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of the Scientific Committee on Cosmetology

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FOREWORD

The Scientific Committee on Cosmetology was set up by Commission Decision 78/45/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.

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REPORT BY THE SCIENTIFIC COMMITTEE ON COSMETOLOGY CONCERNING CERTAIN COLOURING AGENTS

(Opinion expressed on 1. July 1986)

TERMS OF REFERENCE OF THE COMMITTEE

To give its opinion on the use, in cosmetic products, of the colouring agents listed in Part 2, 3A and 3B of Annex IV to Directive 76/768/EEC.

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BACKGROUND

1. In accordance with Article 5 of Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products, as last amended by Directive 87/139/EEC, Member States must allow the marketing of cosmetic products containing the colouring agents listed in Part 2, 3A and 3B of Annex IV, within the limits and under the conditions referred to, until 31 December 1985.

2. On 1 January 1986 these colouring agents will have to be :
   - either definitively permitted;
   - or definitively prohibited;
   - or maintained for a specified period;
   - or deleted from all the Annexes.

3. The Committee was therefore requested to express an opinion on the use in cosmetic products of the colouring agents listed in Part 2, 3A and 3B of Annex IV of Directive 76/768/EEC (Annex 1).

DISCUSSION

CI 10006 Sodium ferric complex of 1-nitroso-2-hydroxynaphthalene

$C_{30}H_{18}FeN_3O_6Na$ CAS N° 16143-80-9
MW : 595

Synonyms : - Pigment Green 8
- C-ext. Grün 1

Insoluble in water.

Use level 5% in rinsed off products.

The oral LD_{50} in rats was > 10 g/kg.

Rabbits treated on the intact or abraded skin with 0.5 g of a 50% aqueous suspension, or with 0.5 g undiluted substance showed no irritation.

An eye irritation test with 0.1 ml of 33% suspension in saline, or with 0.1 g of the undiluted colour was negative.

Information on short-term oral toxicity and on possible mutagenic and sensitizing properties is necessary for an evaluation.

No opinion can be expressed because of a lack of data.

Information : Colipa dossier

CI 10020 Ferric Complex of 1-Nitroso-6-sodium-sulfo-2-hydroxynaphthalene

$C_{30}H_{15}FeN_3O_{15}S_3.3Na$ CAS N° 19381-50-1
MW : 987

Synonyms : - Acid green 1
- C-ext. Grün 6
- L-ext. Grün 1

Very soluble in water; insoluble in ether, ethanol and vegetable oil.

Use level in rinsed off products 1%, in not rinsed off products 0.5%.

The oral LD_{50} in rats was $>$ 10 g/kg.

No irritation of rabbit skin occurred with 0.5 g of a 50% aqueous suspension or with 0.5 g of the undiluted powder.

An eye irritation test in rabbits with 100 mg powder was negative.

Daily treatment of rats with 1, or 2 g/kg b.w./day by gavage, on 5 days/week for 13 weeks was reported to induce no deleterious effects.

The Committee wishes to examine the detailed report of the 90-day study and to obtain information on possible mutagenic and sensitizing properties.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier

CI 11680 α-(2-nitro-4-methylphenylazo)-acetylacetanilide

$C_{17}H_{16}N_4O_4$ CAS N° 2512-29-0
MW : 340

synonyms : - C-ext Gelb
- Pigment Yellow 1

Insoluble in water, slightly soluble in ethanol and acetone.

Use level : 0.7% in rinsed off products, 0.3% in non rinsed off products.

The oral LD_{50} in rats was > 8 g/kg.

Topical application of 0.5 g of a 50% suspension in water, or of 0.5 g undiluted substance to intact and abraded skin of rabbits under occlusion did not induce signs of irritation.

An eye irritation test in rabbits with 0.1 ml 33% suspension in saline, or with 0.1 g undiluted substance only showed slight reddening of the conjunctivae.

A sensitization test was conducted in guinea pigs by 4 intradermal injections of 0.1 ml of 0.625% in saline for induction treatment and one intradermal injection of 0.1 ml of 0.25% for the challenge, 14 days later. Because no signs of sensitization occurred both the induction and the challenge treatment were repeated, again with negative results.

In a short-term (30-day) feeding study with 0, 0.2, 1.0 or 5.0% in the diet, the top dose group showed growth depression. There were no changes in haematology, urine composition or organ weights. Gross examination and microscopic examination of 5 different organs were negative.

In another oral 30-day study in rats treated by gavage with 1000 mg/kg b.w./day (equivalent to c. 2% in the diet), 5 times/week, for 4 weeks, there were no changes in growth rate, food intake, haematology, urine parameters, activities of serum enzymes, gross examination, or microscopy of the liver, kidneys, adrenals and spleen.

In a 90-day oral rat study the administration of 1 or 2 g/kg b.w./day, 5 times a week by gavage did not induce overt signs of deleterious effects (only a summary report of this detailed study is available).

An Ames test with the S. typhimurium strains TA 98 and TA 100, and applying 0.25-4.0 mg/plate, was negative. Another Ames test using the strains TA 1538 and TA 1535, with 0.01 mg/plate, was likewise negative.

The available data indicate that the acute and short-term oral toxicity of this colour is low. Tests for skin and eye irritation and for sensitization were negative. The substance did not reveal mutagenic properties in the Ames test, but these studies were not completely adequate.

An adequate Ames test and a chromosome aberration test in a mammalian cell system in vitro is requested.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier

CI 11710 α-(2-Nitro-4-chlorophenylazo)acetyl-o-chloroacetanilide

$C_{16}H_{12}Cl_2N_4O_4$ CAS N° 6486-23-3
MW : 395

Synonyms : - Pigment Yellow 3
- C-ext Gelb 3

Slightly soluble in ethanol and acetone. Insoluble in water.

Use level : 0.1% in non rinsed off products and 0.4% in rinsed off products.

The oral LD_{50} in rats was $>$ 8 g/kg.

No skin irritation was seen in rabbits upon topical application of 0.5 g substance, or 0.5 g of an aqueous suspension.

Eye irritation tests in rabbits with 0.1 g substance, or 0.1 ml of a 33% aqueous saline suspension were negative.

In a short-term (43 days) study, rats received 28 daily dosages of 0.5 g/kg b.w. by gavage as a 1:1 paste with ethylene glycol. There were no changes in haematology or in gross and microscopic pathology. (Summary report only)

A detailed report is requested on the short-term oral study and information on possible sensitizing and mutagenic properties.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier

CI 11725 (2-nitro-4-methoxyphenylazo)-acetyl-o-methylacetanilide

$C_{18}H_{18}N_4O_5$ CAS N° 6371-96-6
MW : 370

Synonyms : - Pigment Orange 1
- C-WR Gelb 7

Insoluble in water, slightly soluble in ethanol and mineral oil.

Used in rinsed off cosmetics at levels up to 0.1%.

The oral LD_{50} in female rats was $>$ 10 g/kg, if applied as a 25% suspension in sesame oil.

No skin irritation was observed in rabbits with 500 mg of the undiluted substance applied to the intact and abraded skin. Skin effects could be examined only after 48 and 72 hours, because after 24 hours possible erythema was invisible due to remnants of the colouring.

An eye irritation test in rabbits with 100 mg of the colouring powder was negative.

The Committee requests information on short-term oral toxicity, and on possible sensitizing and mutagenic properties.

No opinion can be expressed because of lack of data.

CI 12010 1-(4'-ethoxy-phenylazo)-4-hydroxynaphthalene

$C_{18}H_{16}N_2O_2$ CAS N° 6535-42-8
MW : 293.3

Synonyms : - C-ext Braun 3
- Solvent Red 3

Insoluble in water, soluble in organic solvents.

Used up to 0.1% in rinsed off and non rinsed off cosmetics.

Oral LD_{50} values are 11.3 g/kg in male rats and $>$ 10 g/kg in mice (sex not specified);

Skin irritation was examined in rabbits by intracutaneous administration and by topical application of 0.5 ml of a filtrate from a digest of the colourant in aqueous saline prepared at 40 °C. No signs of irritation were observed.

An eye irritation test in rabbits with 0.25 ml of a filtrate from a digest in aqueous saline prepared at 40 °C revealed slight and reversible redness of the mucous membrane.

In a sub-chronic (90-day) feeding study, groups of 5 or 10 rats/sex were treated with 0, 0.5, 1.0 or 5.0% in the diet. Growth retardation was observed at all treatment levels. No mortality occurred and no treatment-related changes were found in haematology, clinical chemical parameters of blood and urine, or in the results of gross and microscopic examinations (Summary report only)

In a lifetime feeding study (conducted before 1951) 20 rats were treated with 0.1% in the diet. Seventeen rats died of pneumonia or of pulmonary abcesses before 2 years. Liver and gastrointestinal tract showed no changes which suggested carcinogenic properties.

