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FORWARD

The Scientific Committee on Cosmetology was set up by Commission Decision 47/45/EEC on 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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(1) Elected Chairman on 17.12.1984
(2) Elected Vice-Chairman on 17.12.1984
(3) Appointed on 19.9.1984

Report by the SCC on the use of hydroquinone as a skin-bleaching product

(Opinion expressed 24.2.1983)

Terms of reference of the Committee

To give its opinion on the use of hydroquinone in creams and lotions for the depigmentation of the skin by local topical application in a maximum concentration in the product of 2%.

Conclusion

In view of the hazard presented by other depigmenting agents, the Committee agrees to the use of hydroquinone at concentrations not exceeding 2 % in cosmetic products for the depigmentation of localized melanotic areas, provided that the usual precautions are fully indicated on the label (see item 14).

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 Directive 82/368/EEC, authorizes hydroquinone only as an oxidation colouring agent for the colouring of hair in a maximum concentration of 2% in the final cosmetic product (Annex III, first part, number 14).

2. The use of hydroquinone as a skin-bleaching product is outside the scope of the Directive mentioned (Annex V), i.e. the Member States can make any provision they see fit in respect of this use.

3. Nevertheless, the Council has invited the Commission to examine hydroquinone to see whether it could be admitted at Community level for uses other than hair colouring.

4. Thus, the Committee is invited to give an opinion on the use of hydroquinone in creams and lotions for the depigmentation of the skin by local topical application in a maximum concentration of 2% in the final cosmetic product.

Discussion

5. The acute toxicity tests carried out in several animal species, using various routes of administration, have shown that hydroquinone is less toxic when given dermally ($LD_{50} > 900$ mg/kg) than when given orally (LD_{50} about 350 mg/kg), intravenously, intraperitoneally or subcutaneously (LD_{50} about 170 mg/kg). (Figures derived from experiments on rats.)

6. When applied in a 5 % aqueous solution, hydroquinone does not irritate the rabbit eye. It proved to be slightly irritant to rabbit skin when applied under occlusion at a 4.6 % concentration in a cream. In man, during depigmenting treatments, irritant effects on the skin were observed when concentrations higher than 4 %, were used.

7. Two maximization tests in guinea-pigs disclosed no sensitizing property.

8. Hydroquinone is slowly absorbed through the human skin and is rapidly eliminated in the faeces and urine.

9. In a short-term toxicity study (63 days) and in a medium-term toxicity study (6 months) involving oral administration of high doses in rats, the following observations were made : effects on the bone marrow, changes in the blood picture, loss of body weight and dystrophic changes in several organs, especially the liver, the kidney and the myocardium. The no effect level was assessed as 0.5 mg/kg b.w./day in rats. The target organs were the same in a short-term toxicity study (50 days) using the percutaneous route in guinea-pigs, but the abormalities observed depended more on the surface area treated than on the concentration of hydroquinone employed. In addition, neuro-motor effects have been observed in several short-term toxicity studies involving oral and subcutaneous administration, in particular in cats, mice and rats.

10. No abnormalities were observed in new-born animals during a teratogenicity study involving dermal application to female rats of doses of up to 810 mg/kg b.w./day.

Reproduction studies, after oral administration in rats, disclosed no foetal abnormalities, but in one of the studies, the number of cases of foetal resorption was greater in the treated animals.

11. Results of mutagenicity tests were inconsistent.

12. Long-term oral studies in rats and dogs showed no carcinogenic effect; furthermore, two studies carried out on mouse skin demonstrated an absence of cocarcinogenic action or of any cancer-inducing action.

13. Industrial exposure in man can give rise to conjunctival and corneal irritation and pigmentation. When the product was used extensively and continuously by Bantu women, cases of deterioration of connective tissue were noted.

14. Insofar as products containing hydroquinone intended as topically applied skin-depigmenting agents are regarded as cosmetic products, within the meaning of Directive 76/768/EEC, the Committee, considering both the dager represented by other depigmenting agents and the toxicological data, concludes that, owing to the relative safety of the substance in use, it is able to agree to the incorporation of hydroquinone at concentrations of not more than 2 % in cosmetics for the depigmentation of localized melanotic areas, provided the following precautions are indicated on the labels :

    - must be used with a sun-screen product;
    - must not be used for more than two months;
    - must not be used near the eyes;
    - must not be used on children under twelve;
    - stop using if there is any irritation;
    - depigmenting effect is low on black skin.

