Commission of the European Communities

environment and quality of life

REPORTS of the Scientific Committee on Cosmetology

(Second series)

Report

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Directorate-General
Environment, Consumer Protection and Nuclear Safety

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S U M M A R Y

This publication contains the second series of reports by the Scientific Committee on Cosmetology on :

- the use of some hair dyes

- the use of 1,3-Bis (Hydroximethyl) imidazolidine-2-thione in hair-care preparations

- supplementary opinion on boric acid

- the use of 4,4-dimethyl-1,3-oxazolidine as a preservative

- the use of 1,2-dibromo-2,4-dicyanobutane as a preservative

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INTRODUCTION

The Scientific Committee on Cosmetology was set up by Commission Decision 78/45/EEC of 19 December 1977 (OJ N° L 13 of 17 January 1978, p. 24) in order to provide the Commission with informed opinions on any scientific and technical problems arising in connection with cosmetic products, and in particular on the substances used in their manufacture, on their composition and on the conditions for their use.

The members of the Committee are independent scientists highly qualified in the fields of medicine, toxicology, biology, chemistry or other similar disciplines.

The Committee is serviced by the Directorate-general for the environment, consumer protection and nuclear safety.

This volume contains a collection of the Committee's second reports setting out the opinions it delivered on the dates given in the headings.

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REPORT

of

THE SCIENTIFIC COMMITTEE ON COSMETOLOGY

CONCERNING SOME HAIR DYES

(Opinion delivered on 2 September 1980)

THE COMMITTEE'S MANDATE

To give its opinion on the use as hair dyes of the following substances:

1-methoxy-2,4-diaminobenzene	(2,4-diamino-anisole)
1-methoxy-2,5-diaminobenzene	(2,5-diamino-anisole)
1,4-diamino-2-nitrobenzene	(2 NPPD)
1,2-diamino-4-nitrobenzene	(4 NOPD)
1-methyl-2,4-diaminobenzene	(2,4-diamino-toluene)
1-methyl-2,5-diaminobenzene	(2,5-diamino-toluene)
1,2-diaminobenzene	(o-phenylenediamine)
1,3-diaminobenzene	(m-phenylenediamine)
1,4-diaminobenzene	(p-phenylenediamine)
1-hydroxy-2-amino-4-nitrobenzene	(2-amino-4-nitrophenol)
1-hydroxy-2-amino-5-nitrobenzene	(2-amino-5-nitrophenol)

CONCLUSION

Hair dyes which are acceptable for use in cosmetic products

1,3-diaminobenzene	(m-phenylenediamine)
1-methyl-2.5-diaminobenzene	(2,5-diaminotoluene)
1,4-diaminobenzene	(p-phenylenediamine)

Hair dyes which are temporarily acceptable for use in cosmetic products until 31 december 1985

1-methoxy-2,4-diaminobenzene	(2,4-diamino-anisole)
1-methoxy-2,5-diaminobenzene	(2,5-diamino-anisole)
1,2-diamino-4-nitrobenzene	(4 NOPD)
1-hydroxy-2-amino-4-nitrobenzene	(2-amino-4-nitrophenol)
1-hydroxy-2-amino-5-nitrobenzene	(2-amino-5-nitrophenol)

Hair dyes the use of which should be discontinued

1-methyl-2,4-diaminobenzene	(2,4-diaminotoluene)
1,4-diamino-2-nitrobenzene	(2 NPPD)
1,2-diaminobenzene	(o-phenylenediamine)

BACKGROUND

1. Article 12 of the Council Directive 76/768/EEC concerning the approximation of the laws of the Member States relating to cosmetic products enables Member States to prohibit provisionally the marketing of a cosmetic product in its territory or subject it to special conditions if it notes, on the basis of a substantiated justification, that this product, although complying with the requirements of the Directive, represents a hazard to health.

