

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

CONCERNING

1-NAPHTHOL

Colipa n° A17

adopted by the SCCNFP during its 16th plenary meeting
of 13 March 2001

Executive Summary

1. General data

- 1.1 Identity of the ingredient : 1-Naphthol (INCI name)
1.2 CAS n° : 90-15-3
1.3 Proposed use : Oxidising colouring agent for hair dyeing; maximum concentration in the finished cosmetic product : 2.0 %

2. Terms of reference

2.1 Context of the question

The adaptation to technical progress of the Annexes to Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products.

2.2 Request to the SCCNFP

The SCCNFP is requested to answer the following questions :

- * Is 1-Naphthol safe for use as an oxidising colouring agent for hair dyeing?
- * Does the SCCNFP propose any restrictions or conditions for its use?

3. Safety Assessment & Classification

The substance was not harmful on acute ingestion (LD50>2g/kg bw). A 30-day study in mice showed gastric lesions at 200 mg/kg bw/day and the NOAEL was 100 mg/kg bw/day. A 12-wk study in rats showed a NOAEL of 20 mg/kg bw/day.

The substance showed neither maternal toxicity nor embryo-toxic or teratogenic effects at levels up to 80 mg/kg bw/day (highest tested dose).

A concentration of 2.5% was not irritant to the rabbit skin. The substance showed minimal eye irritation at levels up to 1.5%, but was irritant to the rabbit eye at 2 and 2.5%. Sensitising potential was not properly assessed.

The substance was not mutagenic or genotoxic *in vitro* or *in vivo*.

Percutaneous absorption in humans under exaggerated exposure conditions (8-hr, occluded application) was high, with rapid urinary excretion of the compound. A different study in rats, under in-use conditions, showed a maximum percutaneous penetration of 0.7%.

On the basis of this information, the SCCNFP concluded that 1-naphthol can be used safely as oxidising colouring agent for hair dyeing at a maximum concentration of 2.0% in the finished product.

Although the sensitising potential was not properly assessed, no further sensitisation test are requested, provided that cosmetic products containing this substance carry a label warning of a risk of sensitisation.

4. Opinion

This opinion replaces the previous opinion adopted by the SCCNFP during its 8th plenary meeting of 23 June 1999.

The SCCNFP is of the opinion that 1-Naphthol can be used safely as a oxidising colouring agent for hair dyeing at a maximum authorised concentration of 2.0% in the finished cosmetic product; in combination with hydrogen peroxide the maximum use concentration upon application is 1.0%.

The sensitisation data in the dossier was generated with a method not conforming with OECD n° 406. However, no further sensitisation data are requested provided that cosmetic products containing this substance carry a label warning of a risk of sensitisation.

5. 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.

Full Opinion

1. Terms of Reference

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- * Is 1-Naphthol safe for use as an oxidising colouring agent for hair dyeing
- * Does the SCCNFP propose any restrictions or conditions for its use?

1.3 Definitions of terms where appropriate.

Not applicable

2. Toxicological Evaluation and Characterisation

2.1. General

2.1.1. Primary name

1-Naphtol (INCI name)

2.1.2. Synonyms

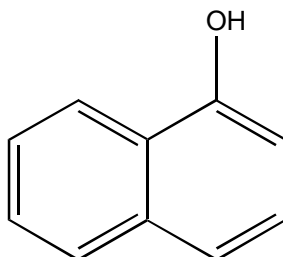
1-Hydroxynaphthalene
 α -Naphthol

2.1.3. Trade names and abbreviations

CI 76 605

2.1.4. CAS no.

90-15-3
201-969-4 (EINECS N°)

2.1.5. Structural formula**2.1.6. Empirical formula**

Emp. Formula : $C_{10}H_8O$
Mol weight : 144.16

2.1.7. Purity, composition and substance codes

> 99.5 %

2.1.8. Physical properties

Subst. Code : /
Appearance : light yellowish-white solid
Melting point : 96 °C
Boiling point : 288 °C
Density : 1.224 (4 °C)
Rel. vap. dens. : /
Vapour Press. : 1 mm Hg (94 °C)
Log P_{ow} : 2.98

2.1.9. Solubility

Slightly soluble in water, soluble in alkali and in organic solvents

2.2. Function and uses

Used as the sulfate monohydrate salt in oxidation hair dyes to a maximum concentration of 2.0%. The in-use concentration upon application is 1.0%.