Ref. : COLIPA file

REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY
ON THE USE OF SILVER NITRATE IN COSMETIC PRODUCTS
FOR DYEING EYELASHES AND EYEBROWS

(Opinion expressed 26 May 1983)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion on the use of silver nitrate in cosmetic products for dyeing eyelashes and eyebrows with a maximum concentration of 4 % in the finished cosmetic product.

CONCLUSION

The Committee can accept the use of silver nitrate in cosmetic products for dyeing eyelashes and eyebrows under the conditions in Directive 76/768/EEC.

BACKGROUND

1. Pursuant to Article 5 of Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 83/191/EEC, the Member States must accept, up to 31 December 1985, the marketing of cosmetic products containing silver nitrate subject to the following restrictions and conditions :

   - field of application and/or use : solely for products intended to dye eyelashes and eyebrows;
   - maximum authorized concentration in the finished cosmetic product : 4 %;
   - conditions of use and warnings which must be printed on the label :

     Contains silver nitrate.
     Rinse eyes immediately if product comes into contact with them.

2. On expiry of that period, silver nitrate will be :

   - either definitively permitted (Annex III);
   - or definitively prohibited (Annex II);

- or retained for a given period in Annex IV;

- or deleted from all annexes.

3. Consequently the Committee is asked to deliver an opinion on the use of silver nitrate in cosmetic products subject to the abovementioned restrictions and conditions.

DISCUSSION

4. In the cosmetology department of Göttingen University, a clinical test has been carried out by estheticians on 380 women aged from 18 to 62, by applying to the eyelashes a product containing a 2.8 % concentration of silver nitrate.

5. The desired colouring effect is obtained after a period varying from 40 to 180 minutes.

6. At periods of from three to eight weeks after the application, no irritation or allergy, or fragility of the eyelashes, was observed.

7. For treatment purposes, $AgNO_3$ is used in a concentration of 1 % for gingivitis and injuries in newborn infants.

8. Oral intake of $AgNO_3$ can cause problems resulting from argyria but cutaneous absorption is naturally limited by a self-regulating mechanism of the skin. The $AgNO_3$ is precipitated in the form of metallic silver by the skin proteins.

9. In view of the good skin tolerance and absence of cutaneous absorption of $AgNO_3$, the Committee concludes that it can accept the use of $AgNO_3$ for dyeing eyelashes and eyebrows under the conditions laid down in the Directive on cosmetic products.

REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY ON THE USE OF SELENIUM DISULPHIDE IN SHAMPOOS

(Opinion expressed 20 September 1983)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion on the use of selenium disulphide in shampoos at a maximum concentration of 1 % in the finished cosmetic product.

CONCLUSION

The Committee can accept the use of selenium disulphide in shampoos at a maximum concentration of 1 % in the finished cosmetic 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 Directive 83/341/EEC , prohibits under Article 4 the marketing of cosmetic products containing selenium and selenium compounds (substance 297 in Annex II).

2. The industry has requested that an exception be made in the case of selenium disulphide in shampoos in view of the valuable anti-dundruff properties of this compound.

3. Consequently, the Committee is requested to give an opinion on the use of selenium disulphide in shampoos with a maximum content of 1 % in the final cosmetic product.

DISCUSSION

4. The acute toxicity of selenium disulphide administered orally to rats, mice and rabbits varies considerably from one study to another (LD_{50} of 62 to 200 mg/kg b.w. in some studies and 490 to 3690 mg/kg b.w. in others).

5. At a concentration of 2.5 % in a shampoo, selenium disulphide has a slightly irritant effect on the intact or abraded skin of rabbits. With repeated application of a 1 % shampoo, reversible erythema and edema are observed at the point of application.

6. Selenium disulphide is well tolerated by the rabbit eye at a concentration of 0.5 % in an ointment; it is irritating at 1 % in an ointment and at 2.5 % in a shampoo.

