

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

Atranol and Chloroatranol present in natural extracts (e.g. oak moss and tree moss extract)

Adopted by the SCCP
during the 2nd plenary meeting of 7 December 2004

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1. BACKGROUND

Chloroatranol is an ingredient present in natural extracts such as oak moss. Oak moss extract (CAS No 900028-68-5) is listed in Annex III of Directive 76/768/EEC with the following requirements: “The presence of the substance must be indicated in the list of ingredients referred to in Article 6(1)(g) when its concentration exceeds 0.001 % in leave-on products and 0.01 % in rinse-off products”. Chloroatranol and atranol as such are not regulated in an annex to the Cosmetics Directive.

The European Commission received a letter from the University Louis Pasteur, Strasbourg, France, with data demonstrating that chloroatranol is a potent fragrance allergen in cosmetic products.

The European Flavour and Fragrance Association (EFFA) submitted a study “Local Lymph Node Assay (LLNA) – Sensitisation dossier on Atranol and Chloroatranol” and information on the levels of these substances in oak moss and tree moss.

2. TERMS OF REFERENCE

The SCCP is requested to answer the following questions:

* *On the basis of currently available information, the SCCP is asked to assess the risk to the consumer when atranol and chloroatranol are present in cosmetic products, and if necessary to revise atranol and chloroatranol maximum concentration in fragrances used in cosmetic products.*

* *Does the SCCP recommend any further restrictions with regard to the presence of chloroatranol and atranol as an ingredient of fragrances used in cosmetic products?*

3. OPINION

Introduction

Oak moss absolute is a natural fragrance derived from the lichen *Evernia prunastri* and widely used in fine perfumes, aftershave lotions and other cosmetic products. Oak moss absolute is known for its strong allergenic potential (1). It is a frequent cause of allergic contact reactions, accounting for about 1/3 of reactions to the ingredients of the standard diagnostic marker of perfume allergy, the *fragrance mix*, and showing an increasing frequency over time (2). Oak moss absolute has a very complex chemical composition and several constituents have been suggested as responsible for its strong allergenic properties, including atranorin, chloroatranorin, evernic acid and usnic acid (3, 4).

It has been shown that atranol and chloroatranol - degradation products of atranorin and chloroatranorin, respectively - are the most potent allergens of oak moss absolute (1).

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Quantitative exposure to chloroatranol and the chemically related substance atranol have been studied in some popular perfumes, eaux de parfum and eaux de toilette available on the European market. In total, 31 products were analysed by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS-MS) for their contents of atranol and chloroatranol. (5)

The 2 substances were found in 87% (n = 27) of the products. The median concentration of atranol in perfumes was 0.502 µg/ml and 0.012 µg/ml in eaux de toilette, and 0.235 µg/ml and 0.006 µg/ml for chloroatranol, respectively, in perfumes and eaux de toilette.

Chloroatranol was found at a maximum concentration of 53 µg/ml and atranol at 190 µg/ml. The wide exposure to oak moss allergens, together with significant amounts of these potent allergens in at least half of perfumes and some eaux de toilettes explains the high frequencies of oak moss absolute allergy.

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Atranol
Chloroatranol

3.1.1.2. Chemical names

2,6-Dihydroxy-4-methyl-benzaldehyde (atranol)
3-Chloro-2,6-Dihydroxy-4-methyl-benzaldehyde (chloroatranol)

3.1.1.3. Trade names and abbreviations

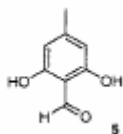
/

3.1.1.4. CAS / EINECS number

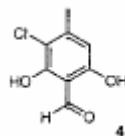
Atranol	CAS	:	526-37-4
	EINECS	:	/
Chloroatranol	CAS	:	57074-21-2
	EINECS	:	/

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3.1.1.5. Structural formula



Atranol



Clororatranol

3.1.1.6. Empirical formula

Atranol : $C_8H_9O_3$

Chloroatranol : $C_8H_8O_3Cl$

3.1.2. Physical form

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3.1.3. Molecular weight

Molecular weight : 153.16 (atranol)

Molecular weight : 187.60 (chloroatranol)

3.1.4. Purity, composition and substance codes

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3.1.5. Impurities / accompanying contaminants

/

3.1.6. Solubility

/

3.1.7. Partition coefficient (Log P_{ow})

Atranol : /

Chloroatranol : /

3.1.8. Additional physical and chemical specifications

	Atranol	Chloroatranol
Organoleptic properties	: /	/
Melting point	: /	/

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

3.2. Function and uses

Atranol and chloroatranol are present in natural extracts, such as Oak moss absolute. Oak moss absolute is a natural fragrance derived from the lichen *Evernia prunastri* and widely used in fine perfumes, aftershave lotions and other cosmetic products.