2. On the basis of this Article and with reference to available scientific data, certain or several Member States have prohibited the following substances as hair dyes:

1-methoxy-2,4-diaminobenzene	(2,4-diamino-anisole)
1-methoxy-2,5-diaminobenzene	(2,5-diamino-anisole)
1,4-diamino-2-nitrobenzene	(2 NPPD)
1,2-diamino-4-nitrobenzene	(4 NOPD)
1-methyl-2,4-diaminobenzene	(2,4-diamino-toluene)
1-methyl-2,5-diaminobenzene	(2,5-diamino-toluene)
1,2-diaminobenzene	(o-phenylenediamine)
1,3-diaminobenzene	(m-phenylenediamine)
1,4-diaminobenzene	(p-phenylenediamine)
1-hydroxy-2-amino-4-nitrobenzene	(2-amino-4-nitrophenol)
1-hydroxy-2-amino-5-nitrobenzene	(2-amino-5-nitrophenol)

3. Consequently, the Committee was called to give an opinion on this use.

DISCUSSION

4. The Committee is of the opinion that a conclusion as regards the safe use of hair dyes cannot be reached merely on the basis of the results of mutagenicity tests, which are of value only as an indication.

5. Three decisive criteria were selected for the purposes of evaluating the toxicity of oxidizing colouring agents:

   - the results of mutagenicity tests;
   - the results of carcinogenicity tests on animals;
   - percutaneous resorption, possibly associated with systemic toxicity.

   The sensitizing potential of these substances was not included in the evaluation, since dermatologists have established that this effect is rarely observed in practice.

6. By analogy with certain medicinal products, the Committee considers that the use of nitrobenzene derivatives in cosmetics may possibly be associated with a risk of haematological toxicity.

   The frequency of disorders in man caused by the consumption of such drugs is low (approximately 1/10 000), but the anomalies observed (agranulocytosis, aplasia, anaemia, etc.) are serious and not uncommonly prove to be fatal.

7. In the case of oxidizing colouring agents whose use is provisionally maintained, the Committee recommends that the following implementing measures be adopted:

   1. the provisional authorization shall not exceed five years;

   2. the Committee shall be kept informed of the status of work with a view to an annual appraisal.

8. In the case of all hair dyes for domestic use, the Committee recommends that there should be a warning label with the following indications:

   - "for external use only";

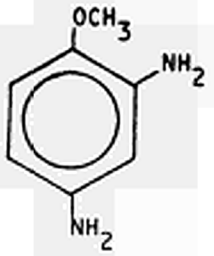
   - "wash hands after use".

9. The Committee recommends that constant attention be paid to epidemiological studies and that all activities along these lines be encouraged.

10. 1-methoxy-2,4-diaminobenzene

10.1 C.I : 76.050

10.2 Structural formula:



$C_7 H_{10} N_2 O$

10.3 Synonyms: 2,4-diaminoanisole
4-methoxy-m-phenylenediamine.

10.4 Among a large number of mutagenicity studies, no positive effects were seen in the dominant lethal test, micronucleus test, yeast and fungi, with questionable effects in cellular lines and positive effects with bacteria and drosophila.

10.5 The oxidized product can be absorbed through the skin. After topical application it has been recovered in the urine of Thesus monkeys, rats and humans. In rats, 0.6-1.7 % of the dose applied was recovered in the urine, in monkeys 0.025 % and in humans a maximum of 0.036 %.

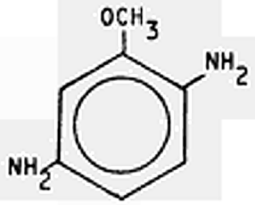
10.6 Six long-term studies were conducted with 2.4 DAA: one oral study in rats and mice and two dermal studies in rats and mice. In the 4 dermal studies carried out with the formulations, of which 2.4 DAA was one of the ingredients, no indication of systemic toxicity or carcinogenicity was observed. In both oral studies carried out with relatively high dose levels, carcinogenicity was observed.

10.7 Due to low percutaneous resorption of the oxidized product, the S.C.C. is in doubt that the results of the latter tests constitute sufficient argument in order to predict a carcinogenic risk for man, arising from topical application at low concentration. Moreover, the S.C.C. does not forsee sufficient reason to ban this substance because of the inconsistency of the results from the mutagenicity tests. It recommends continued provisional usage and requests the repetition of the carcinogenic tests conceived in a more realistic manner than the doses which take account of the resorption levels of the product.

11. 1-methoxy-2,5-diaminobenzene

11.1 C.I : -

11.2 Structural formula:



$C_7 H_{10} N_2 O$

11.3 Synonyms: 2,5-diaminoanisole
2,5-diamino-1-methoxybenzene
2-methoxy-p-phenylenediamine.

11.4 With mutagenicity testing a positive reaction is observed in the majority of bacterial tests and negative one in the rest.