7. A study of oral uptake in mice shows that selenium is concentrated in the blood, liver and kidneys from doses of 125 mg selenium disulphide per kg body weight upwards. With percutaneous application in mice, penetration is slight (about 1 % of the dose applied).
In man, data on percutaneous absorption disagree and are possibly influenced by the fluctuations in the normal daily absorption of selenium.

8. In short-term toxicity studies of oral administration in rats and mice, degeneration of the liver and kidneys is observed. The first anomalies are observed at a dose of 31.6 mg of selenium disulphide per kg body weight. With dermal application,short-term studies in mice reveal, in addition to the local effects observed at all doses (erythema → edema → acanthosis → hyperkeratosis), a systemic effect on the liver and kidneys (hepatic necrosis and interstitial nephritis), the no-effect dose being estimated at 1 mg of selenium disulphide per kg b.w. per day.

9. In long-term studies, oral administration of doses of selenium disulphide of about 15 mg/kg body weight in rats and 100 mg/kg body weight in mice brings about a significant increase in hepatic tumours (hepatocellular carcinoma and adenoma) and in the female mouse an increase in the number of alveolar and bronchiolar tumours is observed.

This finding of carcinogenic activity after oral administration reinforces the biological significance of the long-term tests carried out by dermal application in mice, even though in this case the incidence of the increase in tumours in the target organs is not significant.

10. From a considerable number of recent experiments in mice and rats it appeared that increased ingestion of selenium may result in a significant reduction of both chemically induced and spontaneous mammary tumours. Moreover, indications have been obtained that administration of additional selenium may lengthen the latency period of mammary tumours and may decrease the number of these tumours per tumour-bearing animal. These findings suggest that selenium possesses anti-carcinogenic properties.

11. Bearing in mind the level of the doses having a carcinogenic effect in animals, the fact that selenium is an essential element in the human body, the system for the regulation of blood selenium in man, the low percutaneous absorption and bearing in mind also that selenium has an anti-carcinogenic effect, the Scientific Committee on Cosmetology concludes that the carcinogenic risk for man is negligible and that it can accept the use of selenium disulphide at a concentration of 1 % in shampoos.

REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY ON THE USE OF BENZOYL PEROXIDE IN COSMETIC PRODUCTS

(Opinion expressed 29 November 1983)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion on the use of benzoyl peroxide in lotions, creams and gels for greasy skin in a maximum concentration of 3% in the finished cosmetic product, provided that the following warnings appear on the label :

- Contains benzoyl peroxide
- Avoid all contact with the eyes and mouth
- Discontinue use if irritation occurs
- Do not use simultaneously with other cosmetic products.

CONCLUSION

The Committee can agree to the use of benzoyl peroxide in cosmetic products in a maximum concentration of 3% in the finished cosmetic product, subject to the above-mentioned warnings. It recommends that the following warning be added thereto : "Do not expose yourself to sunlight immediately after applying the product !"

BACKGROUND

1. Article 12 of Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 83/574/EEC, provisionally allows each Member State to prohibit or to subject to special conditions on its territory the placing on the market of a cosmetic product if it notes, on the basis of a detailed statement of reasons, that that product, although complying with the requirements of the Directive, represents a hazard to health.

2. On the basis of that Article, a Member State has prohibited the use of benzoyl peroxide in cosmetic products in view of the irritant and sensitizing properties of that substance.

3. Consequently, the Committee was requested to deliver an opinion on the use of benzoyl peroxide in cosmetic products under the conditions envisaged.

DISCUSSION

4. Acute toxicity in rodents is not severe. The oral LD_{50} in rats is higher than 5 000 mg/kg.

5. Cosmetic preparations containing 5 to 10% concentrations of benzoyl peroxide irritate rabbits' skin. The severity of the irritation depends on the duration of exposure and the quantity applied.
At the same concentrations in cosmetic creams, lotions and gels, applied with or without rinsing, the substance has a slight to severe irritant effect on rabbits' eyes.

6. The results of the phototoxicity tests in guinea-pigs are equivocal A 5% benzoyl peroxide cream produces a phototoxic effect whereas a 5% lotion exerts no effect.

7. In a sensitization study in guinea-pigs, a sensitizing effect was observed with a preparation containing 10% of benzoyl peroxide and 1% of sulphur.