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

LLNA studies

Atranol was tested at 0.5, 1.0, 2.5, 5.0 and 10%. Chloroatranol was tested at 0.25, 0.5, 1.0, 2.5 and 5.0 %. The vehicle used in each assay was 1:3 ethanol/diethylphthalate.

Groups of female CBA/Ca mice (n=4) were dosed topically on the dorsum of both ears with 25 µl of test material. The same volume of vehicle alone acted as a control.

Dosing occurred daily for three consecutive days. On day 6 after the first application, all mice were injected intravenously by the tail vein with 250 µl of phosphate buffered saline containing 20 µCi of radiolabelled methyl thymidine (³HTdR). Five hours later, the mice were killed and draining auricular lymph nodes were excised and pooled for each experimental group.

Results

Atranol was shown to have the capacity to cause skin sensitisation when applied as 1.0, 2.5, 5.0 and 10 % w/v preparations in 1:3 ethanol/diethylphthalate. The estimated concentration giving rise to a 3-fold increase in lymphocyte proliferation (EC3) was 0.6% w/v (150 µg/cm²).

Chloroatranol was shown to have the capacity to cause skin sensitisation when applied as 0.5, 1.0, 2.5 and 5.0 % w/v preparations in 1:3 ethanol/diethylphthalate. The estimated concentration giving rise to a 3-fold increase in lymphocyte proliferation (EC3) was 0.4% w/v (100 µg/cm²).

Atranol and chloroatranol are strong skin sensitisers under the conditions of the test.

Ref.: 9, 10

Oak moss absolute was tested at 2.5, 5.0, 10, 25 and 50 % w/v preparations in 1:3 ethanol/diethylphthalate.

Groups of female CBA/Ca mice (n=4) were dosed topically on the dorsum of both ears with 25 µl of test material. The same volume of vehicle alone acted as a control.

Dosing occurred daily for three consecutive days. On day 6 after the first application, all mice were injected intravenously by the tail vein with 250 µl of phosphate buffered saline containing 20 µCi of radiolabelled methyl thymidine (³HTdR). Five hours later, the mice were killed and draining auricular lymph nodes were excised and pooled for each experimental group.

Results

The test substance was shown to have the capacity to cause skin sensitisation when applied as 5.0, 10, 25 and 50 % w/v preparations in 1:3 ethanol/diethylphthalate. The estimated concentration giving rise to a 3-fold increase in lymphocyte proliferation (EC3) was 3.88 % w/v (970 µg/cm²).

Oak moss absolute is a strong skin sensitiser under the conditions of the test.

Ref.: 8

Treemoss absolute was tested at 0.5, 1.0, 2.5, 5.0 and 10 % w/v preparations in 1:3 ethanol/diethylphthalate. Further groups of animals were dosed with 10 or 20 % w/v preparations in 1:3 ethanol/diethylphthalate.

Groups of female CBA/Ca mice (n=4) were dosed topically on the dorsum of both ears with 25 µl of test material. The same volume of vehicle alone acted as a control.

Dosing occurred daily for three consecutive days. On day 6 after the first application, all mice were injected intravenously by the tail vein with 250 µl of phosphate buffered saline containing 20 µCi of radiolabelled methyl thymidine (³HTdR). Five hours later, the mice were killed and draining auricular lymph nodes were excised and pooled for each experimental group.

Results

The test substance did not have the capacity to cause skin sensitisation when applied as 0.5, 1.0, 2.5, 5.0, 10 or 20 % w/v preparations in 1:3 ethanol/diethylphthalate. The estimated concentration giving rise to a 3-fold increase in lymphocyte proliferation (EC3) was greater than 25 % w/v (> 6250 µg/cm²).