A sensitization test, an Ames test and a chromosomal aberration test should be conducted.

The Committee sees no objection to maintaining the use of this substance in cosmetic products for the time being.

Information : Colipa dossier, December 1983

CI 12120 1-(2-Nitro-4-methylphenylazo-2-hydroxy naphtalene

$C_{17}H_{15}N_3O_3$ CAS N° 2425-85-6
MW : 307

Synonyms : - Pigment Red 3
- Toluidine Red
- DC red N° 35

Insoluble in water, slightly soluble in ethanol and aceton.

Used in rinsed off cosmetics up to 1.0%.

The oral LD_{50} in mice and rats was $>$ 10 g/kg.

Application of 500 mg undiluted substance to abraded and non abraded skin of rabbits under occlusion did not produce observable irritation.

An eye irritation test in rabbits with 100 mg undiluted substance showed slight conjunctival changes only after one hour, which allows classification as non-eye irritating.

In a sensitization test, 10 guinea pigs received an induction treatment by 4 intradermal injections of 0.1 ml 0.025% given at one time, and one challenge treatment of 0.1 ml 0.01% intradermally 14 days later. Because none of the test animals showed a positive response, the induction was repeated and the animals were challenged again after 14 days. The repeat test was also negative.

Patch tests and photopatch tests in 38 patients suffering from pigmented cosmetic dermatitis showed positive reactions in 10 and 3 patients respectively, when tested with a 5% dilution of the colourant.

In a short-term (90-day) study, groups of weanling rats, 5/sex/group, received diets with 0, 0.25, 0.50, 1.0 or 2.0% colourant. There were no changes in mortality, growth rate, or haematology. Slight increases in

liver weight were not clearly dose-related. Spleen weight was increased in males of the top-dose group. Microscopy of the six organs examined showed no relevant changes.

It was known that long term oral studies are being made in mice and rats. The results will be examined when they become available. In addition an Ames test and a chromosomal aberration test should be conducted. An explanation is requested on the positive findings in a photosensitization study.

The Committee sees no objection to maintaining the use of this colouring agent for the time being in rinsed off products only.

Information : - Colipa dossier, Submission I March 28, 1983
- Colipa dossier, Submission II June 19, 1984
- National Toxicology Program FY 1983, page 116/039

CI 12140 1-(2,4-dimethyl phenylazo)-2-hydroxy naphthalene

$C_{18}H_{16}N_2O$ CAS N° 3118-97-6
MW : 276

Synonyms : - CI Solvent Orange 7
- Orange KB oil
- Sudan II
- Ext DC red N° 14

Insoluble in water, soluble in ethanol, acetone and oils.

Used in rinsed off cosmetics up to 0.3%.

The oral LD_{50} in mice was c. 20 g/kg.

In an occlusive skin irritation test in rabbits with 0.2 g of either the undiluted substance or a 40% solution in PEG 400, slight erythema and oedema was observed. Indications of irritant properties for the rabbit skin were obtained also from an intradermal injection test with 0.1 ml of dilutions of 2, 1, 0.1 and 0.01%.

A test in rabbits showed the pure substance to be a slight eye irritant.

Patch testing with 1% in petrolatum of patients suffering from pigmented contact dermatitis caused by Brilliant Lake R (CI 15800) provoked a positive response in 2/8 test persons (1).

Short-term feeding of rats with 2 mM pure dye/100 g food (c. 0.5%) showed slight potency to induce Heinz bodies, which is a characteristic of certain azodyes (2).

Mice fed 1000 ppm in the diet for 52 weeks developed benign intestinal tumours in 4/15 animals examined, compared with 1/13 controls. The feeding of 1000 or 2500 ppm in the diet of rats for 2 years caused increased mortality, but no tumour development was described. Rats fed 300, 7500 or 15.000 ppm showed a dose-related increase in mortality (3).

In a bladder implantation experiment in mice, a sample of Oil Orange KB, mixed with paraffin wax for pelleting, induced a high incidence of bladder tumours (4).

The colourant showed mutagenic activity in an Ames test with TA 1538 at levels of 50 and 100 µg/plate with metabolic activation (5).

Available data indicate mutagenic and carcinogenic properties of this colourant. Since, moreover, no information is available on dermal absorption and there is insufficient information on systemic toxicity, the use in cosmetics does not seem justified.
The substance has been withdrawn as an approved food colour in several countries already many years ago, and more recently it was removed from the list of permitted colours in externally applied drugs and cosmetics in the US.

Information : - Colipa dossier
(1) Takehito et al. Contact Dermatitis - (1980) 330-336
(2) Rofe, P., Brit. J. industr. Med. 14 (1957) 275-280
(3) IARC Monograph 8 (1974) 233-240
(4) Clayson et al., Brit. J. Cancer 22 (1968) 825-832
(5) Garner, R.C. and C.A. Nutman, Mut. Res. 44 (1977) 9-19

CI 12370 3-Hydroxy-4(2,4,5-trichloro-phenylazo)-2(N(o-tolyl)-naphthamide

$C_{24}H_{16}Cl_3N_3O_2$ CAS N° 6535-46-2
MW : 484.5

Synonym : Pigment Red 112

Insoluble in water, fats and organic solvents.

Used at levels up to 0.01% in rinsed off cosmetics.

The oral LD_{50} was $>$ 15 g/kg in female rats and $>$ 10 g/kg in mice.

A skin irritation test in rabbits with 0.5 ml of a 1% aqueous dispersion without occlusion was negative.
Repeated application of a 0.8% aqueous suspension to the skin of female guinea pigs on 2 days, three times a day, without occlusion, did not produce any sign of irritation.

In an eye irritation test in guinea pigs with the very small amount of 0.8 mg colourant in an aqueous preparation the colourant was found to be non-irritating.

A sensitization test in guinea pigs by intracutaneous injections of 0.1 ml of a 2% aqueous solution of a 40% colour paste (= 0.8 mg colourant), 3 times a day on 5 consecutive days and challenge treatment with up to 0.2% of a 40% colour paste, 4 weeks after induction, was negative.

In a sub-acute (43-day) oral study, rats were dosed 28 times by stomach tube with 500 mg of the colourant/kg b.w. as a 50% paste in ethylene glycol/water (1:1). There were no changes in behaviour, urine composition, haematology, or in gross or microscopic pathology. The colourant was excreted in the faeces.

The sub-acute oral study with 500 mg/kg b.w./day did not produce any clear sign of toxicity. Although human exposure by cosmetics is low, the Committee wants to see results of genotoxicity tests (if such tests are practicable in spite of the insolubility of the colourant).

The Committee sees no objection to maintaining the use of this colouring agent for the time being in rinsed off products.

Information : Colipa dossier, February 1984.

CI 12420 1-(4-chloro-2-metyhylphenylazo)-3-(4'-chloro-2'-methyl carboxyanilido) 2-hydroxynaphthalene

$C_{25}H_{19}CL_2N_3O_2$ CAS N° 6471-51-8
MW : 463

Synonym : Pigment Red 7

Insoluble in water.

Used in rinsed off products; in soaps at levels up to 0.3%.

The oral LD_{50} in rats was $\geq$ 5 g/kg.

Repeated application of 100 mg of the substance on the intact skin of rabbits for 6 days produced no reactions. In another rabbit skin test a single treatment with 0.5 g applied as a paste with water, the substance was not found to be an irritant.

In an eye irritant test in the rabbit, with 100 mg of the colour, the product was found to be practically non-irritating.

A sensitization test in guinea pigs with 0.1 ml of a 10% suspension did not provoke any response either during the induction treatment or upon the challenge treatment.

Information is requested on short-term oral toxicity, and mutagenicity.

No opinion can be expressed because a lack of data.

Information : Colipa dossier

CI 12480 1-(2,5-dichlorophenylazo)-3-(2',5'-dimethoxycarboxy-anilido)-2-hydroxy naphthalene

$C_{25}H_{19}Cl_2N_3O_4$ CAS N° 6410-40-8
MW : 495

Synonyms : - CI Pigment Brown 1
- Permanent Brown EG

Insoluble in water.

Used in rinsed off products up to 0.2%.

The oral LD_{50} in female rats : $>$ 15 g/kg.

No skin irritation occurred in rabbits with 0.5 ml of a 10% aqueous dispersion applied on the skin, nor with 0.02 ml of a 10% aqueous dispersion injected intracutaneously.

No eye irritation was found in rabbits with 0.1 ml of a 10% dispersion in 0.9% NaCl solution.

Since no further information is available a toxicological evaluation is not possible. The Committee requests information on short-term oral toxicity, and on possible sensitizing and mutagenic properties.