TOXICOLOGICAL CHARACTERISATION**2.3. Toxicity****2.3.1. Acute oral toxicity**

LD₅₀ : Rats, oral 2300 (1700 - 3300) mg/kg b.w. (1a, 1b)
Rats, oral 2590 mg/kg (1a)

Ref. : 1a, 1b

2.3.2. Sub-chronic oral toxicity

1-Naphthol orally administered to rats (20 males and 20 females) for 12 weeks (5 times a week) showed that the dose of 20 mg/kg b.w./day (10 ml/kg) does not represent a toxic cumulative dose.

Ref. : 6

In a 30-day repeated dose study in mice treated with 200, 100, and 50 mg/kg b.w. (five animals/sex/group; controls included undosed and solvent groups) gastric lesions related to the treatment were observed only at the dose of 200 mg/kg in male mice. No other sign of toxicity was observed.

Ref. : 18

2.3.3. Sub-chronic dermal toxicity

A formulation containing 1-naphthol (0.5 %), mixed 1:1 with hydrogen peroxide, topically applied for 13 weeks (twice weekly) on abraded and intact skin of rabbit showed no evident toxic effect.

Ref. : 7

2.3.4. Chronic toxicity

Chronic toxicity and carcinogenicity : One oxidative formulation (7403, mixed 1:1 with 6 % hydrogen peroxide) containing 0.5 % 1-naphthol was tested on Swiss Webster mice by dermal application (0.05 ml/cm² x 21 months). No adverse effects were reported.

Ref. : 8

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

The compound was applied to intact and abraded skin of rabbit at doses of 2.5 % (0.5 % aqueous gum tragacanth solution with 0.05 % sodium sulphite, pH = 7); it resulted not irritating after reading at 24 and 72 hours (primary irritation index = 0). No signs of irritancy were noted.

Ref. : 1a, 3

2.4.2. Irritation (mucous membranes)

The compound was instilled into one eye of 12 rabbits at concentrations of 0.5 % - 1.5 % - 2.0 % - 2.5 % w/v (0.5 % in aqueous gum tragacanth with 0.05 % sodium sulphite, 3 animal/doses) and the eyes were washed out 10 sec after treatment. The results (ocular reaction evaluated at 1 h and 1-2-3-4-7 days) showed the minimum irritant level, between 1.5 % and 2.0 %: positive reactions were observed in 2/3 of the rabbits at 2.0 % w/v and 1/3 of the rabbits at 2.5 % w/v.

Ref. : 2

2.5. Sensitisation

1-Naphthol (3 % in water with 2.0 % Natrosol, 2 % Tween 80, 0.05 % Sodium sulphite and 10 % isopropanole) showed no allergic reaction in guinea pig by open epicutaneous method.

Ref. : 4

Sensitisation was induced in 20 guinea pigs by simultaneously intradermal injections in the shoulder region of 0.1 ml of Freund's Complete Adjuvant (FCA), 0.1 ml 1-naphthol (0.1 % in water) and a 1:1 mixture of test compound and 0.05 ml Adjuvant at day 0. The test compound was dermally applied (0.1 % in water) 7 days later, under occlusion, on the injection site for 48 hours. 14 days later the guinea pigs were challenged by dermal application on the flank with 0.1 % and 0.05 % of 1-naphthol (aqueous solutions), under occlusion for 24 hours. The results evaluated after 24 and 48 hours of challenge showed that 1-naphthol was not a sensitiser in guinea pigs.

Result :

The sensitisation capacity was not properly assessed because the choice of concentration, for induction and challenge, may have been too low.

Ref. : 5

2.6. Teratogenicity/ Embryo-toxicity

A formulation containing 1-naphthol (0.5 %, 1:1 with hydrogen peroxide) was topically applied (2 mg/kg/day) to the shaven skin of rats on day 1-4-7-10-13-16-19 of gestation. Only a significant reduction of the mean number of corpora lutea was observed between treated and two control groups (12.85 vs. 15.35 or 13.55). There was no evidence of any teratogenic or other adverse effect in the developing embryo/foetus.