11.5 No data are available on percutaneous resorption.

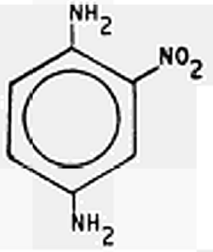
11.6 A carcinogenicity study was conducted testing the skin of mice during 21 months. The results were negative. The results at present available of carcinogenicity studies in this compound do not provide an adequate basis for the SCC to make an assessment.

11.7 The SCC does not have sufficient data available for a final toxicological assessment of this substance. They wish to obtain additonal information concerning percutaneous resorption and possible carcinogenicity in animals after dermal application of adequate doses. The SCC recommends continued provisional usage.

12. 1,4-diamino-2-nitrobenzene

12.1 C.I : 76070

12.2 Structural formula:



$C_6 H_7 N_3 O_2$

12.3 Synonyms: 2-nitro-1,4-phenylenediamine
2-nitro-1,4-benzenediamine
2-nitro-4-aminoaniline
2-nitro-1,4-diaminobenzene
2-nitro-p-phenylenediamine (2 NPPD)
o-nitro-p-phenylenediamine
diaminonitrobenzene
m-nitro-p-phenylenediamine
o-nitro-p-phenylenediamine.

12.4 For mutagenicity the dominant lethal test and micronucleus test were negative but positive results were obtained in several bacterial and mammalian cell systems.

12.5 Cutaneous resorption of the oxidized product is relatively slight (0,2 % in the skin of monkeys).

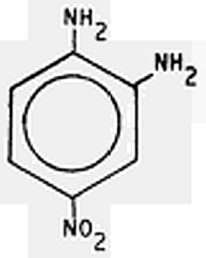
12.6 Several long-term toxicity studies have been carried out both orally and dermally in dogs, rats and mice. In one dermal study with among other 0.0015 % 2 NPPD, a higher tumour rate was observed in only one strain of mice. In an oral study, with relative high dose levels, hepatocellular adenomas and carcinomas were observed in female mice. In a rat study the incidence of thyroid tumour was higher.

12.7 In view of the positive carcinogenicity findings in animals, at the doses used, the SCC recommends that its use might be discontinued. Nevertheless, this decision could be modified because of the product's low percutaneous resorption and because the carcinogenicity tests by the dermal route were conducted on a mixture of the substance and not with 2 NPPD alone.

13. 1,2-diamino-4-nitrobenzene

13.1 C.I : 76.020

13.2 Structural formula:



$C_6 H_7 N_3 O_2$

13.3 Synonyms: 4-nitro-o-phenylenediamine (4 NOPD)
2-amino-4-nitroaniline
4-nitro-1,2-diaminobenzene
4-nitro-1,2-phenylenediamine
p-nitro-o-phenylenediamine.

13.4 From mutagenicity testing: positive reactions were found in most bacterial tests and negative reactions in the micronucleus and dominant lethal tests.

13.5 No data were available on cutaneous resorption.

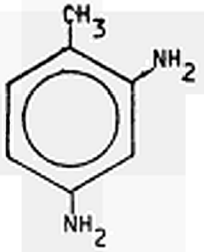
13.6 The NCI studies showed that 4 NOPD, administrated daily for two years in food was not carcinogenic in either rats or mice. When oxidized 4 NOPD was applied topically to mice over a period of two years it did not cause the development of tumours, but when 4 NOPD mixed with 2 NPPD was tested, under similar conditions, the development of lymphomas and genital carcinomas was observed.

13.7 In view of the absence of conclusive carcinogenic effects in animals, the SCC sees no reasons for prohibiting 4 NOPD at present but wishes to obtain additional information concerning percutaneous resorption and the repetition of more realistic carcinogenicity tests and in the meantime it can accept its continuing use on a provisional basis. The implementation of this recommendation will be reviewed each year.

14. 1-methyl-2,4-diaminobenzene

14.1 C.I : 76.035

14.2 Structural formula :



$C_7 H_{10} N_2$

14.3 Synonyms: 2,4-diaminotoluene
2,4-diaminobenzene (mTD).

14.4 The mutagenicity tests are not adequate. Most of the findings so far are positive.

14.5 Percutaneous uptake of the non-oxidized product in the skin of monkeys indicate a high level of percutaneous absorption (16-18 %) (unpublished).