CI 12700 1-Phenyl-3-methyl-4-phenylazo-5-pyrazolonone

$C_{16}H_{14}N_4O$ CAS N° 4314-14-1
MW : 278.32

Synonyms : - CI Solvent Yellow 16
- CI Disperse Yellow 16

Soluble in ethanol and CCl_4.

Use level : 0.003% in rinsed off products and 0.02% in non-rinsed off products.

The oral LD_{50} was > 15 g/kg in female rats.

Intradermal injection of rabbits with 0.02 ml of the filtrate of 5 g substance in 50 ml saline did not induce any specific reactions. Local skin application of 0.5 ml of the same filtrate, 5 times on 5 days, caused no specific response either. Slight irritation was observed with a 10% dilution of the colouring in sesame oil, but lower concentrations were negative.

An eye irritation test in rabbits with 0.1 ml of the filtrate of 5 g substance in 50 ml saline was negative.

A short-term (6-wk) oral study in rats, with 100 or 500 mg/kg b.w./day administered by gavage as a 1 or 5% dilution in starch-paste, on 30 days during the study, did not reveal growth depression nor gross or microscopic changes of the heart, lungs, liver, kidneys, adrenals or spleen.

In a long-term study in rats, 60 ppm of the colourant mixed in the diet was administered to one group of 20 rats for their lifetime. Survival at 1 year was 19/20, and at 2 years 2/20. No tumours occurred.

Possible sensitizing properties of the substance should be examined. Because the short and long-term studies available show many deficiencies a well conducted short-term oral toxicity study and mutagenicity tests are desirable.

No opinion can be expressed.

Information : Colipa dossier

CI 13065 m(p-Anilinophenylazo)benzene sodium, sulfonate

$C_{18}H_{15}N_3O_3S.Na$ CAS N° 587-98-4
MW : 376.41

Synonyms : - Acid Yellow 36
- Ext. D. and C. Yellow No. 1
- C-ext Gelb 10

Soluble in water and ethanol.

Used at levels up to 0.5% in non rinsed off products, and up to 0.1% in rinsed off products.

Oral LD_{50} values in rats are 5.3 and 4.2 g/kg.

A skin irritation test in rabbits with 0.5 g colourant, or with 0.5 g of a 50% aqueous suspension was negative. With 0.5 ml of a 0.25% solution in water/propylene glycol (1:1) no signs of irritation were observed.

In an eye irritation test in rabbits with a 1.25% suspension in saline no changes were observed; with higher concentrations (up to 33%) moderate conjunctival reactions occurred. In another test in rabbits, 0.1 ml of a 0.25% solution in water/propylene glycol (1:1) was found to be non-irritating.

A 90-day, oral toxicity study was conducted in male rats by feeding diets containing 0, 0.1, 0.5 or 3.0%. The top-dose induced haematological changes, including decreased counts of neutrophils and eosinophils, and increased counts of lymphocytes and monocytes. Heinz bodies were not observed. In this study only a possible effect on the haemopoietic system was examined.

In another 90-day oral study in rats of both sexes, 0.025, 0.05 and 0.1 g/kg b.w. was administered daily by gavage. The two high levels induced mortality. Diarrhoea and growth depression occurred in all treated groups. Pathological examination revealed degenerative changes of the heart muscle, oedema of the lungs and atrophy of the testicles. Only a summary report is

available. The authors recommend not to use this substance owing to its high toxicity. Degenerative changes in the testicle were observed also in guinea pigs fed 3% in the diet, but not in those fed 0.5% for 90 days.

Intraperitoneal administration of 25 mg/kg/day to male mice for 15, 30 or 60 days induced damage to the seminiferous tubules and spermatocytes accompanied by various chromosomal changes (stickyness, clumping, chromating bridges). No influence on body weight or on the pathology of other organs was observed.

A dermal (28-day) study in 10 rabbits with 20 mg/kg/day on the intact and abraded skin, 5 times/week for 4 weeks, did not reveal changes in body weight, haematology, organ weights, or in the microscopy of the organs examined.
In a similar dermal study in 10 rabbits treated daily with 20 mg/kg, 5 times/week for 13 weeks no treatment-related changes were found in body weight, haematology, organ weight, or in histopathology of the organs examined.

A chronic (2-year) skin painting study in mice with a 1.0% solution applied once weekly, failed to show skin tumours or microscopic changes attributable to the compound. (The report provided no information on the quantity applied, the number of animals at the initiation and at termination of the study, and lacks many other details.)

An Ames test with 0.2 - 400 µg/plate in 4 strains of S.typhimurium, and a second Ames test with up to 25 mg/plate in 5 strains of S.typhimurium did not show mutagenic properties.

The percutaneous absorption through human skin was examined in screening tests by application of the colourant at several locations of the skin, and photometric determination of the amounts recovered with Tesafilm after different periods of time. Upon application of the dye in isopropanol, 92 - 93% was recovered, while 100% recovery was obtained when applied in a formulation.

The substance possesses considerable systemic toxicity and may adversely affect spermatogenesis. The two short-term oral rat studies gave contradictory results. A clear no-effect level by oral administration should be established. A sensitization test and a chromosomal aberration test are required.

The Committee sees no objection to maintaining the use of this colouring agent for the time being in rinsed off cosmetic products. No opinion can be expressed for non rinsed off products.

Information : Colipa dossier, Submission I, March 1984
Submission II, October 24, 1984

CI 14700 3-[(2,4-dimethyl-5-sulphophenyl)azo]-4-hydroxy-1-naphthalenesulphonic acid, disodium salt

$C_{18}H_{14}N_2O_7S_2Na_2$ CAS N° 4548-53-2
MW : 480

Synonyms :
- Food Red 1
- FD and C Red 4
- C-Rot 57
- Ponceau SX

Soluble in water, slightly soluble in ethanol, insoluble in organic solvents.

Use level 2%, but 1% for use in contact with mucous membranes.

The oral LD_{50} in male rats was $>$ 2 g/kg.

No skin irritation occurred in rabbits upon repeated daily treatment with concentrations up to 1.0% in formulations.

An eye irritation test in rabbits with a 5% formulation was negative.

A sensitization test in 25 healthy adults, using the Kligman maximization test, with concentrations up to 0.3% in petrolatum applied under occlusion in amounts of 0.3 g for 48 hours was negative. The Kaidbey-Kligman photomaximization test, conducted with 25 healthy adults, treated with up to 0.3% in petrolatum under occlusion and exposed to UV-light six times, was also negative.

No systemic toxicity was observed in rabbits with daily dermal applications of a 1% ointment (amount and treated area not indicated) for 21 days on the abraded skin, and for 90 days on the intact skin.

Teratogenicity studies in rats and rabbits with oral doses up to 250 mg/kg b.w. day during gestation were negative.

No deleterious effects were observed in a three generation study in rats with various dose levels up to 1000 mg/kg b.w. administered in the diet.

Nine long-term studies in several strains of rats and mice with oral, topical or subcutaneous administration of high dosages up to 5% in the diet provided no evidence of carcinogenicity. From one other life-time study in rats fed 2% in the diet the author concludes that the substance is mildly carcinogenic (1). This conclusion is, however, not convincing because of the small number of tumours reported, viz. 4/38 test rats and 0/55 control rats.

In a 2 year oral dog study, daily administration (by gelatin capsule) of levels up to 250 mg/kg body weight was reported to be negative. In a 7-year dog study in which 1% or 2% was fed in the diet of groups of 5 females, pathological changes in the adrenals and urinary bladder were found in both test groups. JECFA has asked for a new dog study to establish a no-effect level (2). From the long-term studies in rats, mice and dogs, IARC concluded that the results did not indicate a carcinogenic effect (3).

In an absorption and excretion study in rats 1.7% of an oral dose was absorbed.

In 8 out of 9 mutagenicity tests negative results were obtained (4).

Ponceau SX has been extensively examined. The available information justifies its use in cosmetic products.

Information : - Colipa dossiers

(1) Voprosyi Pitaniya 29(5) 1970, p. 61
(2) 21st Report of the JECFA 1978
(3) IARC Monograph Vol. 8 (1974) 207-215
(4) Mutation Research 98 (2) 1982, p. 125

CI 15620 Sodium salt of 1-(4-sulfonaphthylazo)-2-hydroxy naphthalene

$C_{20}H_{14}N_2O_4S.Na$ CAS N° 1658-56-6
MW : 400.4

Synonyms : - Acid Red 88
- C-WR Rot 13
- Echtrot AV
- Ext DC Red N° 8

Soluble in water

Used up to 0.01% in rinsed off cosmetics.

The oral LD_{50} in rats was $>$ 3.66 g/kg; the intraperitoneal LD_{50} in mice was c. 512 mg/kg. Inhalation exposure of rats to dust particles for up to 7 hours did not produce mortality or signs of intoxication.

