

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

CONCERNING

HEXAMIDINE AND ITS SALTS,
INCLUDING DI-ISETHIONATE AND DI(P-HYDROXYBENZOATE)

Colipa n° P8

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.

Hexamidine and its salts bear 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 hexamidine and its salts 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 hexamidine and its salts be safely used for non-preservative purposes in face care products (leave on and rinse off) at a maximum concentration of 0.2 % ?

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.

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.

Hexamidine its salts has been already subject for evaluations on the background of earlier submissions:

Submission I: July 1979
 Submission II: September 1982
 Submission III: July 1988
 Submission IV: May 1989
 Submission V: November 1990
 Submission VI: October 1991

The result of the respective evaluation and the opinion of the SCC is laid down in CSC/824/91 (46th SCC 2/91) SPC/305/91 (49th SCC 2/92).

Submission VII (January 2001) has been presented in order to defend the use of hexamidine and its salts (P 8) as “other use” in face care products (leave on and rinse off) at a concentration of 0.2 %.

2. Toxicological Evaluation and Characterisation

2.1. General

2.1.1. Primary name

Hexamidine (INCI)

2.1.2. Synonyms

1,6-di(4-amidino phenoxy)-n-hexane and its salts including di-isethionate and di(p-hydroxybenzoate)

2.1.3. Trade names and abbreviations

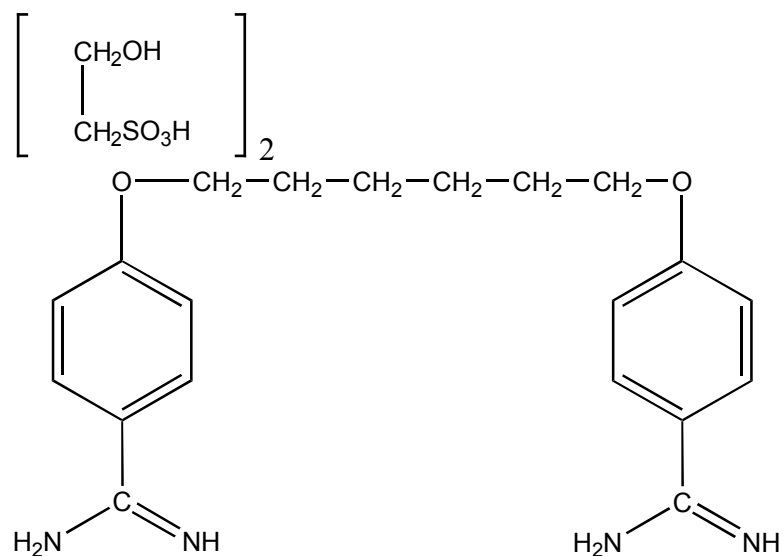
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2.1.4. CAS number

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2.1.5. Structural formula



2.1.6. Empirical formula

Emp. Formula : $C_{20}H_{26}N_4O_2$
 Mol weight : 354.45

2.1.7. Purity, composition and substance codes

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2.1.8. Physical properties

Appearance : /
 Melting point : /
 Boiling point : /
 Density : /
 Rel. vap. dens. : /
 Vapour Press. : /
 Log P_{ow} : /

2.1.9. Solubility

Soluble in water. Insoluble in organic solvents.

2.2. Function and uses

Hexamidine is permitted and used in cosmetics as a preservative at a maximum dose level of 0.1 %. For “other uses” e.g. in face care products (leave on and rinse off) it is newly applied (Submission VII) at concentrations up to 0.2 %.

TOXICOLOGICAL CHARACTERIZATION**2.3.1. Toxicity**

The acute toxicity of hexamidine has been investigated in different species: Oral LD₅₀ values (in mg/kg bw) are 710-2500 in mice, 750 in rats, 500 in rabbits. Intraperitoneal toxicity values of 17-51 mg/kg bw. and 57 were reported for mice and rats, respectively. Intravenous values are 17 mg/kg bw. for mice and 8 for rabbits. A dermal value for rats was >4000 mg/kg bw.