Treemoss absolute is unlikely to be a skin sensitiser under the conditions of the test.

Ref.: 11

Opinion on Atranol and Chloroatranol present in natural extracts (e.g. oak moss and tree moss extract)

Treemoss absolute was tested at 5.0, 10 and 20 % w/v preparations in 1:3 ethanol/diethylphthalate.

Groups of female CBA/Ca mice (n=4) were dosed topically on the dorsum of both ears with 25 µl of test material. The same volume of vehicle alone acted as a control.

Dosing occurred daily for three consecutive days. On day 6 after the first application, all mice were injected intravenously by the tail vein with 250 µl of phosphate buffered saline containing 20 µCi of radiolabelled methyl thymidine (³HTdR). Five hours later, the mice were killed and draining auricular lymph nodes were excised and pooled for each experimental group.

Results

The test substance did not have the capacity to cause skin sensitisation when applied as 5.0, 10 or 20 % w/v preparations in 1:3 ethanol/diethylphthalate. The estimated concentration giving rise to a 3-fold increase in lymphocyte proliferation (EC3) was greater than 20 % w/v (> 5000 µg/cm²).

Treemoss absolute is unlikely to be a skin sensitiser under the conditions of the test.

Ref.: 12

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

Chloroatranol and atranol were identified as the main allergens in oak moss absolute by a bioguided chemical fractionation procedure (1). Following this, chloroatranol was further subjected to investigation of its elicitation potential in sensitized eczema patients (6). It was shown that 92% of oak moss-sensitized individuals developed an eczematous reaction to the repeated open application of 5 µg/ml chloroatranol in ethanol (6). The same study also showed that the dose eliciting a reaction in 50% of the test subjects under patch test conditions was 0.15 µg/ml (6). These results are put into perspective by the current investigation showing that the range of chloroatranol in the investigated cosmetic products was from 0.004 µg/ml to 53 µg/ml, median 0.2 µg/ml and the 90% percentile 10 µg/ml. There are indications that atranol is a weaker allergen than chloroatranol (1). However, it is also present in higher quantities in the products and this will contribute to the allergenicity of oak moss absolute. The wide exposure to oak moss allergens, together with significant amounts of the potent allergens in at least half of the perfumes and some eaux de parfumes, as well as in eaux de toilette may explain the high frequencies of oak moss absolute allergy and the clinical problems of these patients (5).

In accordance with the opinions of the SCCNFP (doc. n° SCCNFP/0017/98 of 8.12.99 and SCCNFP/0421/00 of 24.10.00), information should be provided to the consumer regarding the presence of oakmoss/treemoss extracts in cosmetic products. (9). An oak moss absolute sample was found to contain approximately 2.1% atranol and 0.9% chloroatranol (5). Considering this as representative of atranol and chloroatranol content in different oak moss absolute samples, cosmetic products may contain up to 0.0021% (21 ppm) atranol and 0.0009% (9 ppm) chloroatranol. However, the content of atranol and chloroatranol in cosmetic products will depend upon the oak moss absolute used, the degradation of atranorin and chloroatranorin in the product matrix, and finally, upon the matrix effect in the determination of these molecules. It should be noted that recovery of chloroatranol from perfume/eau de toilette was found to be nearly 100%, while that for atranol was close to 55% (5).

The control of consumer exposure to chloroatranol and atranol in oak moss absolute-containing products is important to reduce fragrance contact allergy.

4. CONCLUSION

Because chloroatranol and atranol are components of a botanical extract, oak moss absolute, it has been impossible to trace exposure.

Chloroatranol was shown to cause elicitation of reactions by repeated open exposure at the ppm level (0.0005%) and at the ppb level on patch testing (50% elicit at 0.000015%).

As chloroatranol and atranol are such potent allergens (and chloroatranol particularly so), they should not be present in cosmetic products.

Although the mandate requested an opinion on cosmetic use only, the risks to consumer health from presence of chloroatranol/atranol in other types of consumer products should be assessed.

5. MINORITY OPINION

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6. REFERENCES

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