In a primary skin irritation test in rabbits with 500 mg moistened with water the colourant was slightly irritating.

An eye irritation test in rabbits with 100 µl of the powder was negative.

An in vitro mutagenicity test with up to 100 µg/ml in E. coli (by the method of G. Mohn) was negative.

Information is necessary on possible sensitizing properties. A short term oral toxicity study is needed in which also possible Heinz body formation is examined. A chromosomal aberration test is required.

No opinion can be expressed because a lack of data.

Information : Colipa dossier, December 1983

CI 15800 1-Phenylazo-3-carboxy-2-hydroxynaphthalene

$C_{17}H_{12}N_2O_3$,1/2Ca CAS N° 6371-76-2
MW : 311

Synonyms : - Pigment Red 64
- D and C Red 31
- C ext Rot 57

Insoluble in water, slightly soluble in ethanol and glycerol.

Used up to 0.5% in rinsed off and non rinsed off products, and up to 5% in products for mucous membranes.

Oral LD_{50} values of $>$ 0.75 g/kg, and 1.2 g/kg have been reported for rats. The dermal LD_{50} in rabbits was $>$ 43 mg/kg.

In a skin irritation test in rabbits, a formulation containing 2.18% colourant was found to be slightly irritating. In a repeated skin application study 0.1% or 1.0% of the material was applied to rabbits both in hydrophilic ointment and in USP ointment in an amount of 0.5 g/kg b.w./day on 5 days a week for 13 weeks. Apart from alterations of the treated skin no treatment-related changes were observed. (The many deficiencies of this study have been examined by an independent consultant and corrected when possible)

Patch testing for 2 days with 1% of the free acid in petrolatum in 8 humans suffering from pigmented contact dermatitis induced by azo dyes suggested that the colour is a weak sensitizer or a cross-reacting substance.

Chronic (18-month) topical treatment of mice with 1 mg in water twice weekly did not induce increased mortality or neoplastic changes of the skin or of the internal organs.

In another dermal study in mice, 0.1 ml of a 1% dispersion in 0.1% aqueous sodium laurylsulphate was applied weekly for 26 months. No evidence of carcinogenic properties was obtained.

An Ames test conducted both as a spot test and as a plate incorporation assay was negative.

Although the data available did not reveal mutagenic or carcinogenic properties, the structure of the colourant indicates the need for further information on possible genotoxic properties. In addition a sensitization test, a short-term oral toxicity study and information on dermal absorption is required. A long term oral study may be required if the genotoxicity tests show positive results.

However the Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier Dec. 1983

CI 16035 1-(2-methoxy-5-methyl-4-sulfophenyl-1-azo)-6 sulfo-2-hydroxy-napthalene, disodium salt

$C_{18}H_{14}N_2Na_2O_8S_2$ CAS N° 25956-17-6
MW : 496

Synonyms : - Food Red 17
- F.D. & C. Red 40

Very soluble in water, insoluble in ethanol.

Use level : 6% in cosmetics for use in contact with mucous membranes, and 0.1% for rinsed off-, and non rinsed off products.

The oral LD_{50} in rats was $>$ 10 g/kg, in dogs $>$ 5 g/kg.
The dermal LD_{50} in rabbits was $>$ 10 g/kg.

No gross signs of dermal irritation were observed in an acute dermal rabbit study with an aqueous paste. However, erythema could not be judged due to the colour of the substance.

An eye irritation test in rabbits with 0.1 ml of a 1.0% aqueous solution did not induce any changes.

Application of the powder and of a 25% aqueous solution to the skin of 200 human subjects for 72 hours followed by one 48 hours application 10-14 days later did not produce irritation or sensitization.
In another human sensitization test a 5% water-insoluble formulation and a 2% water-soluble formulation was applied 10 times on 10 alternate days for 24 hours. A challenge patch applied after a 14-day rest period was also negative.
The same formulations were applied to 25 human subjects 5 times for 48 hours on alternate days and the application sites irradiated for 5 minutes with Xenon light. After a 10-day rest period the challenge application with irradiation did not provide evidence of photosensitization.

A short-term (6-week) feeding study in rats with various levels up to 5.19% in the diet did not produce treatment-related changes in haematological and urinary examinations, or in clinical chemistry of the blood. Gross and microscopic examinations only revealed discolouration of the liver and kidneys attributable to the colourant.

Groups of 1 male and 1 female dog were treated orally by capsule with dose levels up to 500 mg/kg b.w./day for 6 weeks. The dogs of the top-dose group showed minor microscopic changes in the liver.

The short-term dermal toxicity was examined in rabbits for 3 and 13 weeks by daily application of 0.5 g/kg b.w. of 0.1 and 1.0% in water and in USP hydrophilic ointment. The treatment caused slight to moderate irritation in some groups, but there were no changes in clinical chemistry. Microscopically, the skin of rabbits treated with the compound in hydrophilic ointment showed an increased incidence of slight acanthosis and of minimal infiltration of lymphoid cells in subcutaneous tissue.

In a chronic (21-month) oral study in rats with 0, 0.37, 1.39 or 5.19% in the diet, the top-dose induced growth depression. No treatment-related changes were noted in any of the other parameters examined. In animals killed after 6 months, microscopical changes were seen in the kidneys, which were attributed to treatment. These changes were, however, not confirmed by another pathologist. No treatment-related changes in the kidneys or in other organs were found in rats sacrificed after 12 or 21 months.

In a chronic (2-year) oral study in dogs dietary levels of 0, 0.37, 1.39 or 5.19% were fed to groups of 4 dogs/sex. One dog/sex/group was sacrificed after one year. The top-dose animals showed increased vacuolation of cells in the zona fasciculata and glomerulosa, while in all test groups a deposition of a granular pigment was seen in the Kupffer cells. No compound-related changes were found in the dogs sacrificed after 2 years.

The chronic oral toxicity/carcinogenicity was examined in mice, which had been exposed already in utero, through lactation and then for 2 years to diets containing 0.37, 1.39 or 5.19% of the colourant. Growth rate and food intake were slightly reduced in the top-dose group. No changes, considered

relevant, were seen in haematology and organ weights or in gross or microscopic pathology. Incidence of tumours was not significantly affected by treatment.

A similar oral study with in utero exposure to the same diets was conducted in rats for c. 120 weeks after weaning. Gross examination revealed increased incidences of kidney discolouration and firm granular material in the pelvis of all groups of males. Microscopically there was an increased incidence of renal calculi and of focal epithelial proliferation in high-dose rats. There were no indications of tumourigenic properties.

In a dermal carcinogenicity study, one group of 50 mice/sex received 0.1 ml of a 5% aqueous solution twice weekly for 20 months. A relatively large proportion of the test animals showed a grossly abnormal urinary bladder and, microscopically, a relatively high incidence of cystitis. The incidence of neoplasia was low, both in control and treated mice.

Three Ames tests have been conducted with several modifications of the testing procedure and using the 5 Salmonella typhimurium strains and Saccharomyces cerevisiae. The results gave no evidence of mutagenic properties.

Absorption and excretion studies upon oral dosing of rats and dogs showed 76-95% excretion in the faeces within 72 hours. No storage of the compound in the tissues was detected. The main metabolite was 4-amino-5 methoxy-O-toluene in urine as well as in faeces of both species.

Teratogenicity studies in rats with increasing dose levels up to 200 mg/kg b.w./day by gavage, or with 260 mg/kg b.w./day in the drinking water did not reveal signs of embryotoxicity, or teratogenicity.
A teratogenicity study in rabbits with 200 and 700 mg/kg b.w./day by gavage from day 6 through 18 of pregnancy was likewise negative.

In a multigeneration study in rats the feeding of 0.37, 1.39 or 5.19% in the diet only induced growth depression in the pups of the top-dose group.

From the extensive examinations it appears that high levels of the compound are well tolerated both orally and dermally. No indications of teratogenicity, mutagenicity or carcinogenicity were obtained.

The available information justifies the use of this colouring agent in cosmetic products.

Information : Colipa dossier, August 1983

CI 16230 Disodium-7-hydroxy-8-phenylazonaphthalene-1,3-disulphonate

$C_{16}H_{12}N_2O_7S_2.2Na$ CAS N° 1936-15-8
MW : 452.4

Synonyms : - Acid Orange 10
- C-ext Orange 11
- Orange G, D and C
- Orange N° 3

Soluble in water, slightly soluble in ethanol, generally insoluble in organic solvents.

Used up to 0.02% in rinsed off and non rinsed off cosmetics.

In a sub-chronic (90-day) study, groups of 5 rats/sex were fed 0, 0.25, 0.5, 2.0 or 5.0% in the diet. Enlarged spleens occurred at all levels, anaemia at 0.5% and above, and mortality at 5% (summary report only).