Ref. : 7

Embryo-toxicity :

25 female Sprague-Dawley Albino rats/group

Dosage 20, 40, 80 mg/kg bw. 1-Naphthol daily day 6 to 15 of gestation

Blank control (solvent); positive control 15 mg/kg vit. A

Acknowledged methodologies

Results : At any dose level no treatment related effects. No maternal nor embryonic or foetal signs attributable to the test substance. In conclusion no maternal or embryo-toxicity, no incidence of embryo-lethality or growth retarding effects; no teratogenicity up to the highest tested dose of 80 mg/kg.

Ref. : 20

2.7. Toxicokinetics (incl. Percutaneous Absorption)
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Metabolism :

1-naphthol was administered to 6 male and 6 female white rats (20 % w/v in corn oil, 0.67 ml/rat, total amount of the compound = 6.4 g) by injection under the skin of the back for 4 days after the feeding period. The urine analysis, after extraction and using chemical methods, showed the following data (percentages of 1-naphthol administered are indicated by brackets): p-toluidine 1-naphthylglucuronidate: 2.8 g (14.7 %), 2.0 g (15.2 %) and 3.2 g (16.8 %); p-bromoaniline 1-naphthylsulphate: 0.063 g (0.4 %), 0.087 g (0.5 %), 0.008 g (0.6 %). These results showed that 1-naphthol was excreted in urine as 1-naphthylglucuronidate and 1-naphthylsulphate after subcutaneous injections. The study was performed in 1950.

Ref. : 17

Human absorption :

An ointment containing 1-naphthol-[1-¹⁴C] (3 g, 50 % soft soap and 50 % white soft paraffin) was applied in the inter-scapular region (10 cm, circular area) of the skin of 3 subjects, under occlusion for 8 hours. The percutaneous study showed a rapid and efficient absorption of the compound (3 days): 65.0-23.8-48.1 % (mean = 45.6 %) of the applied dose not recovered from the skin. The estimation of total urinary radioactivity was calculated only in one subject: 88.55 % (day 1), 5.2 % (day 2) and 2.8 % (day 3) of the dose not recovered from the skin (ca 97 %). The analysis of the major metabolites showed the following results (percentage of the dose not recovered from the skin): Subject 1: glucuronide fraction (day 1: 31.0 %; day 2: 1.0 %; day 3: 0.8 %), sulphate fraction (day 1: 1.3 %; day 2: 1.0 %; day 3: 1.2 %); acid hydrolysable fraction (day 1: 2.6 %; day 2: 0.2 %; day 3: 0.9 %); Subject 2: glucuronide fraction (day 1: 1.3 %; day 2: 1.0 %; day 3: 1.2 %), sulphate fraction (day 1: 0.8 %; day 2: 0.0 %; day 3: 0.03 %); acid hydrolysable fraction (day 1: 0.26 %; day 2: 0.04 %; day 3: 0.04 %); Subject 3: glucuronide fraction (day 1: 2.6 %; day 2: 0.3 %; day 3: 0.9 %), sulphate fraction (day 1: 0.0.8 %; day 2: 0.03 %; day 3: 0.0 %); acid hydrolysable fraction (unmeasurable). In the end, the radiolabelled compound, when applied topically under occlusion for 8 hours, shows an absorption value of 45.6 %; ca. 97 % of the absorbed dose is found in the urine during 3 days of analysis.

However, the human study exposure conditions were exaggerated and the formulation did not contain hydrogen peroxide.

Ref.: 16

Percutaneous absorption

In Sprague-Dawley rats (female and male Him : OFA) 1-Naphthol labelled on the C1 atom, radioactive purity 98 %, was investigated in five different preparations including two, mixed with hydrogen peroxide (1:1), as used in finished products sold in the market and containing 0.25 %, 0.5 % and 1 % a.i. These preparations were applied (ca. 2.0 to 9 cm²) under practical conditions, after 30 min. wiped off and then gently washed with a 3% shampoo-water solution. – In order to avoid leaking effects these areas were covered by gauze pads and the animals further kept in metabolic cages for three consecutive days. – In addition to the fore-described part in the same investigation also kinetic parameters as to absorption after oral application, distribution phenomena as well as metabolic pathways and the excretion were observed.

Results :

After cutaneous application, different amounts of ¹⁴C activities were measured. Besides sex differences (quality of hair) this was primarily due to the absence (shaved area) or presence (unclipped) of hair.

The excretion of the incorporated activity occurs very fast mostly via the urine (82-92 % within 24^h). There is obviously no excretion by exhalation; thus this way is regarded as of no importance.