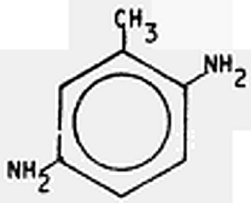
14.6 Long-term feeding of rats led to the formation of liver tumours, but topical application to mice of the compound was followed by no neoplastic changes.

14.7 On the balance of evidence and in the cause of prudence the SCC recommends that the use of mTD should be discontinued pending further studies on the percutaneous resorption of this compound under conditions of use in accord with those in practice.

15. 1-methyl-2,5-diaminobenzene

15.1 C.I : 76.042

15.2 Structural formula:



$C_7 H_{10} N_2$

15.3 Synonyms: 2,5-diaminobenzene
2,5-diaminotoluene (pTD)
p-diaminotoluene
2-methyl-1.4-diaminobenzene
4-amino-2-methylaniline
2-methyl-p-diaminophenylene.

15.4 From mutagenicity testing: a positive reaction was observed in the majority of the bacterial tests, whereas no mutagenic effect was observed in the other tests.

15.5 Percutaneous resorption of the oxidized product is slight (of the order of 0.2 % in the skin of rats, dogs and man).

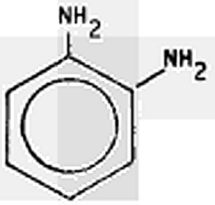
15.6 Long-term toxicity studies have shown that oxidized pTD is not carcinogenic in rats and mice when administered either orally or topically.

15.7 The SCC recommends continued usage of pTD in view of its low cutaneous resorption and the absence of carcinogenic effects.

16. 1,2-diaminobenzene

16.1 C.I : 76.010

16.2 Structural formula:



$C_6 H_8 N_2$

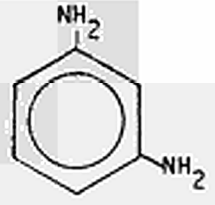
16.3 Synonyms: o-phenylenediamine.

16.4 The SCC is unable to take a decision on this substance due to lack of information. It seems, moreover, that this substance is not used.

17. 1,3-diaminobenzene

17.1 C.I : 76.025

17.2 Structural formula:



$C_6 H_8 N_2$

17.3 Synonyms: n-phenylenediamine.

17.4 The findings from mutagenicity tests were generally positive with bacterial cell lines and negative in such tests as the micronucleus and the dominant lethal study.

17.5 Percutaneous resorption (4 %) of the oxidized product in the skin of dogs is high by comparison with that of other oxidized colorants; nevertheless, long-term toxicity studies on rodents (orally in the case of mPD and topically in the case of oxidized mPD) show no evidence of systemic toxicity.

17.6 Long-term toxicity studies using mPD orally and oxidized in mPD incorporated in a formulation and applied topically, showed no carcinogenic changes in rats or mice.

17.7 Not with standing the percutaneous uptake level of 4 % the SCC recommends continued usage of mPD in view of the lack of systemic long-term toxicity and absence of carcinogenic effects in animals with the dose levels tested.

18. 1,4-diaminobenzene

18.1 C.I : 76.060

18.2 Structural formula:

$C_6 H_8 N_2$

18.3 Synonyms: p-phenylenediamine
4-aminoaniline
p-aminoaniline
p-diaminobenzene.

18.4 With the exception of the tests using the oxidized product for Escherichia coli, no mutagenic effect has been observed in the so far conducted tests.

18.5 Cutaneous resorption of PPD from the dog is relatively low (1 %), being ten times lower in the case of oxidized pPD (0.13 %).

18.6 All long-term animal toxicity studies by the topical and oral routes indicate that pPD is not carcinogenic.

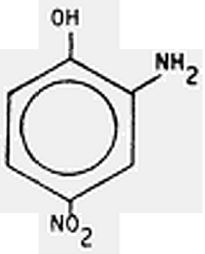
18.7 Epidemiological data indicate that there is no evidence of a carcinogenic effect in man.

18.8 On the basis of the low cutaneous resorption, the lack of carcinogenic effects in animals and the epidemiological data, which suggest that this compound does not constitute a danger to human health, the SCC recommends continued usage of paraphenylenediamine.