8. Dermal studies of metabolism in rats and monkeys showed that benzoyl peroxide penetrates the skin by being converted into benzoic acid which is excreted in the urine, chiefly in the form of hippuric acid.

9. The short-term (three months) oral toxicity studies in rats revealed, at a 2g/kg b.w. intake, effects on the kidneys in particular, as well as loss of weight, general weakness and intermittent irritability.

10. A short-term (thirteen weeks) toxicity study in rats involving cutaneous application of a 3.2g/kg preparation containing 5% of benzoyl peroxide produced irritant effects on the skin and the following systemic effects : retarded growth, reduction of serum aspartate aminotransferase and of spleen weight, together with increase in blood urea nitrogen and kidney weight.

11. Several long-term studies in rats and mice, in which benzoyl peroxide was applied alone, showed no carcinogenic effect; in one oral study in rats, testicular atrophy was observed at all doses (28.26 to 2826 mg of benzoyl peroxide in the diet) as a result of vitamin E deficiency.

12. In a one-year study involving dermal application to mice, benzoyl peroxide caused papillomata and spinocellular epitheliomata, after initiation with 7,4-dimethylbenzanthracene,at all doses (1 to 40 mg of benzoyl peroxide in acetone, two applications per week). This effect was not reproduced in another breed of mice after initiation with U.V.B. irradiation, but this study was scarcely significant; it was prematurely broken off after 62 weeks.

13. In man, in spite of the high percentage of sensitization (40 to 70) observed during maximization tests, the clinical experience of dermatologists revealed that the incidence of allergic reactions in patients treated for acne with benzoyl peroxide was less than 1%.
In the USA, where benzoyl peroxide, classified as an over-the-counter product, is extensively used, the experience of the FDA and of companies belonging to the EPA suggests that the level of sensitization corresponding to widespread use of benzoyl peroxide in cosmetics is between 0.004 and 0.5%. Benzoyl peroxide is unquestionably a primary irritant (17% of cases of primary irritation dermatitis at the beginning of acne treatment).
Clinical studies in man have not revealed any cases of skin cancer (124 patients over nine years) or any systemic effect, except for one case of anaphylactic systemic reaction.

14. The Committee concludes that, apart from its irritant effect on the skin, benzoyl peroxide has the same safety potential as cosmetic ingredients in general and that it can approve its use, in a 3% concentration, in cosmetic products, subject to the labelling recommendations envisaged. It is advisable to add to the latter that of not exposing oneself to sunlight after application of the product.

Nevertheless, several members consider that this substance should be used solely under medical supervision and the Committee reserves the right to review this opinion in the light of the new clinical studies being conducted in the Federal Republic of Germany on the variation in the threshold of the sensitivity of the skin to U.V.B. radiation after short-term application of a preparation containing 3% of benzoyl peroxide.

REPORT
BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY
CONCERNING THE USE OF NICOMETHANOL HYDROFLUORIDE
IN ORAL HYGIENE PRODUCTS

(Opinion expressed 29 November 1983)

TERMS OF REFERENCE OF THE COMMITTEE

To express its opinion on the use of nicomethanol hydrofluoride in oral hygiene products in a maximum concentration in the finished product of 0.15% expressed as fluorine.

CONCLUSION

The Committee can agree to the use of nicomethanol hydrofluoride in oral hygiene products in accordance with the conditions set out in paragraph 2.

HISTORICAL BACKGROUND

1. Directive 76/768/EEC, as last amended by directive 83/574/EEC, authorizes the use in oral hygiene products of a number of fluorine compounds in a maximum concentration of 0.15%, calculated as F, in the finished cosmetic product, subjet to certain conditions of use and warnings which must be printed on the label. The Commission had received a request for the addition of nicomethanol hydrofluoride to the list of fluorine compounds already allowed. According to the dossier submitted by the manufacturer, nicomethanol hydrofluoride offers a particular advantage as regards fluorine fixation on dental enamel, while being free of any toxicity under normal conditions of use.