The highest organ contents of radioactivity were measured already after 35 min (lungs, thyroid, heart, adrenals spleen, thymus, brain in a declining order).

After oral administration the excretion rate of radioactivity was similar to the excretion after cutaneous application but slightly faster. The organ distribution showed the highest value (ca 35 min p. app.) in the Kidneys followed by blood-plasma and later of the skin, liver and thyroid gland.

In conclusion: the percutaneous absorption rate of 1-Naphthol out of finished products as well as out of special and appropriate preparations was measured between 0.16 % to 0.42 % to 0.68 % according to different experimental conditions and using radio labelled (C1 of 1-Naphthol) test preparations. The excretion takes place rapidly, after three days p. appl. only 0,012 % to 0,094 % of the original radioactivity could be measured.

Ref. : 19

2.8. Mutagenicity/Genotoxicity

Mutagenicity/Genotoxicity studies have demonstrated that 1-naphthol does not induce gene mutation *in vitro* in *Salmonella* (9, 10, 11) and in mouse lymphoma L5178Y cells (12), and *in vivo* on *Drosophila* (recessive lethals, Basc test) (11); chromosome aberrations *in vivo* on bone marrow cells by micronucleus test on mice (2x144-288 mg/kg i.p. = 2x1-2 mmoles/kg; 2 doses with an interval of 24 h; analysis 30 h after the second dose) (11) and on rats (2x3000 mg/kg intragastric intubation, 2 doses separated by an interval of 24 h, analysis 6 h after the second dose) (14, 15); genotoxic effects *in vitro* by DNA repair test on *E.coli* (3 strains) and *B.subtilis* (2 strains) (13). Positive results were obtained for DNA repair test in one strain of *E.coli* (JC5547) using the spot test technique.

Ref. : 13

UDS in primary rat hepatocyte cultures

Hydroxynaphthalene gave a negative response when tested for its potential to induce unscheduled DNA synthesis using primary rat hepatocyte culture”.

The AA have demonstrated that a series of 88 chemicals gave a negative response in the newly developed rat hepatocyte UDS: among these chemicals, 1-Naphthol was listed as negative. According to AA the tested dose was generally the highest concentration that did not produce cytotoxicity.

No details are given which could provide more information on this study. The results of the study could not be used by SCCNFP.

The compound is not mutagenic.

Ref. : 21

2.9. Carcinogenicity

See 2.3.4

Ref. :

2.10. Special investigations

/

Ref. :

2.11. Safety evaluation

CALCULATION OF SAFETY MARGIN

1-NAPHTHOL

(Oxidation or Permanent)

The maximum concentration of 2.0 % of 1-Naphthol is mixed before use with H₂O₂. Thus the usage volume of 100 ml contains at maximum 1.0 %

Maximum amount of ingredient applied	I (mg)	=	1000 mg
Typical body weight of human		=	60 kg
Maximum absorption through the skin (rat study)	A (%)	=	0.7%
Dermal absorption per treatment	I x A	=	7.0 mg
Systemic exposure dose (SED)	I x A / 60 kg	=	0.117 mg/kg bw
No observed adverse effect level (mg/kg) (rat: 90 day oral study)	NOAEL	=	20 mg/kg

Margin of Safety	NOAEL / SED =	171
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It should be noted that the no-effect level is based on daily exposure for 90 days.

Taking into account that the application will generally not exceed once a month and that not all of the active ingredient will reach the scalp, the Margin of Safety is considered to be acceptable.

2.12. Conclusions

Classification : 1 under the conditions in use : as an oxidising colouring agent for hair dyeing at a maximum concentration of 2.0 % in the finished cosmetic product; in

combination with hydrogen peroxide the maximum use concentration upon application is 1.0 %.

2.13. References

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3. Opinion of the SCCNFP

This opinion replaces the previous opinion adopted by the SCCNFP during its 8th plenary meeting of 23 June 1999.

The SCCNFP is of the opinion that 1-Naphthol can be used safely as a oxidising colouring agent for hair dyeing at a maximum authorised concentration of 2.0% in the finished cosmetic product; in combination with hydrogen peroxide the maximum use concentration upon application is 1.0%.

The sensitisation data in the dossier was generated with a method not conforming with OECD n° 406. However, no further sensitisation data are requested provided that cosmetic products containing this substance carry a label warning of a risk of sensitisation.

4. Other considerations

Not Applicable

5. Minority opinions

Not applicable