19. 1-hydroxy-2-amino-4-nitrobenzene

19.1 C.I : 76.530

19.2 Structural formula:



$C_6 H_6 N_2 O_3$

19.3 Synonyms: 2-amino-4-nitrophenol.

19.4 The findings from mutagenicity tests were generally positive with bacterial cell lines and negative in such tests as the micronucleous and the dominant lethal study.

19.5 Percutaneous absorption: the oxidized product is absorbed under 2 % by the skin of dogs.

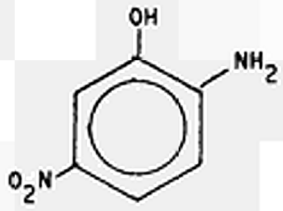
19.6 The only test for carcinogenicity was skin painting experiments on mice for 21 months. As far as can be judged, the results were negative, but in view of some unsatisfactory features of the study, it is difficult to draw firm conclusions for the findings.

19.7 The SCC has insufficient data for a carcinogenic assessment of this substance and wishes to obtain additional information concerning carcinogenicity in animals after dermal application of adequate doses. However, it sees no reason to forbid its continued provisional use of the 2-amino-4-nitrophenol.

20. 1-hydroxy-2-amino-5-nitrobenzene

20.1 C.I : 76.535

20.2 Structural formula:



$C_6 H_6 N_2 O_3$

20.3 Synonyms: 2-amino-5-nitrophenol.

20.4 The findings from mutagenicity tests were generally positive with bacterial cell lines and negative in such tests as the micronucleus and the dominant lethal study.

20.5 No data are available on cutaneous resorption.

20.6 A carcinogenicity study was conducted testing the skin of mice during 21 months. The results were negative. The results at present available of carcinogenicity studies in this compound do not provide an adequate basis for the SCC to make an assessment.

20.7 The SCC does not have sufficient data available for a conclusive toxicological assessment of this substance. The wish to obtain additional information concerning percutaneous resorption and possible carcinogenicity in animals after dermal application of adequate doses. However, it sees no reason to forbid its continued provisional use.

REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY ON THE USE OF 1,3-BIS (HYDROXIMETHYL) IMIDAZOLIDINE-2-THIONE IN HAIR-CARE PREPARATIONS

(Opinion delivered on 2 September 1980)

TERMS OF REFERENCE OF THE COMMITTEE

To give an opinion on the use in hair-care preparations of 1,3-bis (hydroxymethyl) imidazolidine-2-thione in a maximum concentration of 2% in the finished cosmetic product and under the conditions laid down in Directive 76/768/EEC.

CONCLUSION

The Committee is of the opinion that the use of 1,3-bis (hydroxymethyl) imidazolidine-2-thione represents no hazard to health under the conditions laid down in Directive 76/768/EEC provided that the use of this substance is limited to hair-care products with an acid pH.

BACKGROUND

1. Article 5 of Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as amended by Directive 79/661/EEC, obliges Member States to permit, up to 31 December 1980, the marketing of cosmetic products containing 1,3-bis (hydroxymethyl) imidazolidine-2-thione under the following conditions :

Field of application and/or use	Maximum authorised concentration in the finished cosmetic product	Other limitations and requirements	Conditions of use and warning which must be printed on the label
Hair-care preparations	(a) up to 2%	(a) Prohibited in aerosol dispensers	(a) Contains 1,3-bis (hydroxymethyl) imidazolidine-2-thione
	(b) from 2% to 8%	(b) ditto	(b) Rinse hair thoroughly after use Contains 1,3-bis (hydroxymethyl) imidazolidine-2-thione

2. As from 1 January 1981, this substance will have to be :

either

- definitively permitted

or

- definitively prohibited

or

- provisionally retained for a further period

or

- deleted from all Annexes to the Directive.

3. Concentrations of between 2% and 8% are no longer employed.

4. Consequently the Committee is requested to deliver an opinion on the use of 1,3-bis (hydroxymethyl) imidazolidine-2-thione in hair-care preparations in a maximum concentration of 2% in the finished product and under the conditions laid down in Directive 76/768/EEC,i.e. by means of

- prohibition of the use of the product in aerosol dispensers (sprays) and
- a warning, which must be printed on the label.

DISCUSSION

5. Acute toxicity studies using the oral route in mice and rats show that 1,3-bis (hydroxymethyl) imidazolidine-2-thione (DHMT) is of low toxicity.