2. Consequently, the Committee was requested to express an opinion on the use of nicomethanol hydrofluoride in cosmetic products, subject to the following conditions :

Substance	RESTRICTIONS			Conditions of use and warnings which must be printed on the label
	Field of application and/or use	Maximum authorized concentration in the finished cosmetic product	Other limitations and requirements	
Nicomethanol hydrofluoride	Oral hygiene products	0.15 % calculated as F. If mixed with other permitted fluorine compounds, the maximum concentration of F shall still be 0.15 %		Contains nicomethanol hydrofluoride

DISCUSSION

3. Nicomethanol hydrofluoride is more toxic when administered intraperitoneally than when given orally in rats and mice. The oral LD_{50} is approximately 500 mg/kg in rats and mice; expressed as fluorine ions (i.e. approximately 75 mg/kg), the LD_{50} is comparable to that of tin fluoride and slightly greater than that of sodium fluoride. The product is emetic in dogs. The acute toxicity of the organic carrier of the fluorine, namely nicotinic alcohol, is distinctly lower than that of fluorine, being above 5 g/kg when given orally and above 2 g/kg when the intraperitoneal route is used in mice.

4. When applied in a 6.8% aqueous solution, nicomethanol hydrofluoride has no irritant effect on rabbits' eyes and it is well tolerated by the mucous membranes of hamsters' cheek pouches. No bleeding of the digestive nucosae was observed in mice after oral ingestion of doses of 68 mg/kg b.w. daily.

5. A Magnusson and Kligman maximization test using both the intradermal and the epidermal route with weak dilutions corresponding to the maximum non-irritant concentrations (0.04% intradermally and 0.2% epidermally) revealed no sensitizing effect.

6. The 60-day oral toxicity study in dogs was not carried out with a sufficiently high dose (34 mg/kg b.w. daily) for any effect to be observed by means of the usual macroscopic, histological and biochemical examinations, hence it was not possible to determine the no-effect level.

7. A "long-term" oral study in rats at doses of 10.2, 34 and 102 mg/kg b.w. daily, which was broken off after seven months of trials, revealed the usual signs of luorosis in the teeth and in the long and flat bones at upwards of 34 mg/kg b.w. daily and a slight slowing of growth at the highest dose. (The Committee regrets that the study was not carried out in such a way as to enable any risk of carcinogenesis to be determined experimentally.)

8. Mutagenicity studies were carried out :

   1. Using bacteria (Salmonella typhimurium) in an Amestest with and without added liver enzymes.
   2. Using orally treated mice in a micronucleus test.

   The Amestest produced negative results but the micronucleus test was inconclusive due to the inadequacy of the protocol used.
   The Committee could not make an evaluation of the mutagenic potential of this compound on the basis of the data provided.

9. When administered in doses of about 150 to 300 mg daily, nicotinic alcohol has a vasodilator and hypolipaemic action. Its metabolism is well known; its principal metabolite, nicotinic acid, to which the hypolipaemic effect is due, is transformed in vivo into nicotinic amide (vitamin PP).

10. Undesirable effects (reddening, giddiness and liver function disorders) have been reported after absorption of high doses of nicomethanol and nicotinic acid.

11. In conclusion, the Committee considers that the quality of some of the studies contained in the dossier is not entirely satisfactory. It notes, however, that :

    . the chronic toxicity at high doses of nicomethanol hydrofluoride is that of the fluorine ion;

    . although the long-term studies were not continued, there is nothing in the available information to suggest carcinogenic hazard;

    . the pharmacological activity and the untoward effects reported for nicotinic alcohol do not manifest themselves under normal conditions of use unless the doses are at least 120 times (G.Zbinden) those which could be ingested when used normally in toothpaste;

    . the final metabolite of nicomethanol is a vitamin normally found in all foods, especially in meat and cereals.

12. Consequently, the Committee considers that nicomethanol hydrofluoride is not dangerous when used in oral hygiene products in the concentration applied for and recommends that it be added to the list of fluorinated compounds already allowed.

Scientific Committee on Cosmetology

Supplementary opinion concerning the use of 1,1,1-trichloroethane (methylchloroform) in cosmetic products

(Opinion expressed on 22 May 1984)

Pursuant to point 7 of the opinion which it expressed on 25 September 1979 [1], the Committee examined the fresh items of information brought to its notice.

