutive days. Five days after the first topical application, mice were injected intravenously through the tail vein with [^{3}H]methylthymidine (^{3}HTdR) in saline. After 5 hours, draining auricuIar lymph nodes were removed and single cell suspensions were prepared. [^{3}H]TdR incorporation was measured by β-scintillation counting and stimulation indices were determined for each experimental group. Sensitization effects were observed. The Stimulation Index (SI) was 3.6 at 25% concentration, 9.0 at 50% and 16.4 at 100%.

Ref.: 7

In three consecutive LLNA studies (1-3), female CBA/Ca mice were tested with Cresylpropionaldehyde at dose levels of 0% (blank), 2.5%, 5%, 10%, 25%, and 50% in acetone/olive oil (4:1). Each animal received a daily topical application of 25 µl on the dorsal surface of each ear for 3 consecutive days. Five days after the first topical application, mice were injected intravenously through the tail vein with [^{3}H]methylthymidine (^{3}HTdr) in phosphate buffered saline. After 5 hours lymph cells were isolated and cultured. Incorporation of [3H]TdR was measured by β-scintillation counting. Stimulation indices were determined for each experimental group. Sensitization effects were observed. The Stimulation Index (SI) was 1.22 at 2.5% concentration, 1.36 at 5%, 2.61 at 10%, 4.21 at 25% and 10.69 at 50%. The calculated EC3 value was approximately 14%. Cresylpropionaldehyde was classified as a weak sensitizer.

Ref.: 1, 2, 3

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

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3.3.12. Special investigations

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3.3.13. Safety evaluation (including calculation of the MoS)

CALCULATION OF THE MARGIN OF SAFETY

Not applicable

3.3.14. Discussion

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4. CONCLUSION

The provided human and animal data demonstrate that Cresylpropionaldehyde (p-Methyldihydrocinnamaldehyde) is a contact allergen. However, under the conditions of its anticipated use as a fragrance ingredient (maximum 0.2% in the finished cosmetic product), the risk of sensitisation is low.

5. MINORITY OPINION

Not applicable

6. REFERENCES

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