6. DHMT is well tolerated by the skin, even after repeated application, and by the mucous membranes at the pH for cosmetic use (pH/3) while no sensitizing properties have been observed in rabbits and guinea pigs. These observations have been confirmed in man.

7. Percutaneous absorption is low (1.1% - calculated in the case of human skin) and the greater part of the quantity absorbed is rapidly excreted. Furthermore, given its considerable affinity for hair, it has been ascertained that only 2% of the quantity applied can come into contact with the scalp.

8. During in vitro mutagenicity studies no mutagenic effect, with or without microsomial activitation, has been observed.

9. Although certain imperfections in the way the tests were conceived and the way in which they were carried out have been noted, the long-term toxicity studies using the oral and topical routes in mice have shown no indication of carcinogenicity due to DHMT.

10. During acute toxicity studies, using the intraperitoneal route in rats, and subacute toxicity studies, entailing repeated topical administration in rats, under experimental conditions corresponding to doses considerably higher than for human use, no significant variation in serum contents thyroid hormones has been observed.

11. The structural difference between DHMT (Tetrasubstituted thiourea)and its homopolymers, on the one hand, and ethylene thiourea, thiourea, on the other, must be noted. This difference is due to the fact that there is no H atom in an α position to the double bond in the group $C=S$, implying that the tautomeric form - SH -, present in known products exhibiting thyrostatic activity, cannot react.

12. Cosmetic use requires DHMT to polymerize at an acid pH and it decomposes into ethylene thiourea only at an alkaline pH.

13. In view of:

- the low percutaneous absorption of DHMT and the small quantities actually absorbed by the scalp during cosmetic use;
- the absence of any mutagenic effect;
- the absence of evidence of carcinogenicity in mice;
- the absence of any variation in thyroid hormones contents during acute and subacute toxicity studies in rats,

the Committee considers that this is a substance which does not represent any hazard to health under the conditions laid down in Directive 76/768/EEC provided that the use of DHMT is limited to hair-care products with an acid pH.

SUPPLEMENTARY OPINION ON BORIC ACID

(Opinion expressed 28 June 1982)

Pursuant to point 11 of its opinion given on 22 May 1979 (1), the Committee has examined the new information brought to its attention.

1. - From a study to determine the boron content of the blood after the application of a water emulsifying ointment with 3% boric acid to the skin of newborn babies (2), it was found that the amount of boron in the blood of these babies does not change.

   - Nor has any correlation been observed between the boron concentration of the mother's milk and the amount of boron in the blood of newborn babies.

   - On the other hand, large individual variations were observed and the highest blood boron contents were found in the control group which was not studied at the same time as the test group.

2. - From a study of the urinary excretion of boron after the application of a water emulsifying ointment with 3% of boric acid to healthy and to damaged skin in adults (3), it was found that the urinary excretion of boron is unaffected, whatever the state of the skin.

   - It is observed that the total boron excreted during the 24 hours prior to the application of the emulsion is significantly higher than the total boron excreted during the days following the application.

   - The measurement of urinary excretion gives no information on any absorption by organs and tissues matter.

   - Very large individual differences and daily fluctuations in boron content, which probably depend on diet, were observed but not taken into account in the course of the study, thus reducing its degree of accuracy.

3. - In a parallel study carried out with a hydrogel with 3% boric acid (3), a large increase in the boron contents of the blood and urine was observed after application. This proves that the percutaneous penetration of boric acid depends on the nature of the vehicle.

4. - In a new study (4) on oral absorption and on elimination in man, no accumulation of boric acid was observed.
In fact, 93% of the quantity ingested (750 to 1 500 mg) was excreted in the urine, with an estimated half-life of 15 to 20 hours.

There was no significant difference between the urinary excretion of boric acid following ingestion of an aqueous solution and that following application of an ointment with a continuous oily phase.

5. - A comparative in vitro test (5) showed that the release of boric acid from the ointment was slight in the case of a few commercial preparations with a continuous oily phase.

As a result of this new information, the Committee has revised the conclusions of its opinion of 22 May 1979. It feels that there is no need to amend them in the case of talcs and products for oral hygiene. In the case of the other products, however, since the nature of the vehicle can affect the percutaneous penetration of boric acid, the Committee still considers that the warning "Not to be used on damaged skin" should , as a matter of prudence, appear on the labels, unless it has been clearly established that there is no risk of boric acid absorption, as in the case of the water emulsifying ointment (6).