1. Stabilizers of 1,1,1-trichloroethane (TCE) are mixtures, generally patented, of widely differing compositions, among which are to be found carcinogenic substances such as epichlorohydrin and 1,4-dioxane.
   From most of the reports on toxicity studies now available, nothing can be inferred regarding the degree of purity of 1,1,1-trichloroethane and the nature of the stabilizers used.

2. Quantitative determinations carried out over a period of three weeks on F 11, F 12, dichloromethane, isobutane and propane in a hairdressing saloon showed that the maximum concentrations of each of these propellants in the saloon air did not exceed 50 ppm by volume and were therefore considerably lower than the threshold limit values (TLV) specified for each of them.
   1,1,1-Trichloroethane, which was not included in this study but whose physico-chemical properties are fairly close to those of dichloromethane, can be put in the same category as the latter.

3. In the chronic inhalation toxicity studies no effects were observed in the rats, mice and dogs which were continuously exposed to 250 and 1 000 ppm of 1,1,1-trichloroethane.

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4. In an in vitro Ames mutagenicity test with metabolic activation, no mutagenic effect was observed, whereas another test, performed according to the same protocol, showed slight mutagenic activity with and without metabolic activation. The purity of the 1,1,1-trichloroethane samples used in these tests was unknown and it can be assumed that the stabilizer was responsible for the positive result obtained in the second test.
A dominant lethal test in mice, with administration in the drinking water, produced a negative result with concentrations of up to 100 mg/kg.

5. In the three acute in vitro morphology transformation tests carried out on rat embryo cells, SA 7 adenovirus and Syrian hamster embryo cells, an increase in the number of cases of cell transformation was observed which, in the latter two tests, depended on the dose. Although the information supplied by the manufacturer indicates the presence of a 3% concentration of 1,4-dioxane in these two cases, it was not possible to identify this compound by chemical analysis and it was the non-carcinogenic substance 2-methyl-2-butanol which was detected.

6. An inhalation carcinogenicity study with 875 and 1 750 ppm concentrations in rats, which was unfortunately too short (twelve months), showed no increase in the incidence of tumours in these animals when observed for a period of 30 months.

7. In oral carcinogenicity studies carried out by the NCI, the doses administered by gavage were 3 000 and 6 000 mg/kg/day for mice and 750 and 1 500 mg/kg/dag for rats. The survival rate was low both in the rat and in the mouse study.
In the high dose group 3 out of 49 male mice had hepatocellular adenomata and one had a hepatocellular carcinoma. No tumours were observed in the control group of mice. In the rat study no increase in incidence of tumours was observed.
It should be noted that the 1,1,1-trichloroethane used contained 3% 1,4-dioxane, which means that the group of mice treated with the highest dose received 120-180 mg 1,4-dioxane/kg daily.
Owing to the low survival rate, the NCI has repeated an oral carcinogenicity investigation in rats and mice with pure 1,1,1-trichloroethane, but the results are not yet to hand.

8. On the basis of the available reports on carcinogenicity studies, the International Agency for Research on Cancer (IARC) has concluded that the results are at present inadequate for assessing the carcinogenic potential of 1,1,1-trichloroethane.

9. In man, immersion for 30 minutes in a bath containing 1,1,1-trichloroethane showed that this product penetrates the skin, enters the bloodstream and is excreted for the most part via the air passages.
In workers exposed to airborne TCE in their workshops, a high concentration (50 to 70%) was observed in the alveolar air 30 minutes after exposure, while only a small quantitiy was metabolized into trichloroethanol (2%) and trichloroacetic acid (0.5%), both of which were excreted in the urine.
The half-life of 1,1,1-trichloroethane, calculated on the basis of the elimination of these two metabolites, was estimated at 8.7 hours.

10. Again in man, the first appearance of functional CNS depression was at 500 ppm, at which concentration a sedative effect was observed; the first anaesthetic effect occurred at 1 000 ppm.
Exposure to concentrations of 5 000 to 20 000 ppm caused coordination loss and anaesthesia. Sudden death due to ventricular fibrillation and respiratory standstill can occur at the anaesthetic concentrations.
In cases of acute poisoning, a hepatotoxic effect was observed.