In a 15-wk feeding study in rats 500 and 5000 ppm in the diet caused Heinz body formation. With 5000 ppm there was also anaemia, methaemoglobinaemia, reticulocytosis and spleenomegaly.

Groups of 3 pigs/sex were fed 0, 2.5, 25 or 250 mg/kg b.w./day in the diet for 112 days. With 25 and 250 mg/kg, Heinz bodies occurred together with anaemia, reticulocytosis, spleenomegalia, and, at the highest level only, an increased iron content in the spleen. The no-effect level in this study was 2.5 mg/kg.

Heinz body formation has been observed also in rats with 1% in the diet for 44 days, and in cats with 2 mg/kg b.w. for 33 days.

In the ferret, however, no haemolytic anaemia occurred even at the highest feeding level of 150 mg/kg b.w. for one year. This negative finding cannot be used to establish an acceptable exposure level for man, because of the difference in metabolism of this colouring in the ferret and in other species including man.

In an oral carcinogenicity study, mice received 1 mg/day (c. 20 mg/kg b.w.) in the diet for 2 years. There was no evidence of carcinogenic potency.

In another oral lifetime study 50 mg/kg b.w. was fed in the diet to one group of 20 mice. No tumours were attributed to the dye.

A mutagenicity test with S.typhimurium TA 1538 and using up to 100 µg/plate was negative.

Results of a sensitization test should be provided. In addition an adequate Ames test and a chromosomal aberration test are needed.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : - Colipa dossier, December 1983
- IARC Volume 8 (1984) 181-187

CI 17200 Disodium salt of 8-amino-2-phenylazo-1-naphtol-3,6-disulphonic acid

$C_{16}H_{11}N_3O_7S_2Na_2$ CAS N° 3567-66-6
MW : 467

Synonyms :
- D and C Red 33
- Acid Red 33
- Food Red 12
- C-Rot 58

Soluble in water, slightly soluble in ethanol, insoluble in oils, fats, and waxes.

Used up to 1.0% in cosmetics for mucous membranes, 0.15% in rinsed off products, 0.5% in non-rinsed off products, and 2.0% in temporary hair colourants.

Oral LD_{50} values are $>$ 3160 mg/kg in male rats, and $>$ 1000 mg/kg in dogs.

A maximization test in guinea pigs was carried out with an induction treatment by intradermal injection of a 5% aqueous solution and by topical application of 10% aqueous solution. The challenge was made by topical application of 10% and 5% 2 weeks later. There were no positive reactions. It appeared in this test that 10% in distilled water was not irritating to the guinea pig skin.

A 6-wk oral study in rats with 0.1 up to 3.0% in the diet revealed growth depression with 3%, increased spleen weights at all levels, increased kidney weights at the two high levels and microscopial changes in the spleen, liver, kidney, thyroid and bone marrow at the high dose level. Lower levels were not examined microscopically.

In a tentative 90-day oral study in 2 dogs, 3% in the diet induced microscopical changes in the liver, kidneys, and thyroid.

A dermal 90-day study in rabbits with daily applications of 0.5 and 5.0 mg/kg, 5 days a week, did not reveal any deleterious effect.

Daily dermal treatment of rabbits with 20 mg/kg (in 1% aqueous solution with 1.0% surface-active agents) on 5 days/week during 4 weeks, or in another study during 13 weeks did not induce any adverse effect.

In a 2-year study in rats, 0, 0.025, 0.05 or 0.2% was fed in the diet with exposure beginning in utero. There were no compound-related effects other than urine discolouration. The top-dose was considered a no-effect level in this well conducted and well reported study. The higher level of 2.0%, which was examined in a second, similar in utero exposure study, induced growth depression, mortality, signs of anaemia, (decreased haemoglobin, erythrocyte count, haematocrit, and increased reticulocytes) and microscopical changes in the spleen, liver, kidney, bone marrow, and heart. No evidence of carcinogenicity was found.

In another long-term rat study dietary levels of 0, 0.05, 0.2, 0.5 and 2.0% were used. Growth depression occurred with 2.0%. Signs of anaemia were found with 0.2, 0.5, and 2.0%. Increased weights of the liver, spleen and heart occurred with 0.5 and/or 2.0%. Microscopically the liver, spleen, adrenal and/or bone marrow showed increased erythropoiesis, while deposition of pigment (possibly iron) was found in the liver, spleen, and kidneys. These changes occurred with 0.2% and more. No alterations were seen with 0.05%.

A long-term (2-year) feeding study in mice with 0, 0.1, 1.0 and 5.0% showed high mortality, renal lesions and increased splenic weights with 5.0%, and signs of anaemia with 5.0 and 1.0%. The no-effect level was 0.1%. No evidence of carcinogenicity was found.

A 2-year feeding study in dogs with 0, 0.05, 0.4 and 2.0% in the diet did not reveal compound-related changes in survival, growth rate or clinical chemistry. Evidence of a haemolytic process (hepatic and renal pigment deposition and erythroid hyperplasia of bone marrow) was obtained with 0.4 and 2.0%. These levels also induced thyroid enlargement. Indications of similar changes were obtained with 0.05%. Therefore, a clear no effect level was not established.

A skin painting study in mice with 1.0 mg/mouse/week for 95 weeks did not produce any compound related effects. Another skin painting study in mice with a 1% solution (quantity not given) applied once a week for 2 years failed to induce skin tumours or any other treatment related change in the pathological examinations.

Teratogenicity studies in rats and rabbits with daily oral dosages of 2.5, 8.5 and 25.0 mg/kg b.w. did not provide indications of teratogenic properties (IBT-studies).

An Ames test with the strains TA 1537, 98, 1535 and 100, and using up to 400 ug/plate was negative.

The Scientific Committee for Foods evaluated this colourant in 1977. Since then important new information became available including detailed reports of well conducted chronic studies in rats.

The available information justifies the use of this colouring agent in cosmetic products.

Information : - Colipa dossier, Submission I, September 1984
Submission II, November 1984

CI 18050 Sodium salt of 1-hydroxy-2-phenylazo-8-N-acetamidonaphtalene-3,6-disulfonacid

$C_{18}H_{13}N_3O_8S_2Na_2$ CAS N° 3734-67-6
MW : 509.43

Synonyms : - Acid Red 1
- Food Red 10
- Red 2G

Soluble in water and in ethanol.

Use level 0.03% in rinsed off cosmetics and 0.02% in non-rinsed off products.

Oral LD_{50} values reported (in g/kg) are $>$ 5 and 11.44 in rats, 7.35 in mice, 4.81 in guinea pigs, $>$ 5 in rabbits, and $>$ 10 in the chicken. Intraperitoneal values are : 6.35 in rats, 4.76 in mice and 3.00 in guinea pigs.

In a primary skin irritation test in rabbits with 0.5 g moistened with water slight irritation occurred.

Application of only 0.1 mg undiluted substance into the eye of rabbits caused moderate irritation. Rinsing the eyes was of practically no effect.

A sensitization test in guinea pigs with two times 4 induction injections of 0.1 ml of a 7.5% solution in saline and a challenge injection of a 3% solution in saline 14 days after the second induction treatment, did not reveal signs of sensitization.

In a 6-week oral study in mice fed dietary levels of 0, 0.02, 0.1, 0.5 and 1.0% haematological changes occurred at the three higher levels, and comprised formation of Heinz bodies, methaemoglobinaemia, enlargement of the spleen, increased haematopoiesis and increased levels of haemosiderin in splenic macrophages. None of these changes were found with 0.02%.

Similar changes occurred in rats fed the colour (in sausage meat) at 144 ppm in the diet, but not at 24 ppm.
Short-term (3 and 8-wk) feeding studies in rats with dietary levels of 0.1% and above also induced various signs of haemolytic anaemia with Heinz bodies.

In a 96-day mouse study all dietary levels (of 0.01% and above) caused reticulocytosis and Heinz bodies. The time of appearance of Heinz bodies was reduced with increasing dosage.

In a chronic (80-wk) mouse study with 0, 0.005, 0.025, 0.125 or 0.625% in semi-purified diet there were no indications of carcinogenic properties. The haematological effects occurred with 0.125% and above.
Feeding 0.5% in the diet of rats for 2 years did not induce changes in tumour incidence. A diet with 0.2% fed to rats over 2 successive generations did not influence the reproduction parameters.

A mutagenicity test in two strains of S.typhimurium with up to 2.5 mg/plate showed no increase in number of revertants. However, Edwards and Combes (1983) obtained positive results in fluctuation tests, with E. coli. The mutagenic potency could be largely removed by purification of the dye, but returned upon storage or by oxidation of purified samples.
No mutagenic activity was detected by S.typhimurium strains (TA 98 and TA 100) in urine and faeces samples collected from rats treated with a single oral dose of Red 2G (800 mg/kg b.w.).