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REPORT OF THE SCIENTIFIC COMMITTEE ON COSMETOLOGY CONCERNING THE USE OF 4,4 — DIMETHYL-1,3-OXAZOLIDINE AS A PRESERVATIVE

(Opinion delivered on 28 June 1982)

TERMS OF REFERENCE OF THE COMMITTEE

To deliver its opinion on the use of 4,4 - dimethyl-1,3-oxazolidine as a preservative with a maximum concentration in rinse-off cosmetic products of 0.1% of an aqueous solution containing 78% of the active substance.

CONCLUSION

The Committee considers that :

(a) additonal information on mutagenesis is needed;

(b) a study should be carried out on short-term oral toxicity with doses that are sufficient to produce a systemic effect;

(c) unless, in the normal conditions of use, percutaneous absorption is insignificant, a teratogenicity study should be carried out, in view of the fact that percutaneous absorption in animals appears to be substantial.

However, on the basis of the data available, the Committee could accept, for the time being, the use of 4,4-dimethyl-1,3-oxazolidine as a preservative in cosmetic products on a provisional basis under the above conditions.

BACKGROUND

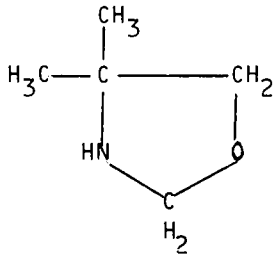
1. Council Directive 76/768/CEE on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Council Directive 82/368/EEC, allows those cosmetic products to be placed on the market that contain as preservatives only the substances listed in Annex VI to the Directive within the specified limits and concentrations.

2. The industry has requested that 4,4 - dimethyl-1,3-oxazolidine be entered on the list in Annex VI and has submitted scientific documentation in support of its request.

3. The Committee is therefore invited to deliver an opinion on the use of 4,4 - dimethyl-1,3-oxazolidine as a preservative with a maximum concentration in rinse-off cosmetic products of 0.1% of an aqueous solution containing 78% of the active substance.

DISCUSSION

4. Chemical name (IUPAC): 4,4 - dimethyl-1,3-oxazolidine



$C_5H_{11}NO$

Generic name: dimethyl oxazolidine

5. Dimethyl oxazolidine is marketed in the form of an aqueous solution containing 78-87.4% of active igredients.

6. Dimethyl oxazolidine is used as a preservative in rinse-off cosmetic products with a maximum concentration in the finished product of 0.1% of the commercial solution.

7. Both the acute oral and acute dermal toxicity are moderate. The oral LD_{50} in the rat is about 950 mg/kg. No signs of toxicity were noted at 400 mg/kg. The dermal LD_{50} in the rabbit is estimated at 970-2000 mg/kg. The animals developed progressive injury to the skin with eschar formation. In view of the fact that acute dermal toxicity is just as severe as acute oral toxicity, it would appear that considerable percutaneous absorption of the substance occurs.

8. An 87.4% solution was severely irritating to the rabbit eye and the changes produced showed no recovery over 72 hours. Dilutions of 1000 ppm and 5000 ppm of the commercial solution (equal to 0.08% and 0.4% of dimethyl-oxazolidine) were not irritant to the eye.

9. In rabbits, a primary skin irritation test, using 0.5 ml of the 87.4 % aqueous solution, with and without occlusion caused slight to severe signs of oedema, erythema and deep tissue reaction.

10. The compound shows skin sensitising properties in the guinea-pig. These were not found in the rabbit. In a well-conducted study in 101 human volunteers no evidence of sensitisation was found in repeated tests with a 3% aqueous solution.

11. A sub-chronic 13-week dermal toxicity test in rats at dose levels of 0, 1.95, 19.5, and 195 mg/kg in a 1:1 ethanol/water solution induced increased haematopoietic activity in the top dose group, as well as severe skin irritation. No other treatment-related abnormalities were found despite extensive clinical, chemical and histological examination.

12. The Ames test showed a reproducible dose-related increase in revertants in two of five strains, which was not regarded as significant by the investigators.

13. It should be noted that this is a nitrostable compound.

14. Thus, the Committee considers that

    a) additional information on mutagenesis is needed;

    b) a study should be carried out on short-term oral toxicity with doses that are sufficient to produce a systemic effect;

    c) unless, in the normal conditions of use, percutaneous absorption is insignificant, a teratogenicity study should be carried out, in view of the fact that percutaneous absorption in animals appears to be substantial.