11. In a large-scale study with workers exposed to 1,1,1-trichloroethane over six years, no signs of cardiotoxicity or chronic hepatotoxicity were observed. No information about carcinogenicity is available.

12. The Committee has decided to await the outcome of the new ongoing carcinogenicity studies by the NCI before expressing a definitive opinion on 1,1,1-trichloroethane.

In the meantime, the Committee hopes to obtain further information on the purity of the 1,1,1-trichloroethane and also on the nature of the stabilizers used, since it appears that the industry is endeavouring to replace stabilizers that are reputed to be toxic by well-known substances which are less toxic or by new substances of which little is known concerning toxicity.

Report by the Scientific Committee on Cosmetology concerning certain zirconium complexes used in antiperspirants

(Opinion expressed 22 May 1984)

TERMS OF REFERENCE OF THE COMMITTEE

To express its opinion on the use as antiperspirants of aluminium zirconium chloride hydroxide complexes and the aluminium zirconium chloride hydroxide glycine complex at a maximum concentration in the finished cosmetic product of 20% expressed as anhydrous hydroxychloride and of 5.4% expressed as zirconium.

CONCLUSIONS

The Committee is able to approve the use of zirconium complexes as antiperspirants, subject to the conditions and restrictions set out in paragraph 1, provided that labelling of the finished product includes the warning : Do not apply to irritated skin.

HISTORICAL BACKGROUND

1. In accordance with Article 5 of Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 83/574/EEC, the Member States must, until 31 December 1985, permit the marketing of cosmetic products containing aluminium zirconium chloride hydroxide complexes and glycine, subject to the following conditions :

Substance	RESTRICTIONS		
	Field of application and/or use	Maximum authorized concentration in the finished cosmetic product	Other limitations and requirements
Aluminium zirconium chloride hydroxide complexes $Al_xZr(OH)_yCl_z$ and the aluminium zirconium chloride hydroxide glycine complex	Antiperspirants	20% as anhydrous aluminium zirconium chloride hydroxide 5.4% as zirconium	1. The ratio of the number of aluminium atoms to that of zirconium atoms must be between 2 and 10 2. The ratio of the number of (Al+Zr) atoms to that of chlorine atoms must be between 0.9 and 2.1 3. Prohibited in aerosol dispensers (sprays)

2. Beyond this deadline, such substances shall be :

   authorized definitively (Annex III);
   or prohibited definitively (Annex II);
   or authorized during a period laid down in Annex IV;
   or deleted from all the annexes.

3. The Committee has therefore been invited to express an opinion on the use of certain aluminium zirconium chloride hydroxide complexes and the aluminium zirconium chloride hydroxide glycine complex, subject to the abovementioned limits and conditions.

DISCUSSION

4. Chemical formula and structure

$$Al_vZr_w(OH)_xCl_y.nH_2O.Z(NH_2-CH_2COOH)$$

Complexe	Empirical formulae
tri	$Al_{3.3}, Zr(OH)_{11.6}, Cl_{2.6}, nH_2O,z\ (NH_2-CH_2-COOH)$

tetra $Al_{3.6}$, $Zr(OH)_{11.6}$, $Cl_{3.2}$, nH_2O,z (NH_2-CH_2-COOH)

penta $Al_{6.5}$, $Zr(OH)_{17.2}$, $Cl_{4.2}$, nH_2O,z (NH_2-CH_2-COOH)

octo $Al_{7.7}$, $Zr(OH)_{19.8}$, $Cl_{7.3}$, nH_2O,z (NH_2-CH_2-COOH)

5. LD_{50} is 400-700 mg/kg by the dermal route in rabbits and 2 420-6 930 mg/kg by the oral route in rats.

6. Studied at various concentrations (9.7%, 15.9%, 22.5%), ZAG is not considered as an irritant on rabbits' eyes although some studies demonstrate a slight but reversible irritation.

7. In a series of studies in rabbits, at concentrations of 9.7%, 22.5%, 35% and 50%, ZAG had a non-irritant to slightly irritating effect on intact and abraded skin, with and without occlusion.

8. In a 28-day study in rabbits, a 34.7% solution of ZAG was applied to the skin at a rate of 2 ml/kg bw. The treated animals did not differ significantly from the control group as regards body weight, clinical symptoms, haematology and macroscopic and microscopic anatomopathology.