No teratological or foetotoxic properties were observed in rats fed 0.004, 0.02 or 0.2% from day 0 - 19 of pregnancy. The only effects in the dams were increased spleen weight and erythropoietic activity at the top dose level. No changes were seen in the foetal spleen.

In rats, more than 60% of an oral dose is excreted in the urine, mainly as p-aminophenol. A smaller part is excreted in the urine as aniline.

Systemic effects of this colourant in rats and mice include decreased haemoglobin levels, methaemoglobinaemia, reticulocytosis, Heinz bodies and increased erythropoiesis. In rats, 0.01% in the diet did not induce any of these changes, but in mice Heinz bodies and reticulocytosis were observed

even at this level. JECFA established an ADI of 0.1 mg/kg b.w. for man, on the basis of the no-effect levels in chronic feeding studies in mice (43-26 mg/kg) and rats (8 mg/kg).

Further information was required to clarify the mutagenicity of the compound, of impurities in the colourant, and the oxidation reaction of the compound, but the Committee noted that this substance was permitted in foods.

The available information justifies the use of this colouring agent in cosmetic products.

Information : - Colipa dossier, Submission I, February 1984
Submission II, November 1984
- 25th JECFA-report, WHO Techn. Rep. Ser. No. 669, 1981
- Edwards, C.N. and R.D. Combes, Mutation Research 117 (1983) 127-134

CI 18130 1-hydroxy-2-(2'-methyl-4'-cyclohexyl phenylazo)-3,6-disulfo-8-N-phenyl-sulfonyl amino-naphthalene

$C_{30}H_{31}N_3O_9S_3Na_2$ CAS N° 10236-37-0
MW : 683

Synonyms : - Acid Red 155
- C-WR Rot 4

Soluble in water and ethanol, insoluble in mineral oil.

Used in rinsed off cosmetics up to 0.1%.

The oral LD_{50} in male mice was $>$ 5 g/kg.

A skin irritation test with a 10% aqueous preparation applied to hairless mice without occlusion twice daily for 5 subsequent days did not induce any changes.

Slight, reversible, conjunctival redness occurred in rabbits, when 0.05 ml of a 5% aqueous preparation was applied in the eye.

A 5% aqueous solution, examined in a maximization sensitization test produced weak erythema in 2/18 guinea pigs, indicating weak sensitizing properties according to the classification of Magnusson-Kligman.

An Ames test with up to 2.5 mg of the colourant per plate with and without metabolic activation did not show mutagenic activity.

Further information on absence of mutagenicity and a short-term oral toxicity test in rats are needed for an evaluation.

No opinion can be expressed because a lack of data.

Information : Colipa dossier

CI 18690 Chromium complex of 1-phenyl-3-methyl-4-(2'-carboxy phenylazo)-5-hydroxy pyrazole

$C_{34}H_{24}CrN_8O_6.H$ CAS N° 5601-29-6

MW :

Synonyms : - Acid Yellow 121
- C-WR Orange 9

Soluble in water and ethanol.

Used in rinse-off products up to 0.01%.

The oral LD_{50} in male and female rats and in female mice is > 1.5 g/kg.

No skin irritation occurred in guinea pigs when a concentration of 0.1% in Cremophor EL : water (15:85) was applied by brush three times a day on two successive days and washed away after 20 minutes exposure.

An eye irritation test in guinea pigs with 0.1 ml of a 0.1% concentration in a Cremophor EL/water mixture was likewise negative.

No signs of sensitization occurred in guinea pigs by intracutaneous injections of 0.1 ml of a 0.1% aqueous solution, three times/day on 5 successive days of the induction period, followed by one intracutaneous challenge injection of the same solution after a 4-week rest period.

Information is requested on a well-conducted short-term oral toxicity study and on genotoxicity.

No opinion can be expressed because a lack of data.

Information : Colipa dossier

CI 18736 Chromium complex of 1-phenyl-3-methyl 4-(2'hydroxy-3'-sulfo-5'-chlorophenylazo)5-hydroxypyrazole

$C_{23}H_{20}Cl_2CrN_8O_{10}S_2.H.Na$ CAS N° 6408-26-0
MW :

Synonyms : - Acid Red 180
- C-Wr Orange 8

Soluble in water and ethanol.

Used up to 0.01% in rinsed off products.

The oral LD_{50} was $>$ 15 g/kg in rats, and 14.5 g/kg in mice.

Repeated application of a 1% aqueous solution in 1% methylcellulose to the skin of guinea pigs (3 times on day 1, and 3 times on day 2) did not produce any skin changes.

In an eye irritation test in guinea pigs a 1% aqueous solution of the dye was found to be slightly irritating.

In a sensitization test, 15 guinea pigs received intracutaneous injections of 0.1 ml 0.01% aqueous solution, 3 x/day on 5 consecutive days as induction treatment. After 4 weeks, a challenge treatment with 0.1 ml of 0.001 - 0.00001% aqueous solutions, also given intracutaneously, showed the substance to be a moderate sensitizer. However, it is stated that during a 16-years period of use in cosmetics not a single case of allergy in humans has been reported.

Because the colourant contains a pyrazole ring in its chemical structure the Committee wants information on the occurrence of cross sensitization and of other complications (Stevens-Johnson syndrome) in patients using orally drugs of similar structure. Moreover, a short-term oral study in rats and short-term tests for genotoxic properties are needed for an evaluation. Additional chemical information is required on the valency of the chromium, the solubility of the chromium and the amount of chromium in the final complex.

No opinion can be expressed because a lack of data.

Information : Colipa dossier, December 1983

CI 18820 1-(4'-sulfophenyl)-3-methyl-4-phenylazo-5-hydroxypyrazole

$C_{16}H_{13}N_4O_4S.Na$ CAS N° 6359-82-6
MW : 380

Synonyms : - Acid Yellow 11
- C-WR Gelb 9

Soluble in water and ethanol, insoluble in organic solvents.

Used at levels up to 0.3% in rinsed off products and up to 0.1% in non-rinsed off products.

Oral LD_{50} values reported (in mg/kg b.w.) are 9120 for male rats, 10120 for female rats and 5500 for female mice. In another rat study the LD_{50} was $>$ 10000. Sedation and ataxy were observed.

Skin irritation tests in rabbits with 100 mg of the undiluted substance, or with 0.1 ml 50% suspension in saline on the intact and abraded skin were negative.

In eye irritation tests in rabbits, the undiluted colourant did not produce any changes. With 25% and a 50% suspensions in saline slight to moderate conjunctival changes occurred, consisting of redness and chemosis.

A sensitization test in guinea pigs, by intracutaneous injections of 0.1 ml 0.5% aqueous solution 3 times per day on 5 consecutive days, and a challenge treatment with 0.1 ml 0.5% aqueous solution after 4 weeks did not reveal any sensitization potential.

An Ames test with up to 5 mg per plate revealed mutagenic activity in the strain TA 1538 both with and without metabolic activation.

The Committee considered this colourant for use in rinsed off cosmetics only. It wanted an adequate short-term oral study and further information on genotoxic properties and sensitization in humans.

The Committee noted the presence of a pyrazole ring in the chemical structure, which may cause cross-sensitization and other complications (Stevens-Johnson syndrome) in patients using drugs containing a comparable structure. The Committee brings strongly the attention of the industry in the problem of cross-sensitization and would like to obtain any information Colipa can provide on the occurrence of such complications in patients exposed to this colourant.
The Committee does not support an extension of the use of this colourant to non rinsed off cosmetics.

No opinion can be expressed because a lack of data.

Information : Colipa dossier, February 1984

CI 18965 1-(2',5'-dichloro-4'-sulfophenyl)-3-methyl-4-(4"-sulfophenylazo)-5-pyrazolone, disodium salt

$C_{16}H_{12}Cl_2N_4O_7S_2.2Na$ CAS N° 6359-98-4
MW : 551

Synonyms : - Acid Yellow 17
- Food Yellow 5
- Yellow 2G

Soluble in water, slightly soluble in ethanol, insoluble in most organic solvents and in vegetable oils.

Used up to 0.1% in cosmetics in contact with the skin and with mucous membranes and up to 0.6% in rinsed off cosmetics.

The oral LD_{50} in rats was $>$ 5 g/kg.

In a skin irritation test in rabbits with 0.5 g suspended in olive oil slight o-dema and erythema occurred.

An eye irritation test in rabbits with 100 mg undiluted substance only showed redness and slight swelling of conjunctivae.

