

OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD
PRODUCTS INTENDED FOR CONSUMERS

CONCERNING

PIROCTONE OLAMINE AND ITS MONOETHANOLAMINE SALT

Colipa n° P59

adopted by the SCCNFP during its 19th plenary meeting
of 27 February 2002

1. Terms of Reference

1.1 Context of the question

Cosmetic products marketed in the EU may only contain those preservatives which are listed in Annex VI of the Cosmetics Directive 76/768/EEC, "List of preservatives which cosmetic products may contain".

The preamble of the Annex states that preservatives marked with the symbol (+) may also be added to cosmetic products in concentrations other than those laid down in the Annex for other specific purposes apparent from the presentation of the products.

Piroctone olamine and its monoethanolamine salt bears the symbol (+) and can therefore be used in cosmetics at much higher concentrations, as long as they are not employed as preservatives.

In its opinion of 17 February 1999 concerning the restrictions on materials listed in Annex VI of Directive 76/768/EEC on cosmetic products, the SCCNFP stated that those substances indicated by (+) in Annex VI, when incorporated into cosmetic formulations for non-preservative functions, should be subjected to the same restrictions in usage levels and warnings as when used for preservative effects.

If a preservative marked with the symbol (+) is added for non-preservative purpose to a cosmetic product in a concentration other than that laid down in the Annex VI, data to substantiate its safety should be submitted to the SCCNFP.

1.2 Request to the SCCNFP

The SCCNFP was requested to review the data submitted to support the safety of piroctone olamine and its monoethanolamine salt when used at concentrations other than those laid down in Annex VI to Directive 76/768/EEC for non-preservative purposes apparent from the presentation of the products and to answer the following question :

* Can piroctone olamine and its monoethanolamine salt safely used for non-preservative purposes in face care products (leave on) at a maximum concentration of 1.0% ?

1.3 Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.

The extend to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

1.4. Definitions of terms where appropriate

Piroctone Olamine (PO) has been already subject for evaluation on the background of earlier submissions.

Submission I : February 1980
Submission II : January 1985

The result of the respective evaluation and the opinion of the Scientific Committee of Cosmetology (SCC) is laid down in Reports of the SCC, sixth series, EUR 11139 EN, 1987.

PO had been approved for use in cosmetic products at a maximal concentration of 1 % (rinse-off products) or 0.5 % in other products.

PO is non-sensitising , non-genotoxic, non-teratogenic and the systemic toxicity has been measured in a 90-day oral test NOEL in rats: 100 mg/kg/day; in 90-day topical application NOEL in rabbits: 16 mg/kg/day (one dose test).

The percutaneous penetration rate in rats was in the order to 4.5 % of a topically applied dose. Since 1983, no reports have appeared in the literature indicating that the substance could be attributed to unwanted adverse effects.

In HRIPT, the test cpd. PO at 0.5 % in a vehicle did not induce irritation or sensitisation. In a human use test 0.2 % or 1.0 % in shampoos provided no evidence of adverse reactions. Rabbit irritation tests indicated that PO was slightly irritating to the skin (at 1 %) and eye (0.5 %).

In “other uses” (within the EU) and outside the EU, the cpd. PO obviously has widely used in skin creams (up to 1 %) already for a long time without any user complaints or even reports in literature.

Submission III (January 2001) has been presented in order to defend the use of Piroctone Olamine (P59) as for “other use” in face care products (leave on products) at a concentration of 1 %. Submission III is primarily dealing with skin and ocular tolerance of PO at higher concentrations as 1 %, namely 2 % and 3 %.

Evaluation and opinion on : Piroctone Olamine and its monoethanolamine salt

2. Toxicological Evaluation and Characterisation

By lack of appropriate and validated in vitro test methods the new experiments have been carried out using in vivo models according to modern test protocols following GLP rules.

2.1. General

2.1.1. Primary name

Piroctone Olamine (INCI)

2.1.2. Synonyms

1-Hydroxy-4-methyl-6(2,4,4-trimethylpentyl)2-pyridon and its monoethanolamine salt

2.1.3. Trade names and abbreviations

Octopirox

2.1.4. CAS number

68890-66-4

2.1.5. Structural formula

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2.1.6. Empirical formula

Emp. Formula : C₁₄H₂₃NO₂ . C₂H₇NO
Mol weight : 298.48

2.1.7. Purity, composition and substance codes

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2.1.8. Physical properties

Appearance : /
Melting point : /
Boiling point : /
Density : /

Evaluation and opinion on : Piroctone Olamine and its monoethanolamine salt

Rel. vap. dens. : /
 Vapour Press. : /
 Log P_{ow} : /

2.1.9. Solubility

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2.2. Function and uses

Piroctone Olamine has been approved for use in cosmetic products at a maximal concentration of 1 % (rinse-off products) or 0.5 % (other products).