2.3.2. Repeated dose oral toxicity

A short-term 28-days (4 wk) oral study was conducted by gavage administration of 50, 100 and 200 mg/kg bw/day to groups of 5 rats/sex. All test animals showed post-treatment symptoms (salivation, wet fur, brown oral staining). The top-dose rats also showed abnormal position and locomotion, and increased counts of white blood cells and lymphocytes. In the two higher dose groups there were increases in the values of GPT, GOT and calcium in blood plasma. All treated rats showed a slight caecal enlargement. The lungs, heart, liver, kidneys and caecum did not reveal treatment-related microscopical changes. Other organs (including spleen and adrenals) were not examined. The clinical signs and the caecum enlargement were not considered to be of toxicological significance. The no-toxic effect level was established at 50 mg/kg, but the study showed several deficiencies (Colipa subm. III, ref. 10).

2.3.3. Repeated dose dermal toxicity

A subacute (28 days) dermal toxicity study in rabbits showed that solutions of up to 2 % were only slightly irritant. Daily application of 4 ml/kg bw of a 0.05, 0.1 and 2 % solution revealed no systemic toxicity.

2.3.4. Sub-chronic oral toxicity

In a 90-day oral study in male rats, daily doses of 400 and 800 mg/kg by gavage induced mortality, growth depression, signs of anaemia, increased liver weight and decreased liver- and kidney function. The lower dose of 200 mg/kg was not a clear no-effect level.

2.3.5. Sub-chronic dermal toxicity

A 90-day dermal study in rabbits with a low dose level of 16 mg/kg b.w. revealed no systemic toxicity.

2.4. Irritation & corrosivity

Three New Zealand White rabbits received concentrations of 0.2 % (left flank) or 0.5% (right flank), exposure time 4 hours according to GLP. Cutaneous reactions were observed and scored: 1, 24, 48 and 72 hours after removal of the dressing.

Results: Only at 24 hours a very slight erythema was observed in one animal treated with 0.2% and two rabbits treated with 0.5%, no other cutaneous reactions were observed. The test substance was rated to be “non-irritant” to the skin of rabbits. Study number 20308 TAL, September 22,2000.

The eyes of three New Zealand rabbits were treated with 0.1ml of concentrations of 0.2 % (left eye) or 0.5% (right eye); the vehicle was propylene glycol. The eyes were not rinsed after application. Ocular reactions were observed and scored: 1, 24, 48 and 72 hours after administration.

Results: Ocular reactions were limited to the conjunctiva. At 0.2% only were slight to slight conjunctival reactions were observed in all animals, persisting up to day three. – At 0.5% very slight to moderate conjunctival reactions were observed in all animals and persisted up to three days. No sign of corneal opacity was observed. The test substance was rated to be a slight irritant in the rabbits eye after direct instillation. Study number 20309 TAL, September 22,2000.

2.5. Sensitisation

Hexamidine did not produce any evidence of sensitisation in guinea pigs nor of photosensitization using a rabbit model. However there is some evidence for sensitisation reactions occurring in man following its use as a topical bactericide.

2.7. Toxicokinetics (incl. Percutaneous Absorption)

Studies using radio-labelled material to investigate skin absorption in the rat indicated very poor absorption. When the compound was applied as a 0.1 % formulation in cold cream under an occlusive dressing for 96 hours a mean of ca. 0.6 % was absorbed (maximum value 1.4 %).

2.8. Mutagenicity

Negative results were obtained in the Ames test Salmonella thyphimurium strains TA1535, 1537, 98 and 100 and concentrations up to 500 µg/plate were used. Negative results were also obtained in a metaphase analysis assay to investigate the clastogenicity of the compound in CHO cells. A small increase in aberrations was seen at the intermediate dose but not at the top dose, and the increase was within the laboratories historic control range.

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2.11. Safety evaluation

CALCULATION OF SAFETY MARGIN

Hexamidine and its salts, including Di-isethionate and Di-(p-hydroxibenzoate)

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	=	
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 hexamidine but also on its salts (including di-isethionate and di(p-hydroxybenzoate)).

2.13. References

Data sheet Council of Europe
 Data sheet National Institute of Public Health, The Netherlands, based on Colipa file May 1980.
 Additional submission from Colipa 27 September 1982.
 Colipa submission III July 1988.
 Colipa submission IV May 1989.
 Colipa submission V November 1990.
 Colipa submission VI October 1991.
 Colipa submission VII January 2001.
 Manciaux X. 2848 – Acute dermal irritation in rabbits. Study number 20308 TAL,
 Centre International de Toxicologie, Evreux, France, unpublished report, Sept. 22, 2000.
 Manciaux X. 2848 – Acute eye irritation in rabbits. Study number 20309 TAL,
 Centre International de Toxicologie, Evreux, France, unpublished report, Sept. 22, 2000.

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