A sub-chronic (13-wk) feeding study in rats with diets containing 0 (control), 100, 1000 or 10000 ppm did not induce changes in body weight gain, haematology, serum chemistry, kidney function or in gross or microscopic pathology of organs. The top-dose induced caecal enlargement. The no-effect level was 80 mg/kg b.w.

Groups of pigs were fed diets providing 0, 5, 50 or 500 mg/kg b.w./day for 15 weeks. Diarrhoea occurred in the top-dose pigs on the first 2 days of treatment. There were no effects on growth, haematology, kidney function, urine composition or organ weights. Gross and microscopic pathology did not reveal abnormal findings.

Chronic (80 weeks) feeding of mice on diets with 0, 100, 1000 or 10000 ppm did not affect mortality, food and water intake, serum analyses, haematology, histopathology or tumour incidence. Slight decreases in weight gain were seen at 10000 ppm, and a decreased renal concentrating ability occurred terminally in rats given 1000 or 10000 ppm together with an increased kidney weight in males at the highest level.

An Ames test with 4 strains of S.typhimurium and a test with E.coli at levels up to 500 and 1000 µg/plate were negative.

As far as the colourant is metabolized, this takes place mainly in the large intestine by the action of microorganisms.

JECFA has evaluated this colourant for use in foods and established a temporary ADI of 0.025 mg/kg b.w.

Because the colourant contains a pyrazole ring in its chemical structure the Committee wants information on the risk of cross-sensitization and of other complications (Stevens-Johnson syndrome) in patients using drugs containing a similar structure. In addition information is requested on dermal absorption.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : - Colipa dossier, 19th June 1984
- WHO Food Additive Series No. 12. Twenty first Report of the Joint WHO/FAO Expert Committee on Food Additives, Geneva, 1977

CI 19120 4-(2'-sulfophenylazo)-1-(o-sulfophenyl)-5-hydroxypyrazol-3-carbonic acid

$C_{16}H_9N_4O_9S_2.3Na$ CAS N° 1934-25-4
MW : 468.2

Synonyms : - CI Acid Yellow 13
- C-ext. Gelb 20

Used at levels up to 0.3% in rinsed off cosmetics.

Soluble in water.

The oral LD_{50} in mice was 10 g/kg.

A skin irritation test in rabbits with the filtrate of a 10% solution in saline (obtained after one hour digestion at 40 °C) did not produce any reaction when injected intracutaneously in various dilutions, or applied undiluted to the intact skin.

In an eye irritation test in rabbits, 0.25 ml of the undiluted filtrate of a 10% solution in saline (obtained after one hour digestion at 40 °C) induced erythema.

In a sub-chronic (90-day) feeding study in rats with 1 and 5% in the diet no changes were seen in behaviour, weight gain, haematology, urine composition, or in gross or microscopic pathology. The colourant was excreted in the faeces.

The substance seems to be of a low order of toxicity. However, information is needed on sensitization and genotoxicity.

In view of the presence of the pyrazole ring in the chemical structure of this colourant, the Committee wants to obtain any information on untoward reactions in patients using pyrazole drugs which are exposed also to cosmetics containing this colourant (cf. CI 18820).

No opinion can be expressed.

Information : - Colipa dossier, February 1984

CI 20040 N, N'-[3,3'-dimethyl(1,1'biphenyl)4,4'-diyl] bis 2-[(2,4-dichlorophenyl)azo]-3-oxo-butanamide

$C_{34}H_{28}Cl_4N_6O_4$ CAS N° 5979-28-2
MW : 726

Synonyms : - CI Pigment Yellow 16
- Helioechtgelb FPV
- Flexonylgelb NCG
- Permanent Yellow NCG Colanyl

Insoluble in water, soluble in ethanol and vegetable oils.

Used up to 0.1% in rinsed off cosmetics.

The oral LD_{50} in female rats was $>$ 15 g/kg. Studies conducted with a suspension of the colourant; vehicle and concentration not indicated.

In a skin irritation test in rabbits, 0.5 ml undiluted substance was found to be non irritating.

An eye irritation test in rabbits with 0.1 ml undiluted substance was negative.

In carcinogenicity studies in mice and rats groups of 50 animals/sex received the colourant in the diet at levels of 0.1, 0.3 and 0.9% for 2 years. There were no signs of intoxication, and no statistically significant differences occurred amo: gst the groups in body weight, mortality or in type or incidence of tumours.

Information is requested on the purity criteria, and on the conditions suitable for the formation of dimethylbenzidine from this substance.

The Committee sees no objection to maintaining the use of this colouring agent in rinsed off products only.

Information : Colipa dossier, Sept. 1984

CI 20170 2,6-(4'-sulfo-2",4"-dimethyl)-bis-(phenylazo)-1,3-dihydroxy-benzene, sodium salt

$C_{20}H_{18}N_4O_5S.Na$ CAS N° 1320-07-6
MW : 448.4

Synonyms : - Acid Orange 24
- D and C Brown N° 1
- C-ext. Braun 4

Soluble in water.

Used at levels of 0.1% in rinsed off cosmetics, 0.4% in not rinsed off products and up to 0.5% in temporary hair colourants.

The oral LD_{50} was $>$ 5 g/kg in female rats, $>$ 4 g/kg in male rats, $>$ 2 g/kg in dogs.

A skin irritation test in rabbits with 0.1 g of a 0.4% solution in propylene glycol was negative. This result was confirmed by microscopical examination of the treated skin.

An eye irritation test in rabbits with 0.1 ml of a 1.0% dilution in propylene glycol revealed changes of conjunctivae, iris and cornea which recovered in 48 hours. The substance was classified as slightly irritating.

A sensitization test was conducted in guinea pigs by 7 successive topical applications of 0.5 ml 1% solution in propylene glycol within 3 weeks, and one intradermal injection of 0.1 ml Freund's complete adjuvant on day 0. After 12 days rest, 0.5 ml 1% solution in propylene glycol was applied in a patch as a challenge treatment. Four out of 20 animals showed a positive respons in the form of oedema. This was confirmed microscopically. Erythema could not be established due to the colour. The substance was classified as a mild sensitizer.

In a 3 week dermal study, guinea pigs were treated with 0.5 g 0.1% or 1.0% dilutions in USP hydrophilic ointment, on 5 days/week for 3 weeks.

No changes were observed in survival, general appearance, weight gain, liver and kidney weight or in the gross and microscopic pathology of the skin, kidneys and liver.

A sub-chronic (91-day) dermal study was conducted in rabbits by applying 0.5 g/rabbit of 0.1% or 1.0% dilutions in USP hydrophilic ointment on 5 days/week. The maximum daily dose was, therefore, only 2 mg/kg b.w./day. The death of 1 rabbit in the high-dose group was attributed to constipation. No treatment-related changes were observed in general appearance, weight gain, weight of the liver and kidneys, or in the gross and icroscopic examination of the skin, liver and kidneys.

In a life time skin painting study, mice received once weekly a dose of 40 mg/kg b.w. in propylene glycol. There was no adverse effect on survival or on incidence of tumours or leukemias.
In a second skin painting study, mice received 0.1 mg of the colourant in a hair dye formulation 3 times weekly for 2 years. There was no clear toxic or carcinogenic effect.

An Ames test conducted both as a spot test and as a plate incorporation assay, using up to 400 µg/plate, was negative.

The dermal toxicity studies were conducted with low doses. Systemic effects have not been established. Therefore, a short-term oral study is necessary to establish the target organ and a no-effect level. An adequate Ames test and a chromosome aberration test is requested to obtain further information on genotoxicity.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being (not to be used on mucous membrane)

Information : Colipa dossier, March 1984

CI 20470 1-Amino-2-(4'-nitrophenylazo)-3,6-disulfo-7-phenylazo-8-hydroxynaphthalene, disodium salt

$C_{22}H_{14}N_6O_9S_2,2Na$ CAS N° 1064-48-8
MW : 616

Synonyms : - Acid Black 1
- C-WR Schwarz 1

Soluble in water and ethanol.

Used in rinsed off cosmetics up to 0.1%, in non rinsed off products up to 0.1% and in hair dye formulations up to 0.5%.

Oral LD_{50} values are 14 g/kg in male rats, and $>$ 5 g/kg in male mice.

A skin irritation test in rabbits with 0.5 ml of a 10% aqueous solution applied on a patch for 2 hours was negative.
A repeated application test in hairless mice with 0.1 ml 10% aqueous solution, twice daily for 5 days was also negative.

No signs of irritant properties were observed when the rabbit eye was exposed to 0.1 ml 5% aqueous solution which was not rinsed.

A maximization test in guinea pigs with 5% aqueous suspension and 5% in vaseline for induction, and 25% in vaseline as a challenge after 14 days rest showed no signs of sensitization.