15. However, on the basis of the data available, the Committee could accept, for the time being, the use of 4,4- dimethyl-1,3-oxazolidine as a preservative in rinse-off cosmetic products with a maximum concentration in the finished cosmetic product of 0.1% of an aqueous solution containing 78% of the active substance.

16. Reference: COLIPA dossier.

REPORT OF THE SCIENTIFIC COMMITTEE ON COSMETOLOGY CONCERNING THE USE OF 1,2-DIBROMO- -2,4-DICYANOBUTANE AS A PRESERVATIVE

(Opinion delivered on 28 June 1982)

TERMS OF REFERENCE OF THE COMMITTEE

To give an opinion on the use of 1,2-dibromo-2,4-dycyanobutane as a preservative at a maximum concentration of 0.1% in the finished cosmetic product.

CONCLUSION

The Committee wishes to obtain information on the effects of 1,2-dibromo-2,4- dicyanobutane on the thyroid gland, with the specific aim of establishing the no-effect dose. On the basis of the existing data, however, it can approve the provisional use of 1,2-dibromo-2,4-dicyanobutane as a preservative in cosmetics at a maximum concentration of 0.1% in the finished product.

BACKGROUND

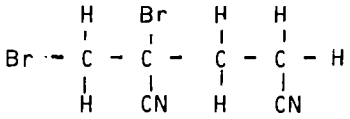
1. Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Council Directive 82/368/EEC, authorizes the placing on the market of cosmetic products containing as a preservatives only the substances listed in Annex VI to the said directive, within the limits and concentrations specified therein.

2. The industry has requested that 1,2-dibromo-2,4-dicyanobutane be added to that Annex and has submitted a scientific dossier in support of its request.

3. The Committee is consequently invited to express an opinion on the use of 1,2-dibromo-2,4-dicyanobutane as a preservative at a maximum concentration of 0.1% o, the finished cosmetic product.

DISCUSSION

4. Chemical name : 1,2-Dibromo-2,4-dicyanobutane



$C_6H_6N_2Br_2$

5. Solubility in water 0.27% at 0°, easely soluble in organic solvents.

6. Used in cosmetics up to 0,1%.

7. The substance possesses moderate acute toxicity upon oral and low toxicity upon dermal and inhalation exposure.

8. It is severely irritating to the eye and moderately irritating to the skin if applied undiluted, but no irritation of the skin or the eye of rabbits and the human skin is observed in a dilution of 0.1% as used in practice. A 0.3% dilution in oil was neither irritating nor sensitizing when applied to the human skin.

9. An oral dose (50 mg/kg) given to rats, was mainly excreted in the urine (84-91%). A small part was excreted in the faeces (6-10%) and a very small part in the respiration air (0.5%). Seven days after a single intragastric dose 0.4% remained in the organs, 0.3% of the dose was in the liver.

10. In a 90-day study, dietary levels of 0 (control), 83.5, 500 or 3000 ppm given to the offspring of rats which had already been fed these diets through the muting, pregnancy and lactation periods, increased the weight of the tyroid in the top-dose group; growth rate was significantly lower for the mid- and high-dose males. Microscopically, increased haematopoieses was observed in the spleen of the top-dose females. No diseased or malformed pups were seen in the litters of the parent rats, which suggests abscence of teratogenic properties.

11. A 90-day study in dogs with feeding levels of 0 (control), 167, 1000 or 4000 ppm showed several changes in the top-dose group, such as changes in body weight, haematology, blood biochemistry, enlarged thyroids (hyperplasia) and increased haematopoieis in the liver and spleen. Clinically the dogs of the highest dose showed inter alia diarrhoea.

12. The lowest feeding level (4.2 mg/kg body weight/day) was a no-toxic-effect in the rat and possibly also in the dog.

13. The Ames test (with or without activation), and a dominant lethal assay in male mice were negative.

14. The Committee requests informations on the effects of the compound on the function of the thyroid specially with regard to establishing the no-effect level. On the base of the existing data, however, it can approve the provisonal use of 1,2-dibromo-2,4-dicyanobutane as a preservative in cosmetics at a maximum concentration of 0,1% in the finished product.

Ref. : COLIPA file.

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