TOXICOLOGICAL CHARACTERIZATION

Only the results of the new investigations from submission III (January 2001) are listed under the respective position number of the SCCNFP standard form. The investigations reported in Submission I (1980) and II (1985) have been proven satisfactorily as to conduct and scientific interpretation and thus the results could be taken under consideration for this safety evaluation.

2.4. Irritation & corrosivity**2.4.1. Irritation (skin)**

OECD 404

Three New Zealand White rabbits were treated topically with concentrations of 2.0 % (left flank) or 3.0 % (right flank). Exposure time was 4 hours. The test compound was kept in contact with the skin by semi-occlusive dressing. Cutaneous reactions were observed and scored 1 hour, 24, 48 and 72 hours after removal of the dressing.

Result: No cutaneous reactions were observed in the study. The test substance was rated to be non-irritant to the skin of rabbits at concentrations up 3.0 %.

Ref. : 48

2.4.2. Irritation (mucous membranes)

OECD 405

The eyes of three New Zealand White rabbits were treated with 0.1 ml concentrations of 2.0 % (left eye) or 3.0 % (right eye). The eyes were not rinsed after application of the test substance. Ocular reactions were observed and scored 1 hour, 24, 48 and 72 hours after administration.

Result: With the exception of a single case of a slight and transient corneal opacity (3.0 %, day 2), ocular reactions were limited to the conjunctiva (redness, chemosis and discharge).

At 2.0 % very slight to moderate conjunctival reactions were observed in all animals and persisted up to day nine of the study. At 3.0 %, very slight to moderate conjunctival reactions (redness; chemosis, discharge) and a single case of mild, transient corneal opacity (day 2 only) was observed in all animals and persisted up to day three. On the basis of the irritation scores, the test substance was rated to be a slight irritant in rabbits.

Ref. : 49

2.10. Special investigations

2.10.1. Human Data

In a double-blind study in humans (report in French language) the tolerance of two cream formulations, i.e. 47JP12 and 47JP2, containing 1.0 % and 0.5 % octopirox (piroctone olamine, PO), respectively. With the exception of the different content of PO, the formulation ingredients were identical.

The creams were applied once a day, morning or evening, to the face of 65 volunteers, 5 times a week, for a total of four weeks.

Result: No difference was noted in the tolerance of these formulations. Both creams showed a good acceptance and tolerance. These data support the tolerance of 1.0 % PO in face creams.

Ref. :

2.11. Safety evaluation

CALCULATION OF SAFETY MARGIN

Piroctone Olamine (Octopirox)

Based on a usage volume of X ml, containing at maximum X %

Maximum amount of ingredient applied I (mg) =

Typical body weight of human = 60 kg

Maximum absorption through the skin A (%) =

Dermal absorption per treatment I x A =

Systemic exposure dose (SED) I x A / 60 kg =

No observed adverse effect level (mg/kg) NOAEL =

Margin of Safety	NOAEL / SED =
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2.12. Opinion

The Committee is of the opinion that the information submitted is insufficient to allow an adequate risk assessment to be carried out.

Before any re-assessment, a complete dossier up-to-modern-standards would be required not only on piroctone olamine but also on its monoethanolamine salts.

2.13. References

Submission III

44. Freeberg FE, Griffith JF, Bruce RD, Bay PHS. Correlation of animal tests methods with human experience for household products. *J. Toxicol. – Cut. and Ocular Toxicol.* 1 (3), 53-64, 1984.
45. N° 57: hydroxy-4-methyl-6(2,2,4-trimethylpentyl)2-pyridon and its monoethanolamine salt. Reports of the Scientific Committee on Cosmetology, sixth series, EUR 11139 EN, 1987.
46. Patil, SM, Patrick E, Maibach HI. Animal, human, and in vitro test methods for predicting skin irritation. In: Dermatoxicology, fifth edition., pp. 411-436, Eds. Marzulli FN and Maibach HI. Taylor and Frances, London, 1996.
47. Manciaux X. 52883 – Acute dermal irritation in rabbits. Study number 20306 TAL, Centre International de Toxicologie, Evreux, France, unpublished report, Sept. 22, 2000.
48. Manciaux X. 2848 - Acute eye irritation in rabbits. Study number 20307 TAL, Centre International de Toxicology, Evreux, France, unpublished report, Sept. 22, 2000.
49. Lemaitre M. Etude en double aveugle de l'efficacité et de tolerance de la creme 47JP12 contre 47JP2 dans la dermie seborreique du visage, unpublished report, August 1997.