   In a 91-day study involving application of a 34.7% solution of ZAG to the intact skin of rabbits (2 ml/kg bw), slight erythema was observed, in addition to histological and haematological changes, a reduction in the weight of the liver and an increase in the weight of the suprarenal glands and ovaries, all statistically insignificant and therefore considered of no biological significance.

   The same effects are observed in parallel studies involving finished products containing 19.9% and 20% of ZAG, respectively. The histopathological evaluation indicates slight acanthosis, practically without any dermal papillary inflammation - the only change considered significant.

9. ZAG does not induce dominant lethal mutations when administered orally to mice at doses of 40, 400 and 4 000 mg/kg over a period of five days.

10. No teratogenic effects were observed following dermal administration of a 31.5% solution of ZAG to rabbits between the 7th and 18th days of gestation at maximum doses of 2 000 mg/kg/day.

11. The available data, derived from several studies of ZAG, Zr hydrochloride, Al hydrochloride and NaZr lactate, indicate that under extreme experimental conditions ZAG can induce delayed hypersensitization reactions; such effects are limited and temporary.

    Intradermal injection of 0.1 ml of a saline solution containing 0.05 mg ZAG in guinea pigs and 0.1 ml of a saline solution containing 0.1 mg ZAG in rabbits can induce granulomatous reactions (histiocytes and gigantoblasts).

12. In a large number of tests on human skin, the application of various complex preparations and of antiperspirant preparations containing between 15.4% and 20% of ZAG, gave rise to a few instances of very slight erythema and slight skin dryness in some subjects. No sensitization reaction was observed.

13. The data indicate that ZAG, tested separately and in antiperspirant preparations, does not induce granulomatous responses or retarded hypersensitivity in subjects previously sensitized to Zr oxide or NaZr lactate.

14. In the USA, antiperspirant products based on ZAG have been on the market for over 20 years and the incidence of adverse reactions (skin irritation) reported is low (2.4 reactions/10^6 units sold - 1977-1978). Although 70 cases of granulomatous reactions induced by NaZr lactate have been reported, and also granulomas induced by application of an ointment containing zirconium oxide to the inflamed skin of a woman, no reaction of this type has been observed with ZAG.

15. Consequently, the Committee can approve the use of zirconium/aluminium/glycine complexes as antiperspirants, subject to the conditions and restrictions set out in paragraph 1, since the available data and observations in human beings offer a sufficient guarantee of safety. Nevertheless, the Committee recommends adopting the following warning : Do not apply to irritated skin.

ADDITIONAL OPINION OF THE SCIENTIFIC COMMITTEE ON COSMETOLOGY CONCERNING THE USE OF BENZOYL PEROXIDE

(Opinion expressed 17.12.1984)

Further to item 14 of its Opinion delivered on 29 November 1983, the Committee has examined the results of the clinical trials carried out in the Federal Republic of Germany on the variation in the threshold of the sensitivity of skin to B ultra-violet rays after short-term application of a preparation containing 3% of benzoyl peroxide.

DISCUSSION

- These trials clearly showed that the irritant effect of benzoyl peroxide was not increased by exposure to UVB radiation at 310 nm but that, on the contrary, it depended on the nature of the excipient.
  One case of photo-allergy had been induced in the course of the trials.
- The Committee still agrees to the use of benzoyl peroxide in lotions, creams and gels for greasy skin in a maximum concentration of 3% in the finished product, provided that the following warnings appear on the label :
  - Contains benzoyl peroxide.
  - Avoid all contact with the eyes and mouth.
  - Discontinue use if irritation occurs.
  - Other cosmetic products should not be applied simultaneously to treated areas.
- Owing to the effect of the excipient on skin tolerance, the Committee does not recommend extending the use of benzoyl peroxide to all products intended to improve the condition of skin containing blackheads, and it draws attention to the fact that alcohol increases the irritant effect of preparations.

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(vi) supplementary opinion concerning the use of 1,1,1-trichloroethane (methylchloroform) in cosmetic products;
(vii) certain zirconium complexes used in antiperspirants;
(viii) additional opinion concerning the use of benzoyl peroxide.