Dermal absorption was examined in a screening test on 10 volunteers treated on 4 different sites of the forearm with 20 µl of a 0.001 M solution in 40% aqueous isopropanol. After 10 min. and after 6, 24 and 48 hours the treated skin areas were stripped by 10 repeated strippings with adhesive tape (Tesafilm-Spezial). The amount of the dye that was removed by the tape was determined. From the recovery rates at the different points of time, and the stability test, it was concluded that dermal absorption did not occur or was negligible.

An Ames test with dose levels up to 2.5 mg/plate with and without metabolic activation was positive at all levels tested.

A short-term oral toxicity study and a chromosomal aberration test are needed.

No opinion can be expressed because a lack of data.

Information : Colipa dossier, March 1984

CI 21100 Butanamide, 2,2'-[3,3'-dichloro (1,1'-biphenyl)-4,4'-diyl] bis(azo) bis N-(2,4-dimethylphenyl)-4-oxo

$C_{36}H_{34}Cl_2N_6O_4$ CAS N° 5102-83-0
MW : 685

Synonyms : - CI Pigment Yellow 13
- Benzidine yellow 11871

Insoluble in water and organic solvents.

The oral LD_{50} in rats was $>$ 10 g/kg, in mice $>$ 10 g and $>$ 20 g/kg.

A skin irritation test in rabbits with 0.2 g of the pure substance produced marginal to slight erythema in most animals which disappeared slowly. A similar test with 0.5 ml of a filtrate (obtained after digesting the colourant in salt solution at 40 °C for one hour) was negative.

A skin injection test in rabbits with 0.1 ml of a series of low concentrations (0.1 - 2.0%) produced less dermal reactions than those observed upon injections of 0.02 - 0.5% sodium lauryl sulphate.

In an eye irritation test in rabbits, 50 mg of the powder caused slight irritation. An eye irritation test with 0.25 ml of a filtrate (obtained by digesting the colourant in salt solution at 40 °C for one hour) was negative.

An oral study in rats with 500 mg/kg b.w. administered in the diet for 97 days did not reveal any treatment-related changes (summary report only).

Information is requested on the purity of this substance particularly with regard to the presence of benzidine and on the conditions suitable for the formation of dichlorobenzidine. Information is also requested on sensitization and genotoxicity. Further information will be looked at on the subject of benzidine derived colouring agents being carcinogenic.

However the Committee sees no objection to maintaining the use of this colouring agent only in rinsed off cosmetic products for the time being.

Information : Colipa dossier, Sept. 1984

CI 21108 bis{4-[1-(chloro-2,5-dimethoxycarboxyanilido)-2-propanone-1-azo]-3-chlorophenyl-1}

$C_{30}H_{30}Cl_4N_6O_8$
MW : 818

Synonyms : - CI Pigment Yellow 83
- Permanent Gelb HR extra

Insoluble in water and aliphatic solvents.

Used up to 0.2% in rinsed off products.

Oral LD_{50} values in rats are $>$ 16 g/kg and $>$ 10 g/kg, and in mice $>$ 10 g/kg.

A skin irritation test in rabbits with 0.5 ml of a filtrate from the colourant (stirred in salt solution at 40 °C) was negative. A second skin irritation test in rabbits conducted with 0.5 g powder (moistened with 0.5 g water) induced only slight changes.
A third skin irritation test in rabbits with 0.5 g of a 50% suspension in polyethylene glycol did not provoke any skin reaction.

An eye irritation test in rabbits with 0.25 ml of a filtrate from the dye (stirred in salt solution at 40 °C) was negative. A second eye irritation test in rabbits with 100 mg of the dye showed slight changes which disappeared slowly.

In a third eye irritation test with 0.1 g of the undiluted substance the irritation scores were 0, for the cornea and iris, and 0.2 for the conjunctivae. Therefore the substance was considered a slight irritant.

In a sub-chronic (97 day) oral study, rats received 500 mg/kg b.w./day, 65 times in 97 days by gavage. No changes were observed in haematology or urine composition. No treatment-related pathological changes were observed (Summary report only).

Carcinogenicity studies have been conducted in mice and rats with groups of 50 animals/sex which were fed the substance in the diet at levels of 0.1, 0.3 and 0.9% for 2 years. There were no signs of intoxication, and no statistically significant differences amongst the groups occurred with respect to body weight, mortality, and type and incidence of tumours.

Information is requested on possible sensitizing properties and on the conditions which may enable the formation of dichlorobenzidine.

However the Committee sees no objection to maintaining the use of this colouring agent only in rinsed off cosmetic products for the time being.

Information : Colipa dossier, Sept. 1984

CI 21110 3,3'-dichloro-4,4'-di[4-azo-1-phenyl-3-methyl-5-pyrazolone]-biphenyl

$C_{32}H_{24}Cl_2N_8O_2$ CAS N° 3520-72-7
MW : 623

Synonyms : - CI Pigment Orange 13
- Permanent Orange G
- Diarylide Orange

Insoluble in water and ethanol, slightly soluble in oils and acetone.

Used up to 0.3% in rinsed off products.

The oral LD_{50} in rats was $\geq$ 16 g/kg, and in mice $\geq$ 10 g/kg.

A skin irritation test in rabbits, with 0.5 ml of a filtrate obtained after stirring the colourant in NaCl solution at 40 °C, was negative.

An eye irritation test in rabbits with 0.25 ml of a filtrate obtained after stirring the colourant in NaCl solution at 40 °C did not produce irritation effects.
A second eye irritation test in rabbits with 100 mg undiluted substance caused slight irritation. Rinsing the eye following instillation did not decrease the irritation. The changes recovered within 7 days.

In a short-term oral study 10 male rats received 500 mg of the colourant per kg b.w. 65 times in a period of 97 days by intubation. The colour was excreted in the faeces. No abnormalities were observed in the blood picture or the urine composition, and no treatment-related changes were found grossly or microscopically (Summary report only).

An Ames test (conducted with S.typhimurium TA 1538, 98 and 1535, by incubating 10 ug colourant in 0.9 ml of the reagents for 30 min. at 37 °C before plating 0.1 ml on minimal plates) did not show any increase in the number of revertants.

Information is requested on sensitization potential. Results of an adequate Ames test and of a chromosomal aberration test are needed.

Information is also requested on :

- the possible liberation of dichlorobenzidine from this substance;
- the occurrence of untoward reactions in patients using pyrazole drugs which are also exposed to cosmetics containing this colourant (cf. CI 18820 and 19120).

No opinion can be expressed because a lack of data.

Information : Colipa dossier, April 1984

CI 21115 bis-[3-chloro-phenyl-4-azo(1-p-tolyl-3-methyl-5-hydroxy-pyrazole-4)]

$C_{34}H_{28}Cl_2N_8O_2$ CAS N° 15793-73-4
MW : 651

Synonyms : - CI Pigment orange 34
- Orange PGR

Insoluble in water.

Used up to 0.3% in rinsed off cosmetics.

The oral LD_{50} was $>$ 16 g/kg in rats and $>$ 20 g/kg in mice.

A skin irritation test in rabbits with 0.2 g on a damp patch produced very slight erythema and very slight oedema.
Single intradermal injection of 0.1 ml 0.1-2.0% (in Tween 80:acetone: saline = 1:3:96) in rabbits caused moderate inflammatory reactions. The diameter of the reaction site increased with increasing concentration. Necrosis did not occur.

An eye irritation test in rabbits with 50 mg of the powder was completely negative. A second eye irritation test in rabbits with 100 mg of the powder was also negative.

Information is requested on the possible liberation of dichlorobenzidine from the substance, and on the incidence of deleterious effects (Stevens-Johnson syndrome) in patients using drugs which contain a pyrazolenucleus and also use cosmetics with this pyrazole containing colourant (cf. CI 18820, 19120, 21110).

Results are required of a sensitization test and a short term oral toxicity test. An adequate Ames test and a chromosomal aberration test should be made.

No opinion can be expressed because a lack of data.

Information : Colipa dossier, April 1984

CI 21230 1,1-bis[1'-5"-cyclohexyl-2"-hydroxy-1"-phenylazo)-2'-methyl-4'-phenyl] cyclohexane

$C_{44}H_{52}N_4O_2$ CAS N° 6706-82-7
MW : 617

Synonyms : - Solvent yellow 29
- C-ext. Gelb 21
- L-ext. Gelb 1

Insoluble in water, slightly soluble in 1% ethanol, soluble in fats.

Use level in rinsed off products 2%, in non rinsed off products 0.2%.

The oral LD_{50} in rats was $>$ 10 g/kg.

No skin irritation occurred in rabbits when 0.5 g of the substance, or 0.5 g of a 25% aqueous suspension was applied to the intact or abraded skin.

An eye irritation test in rabbits with 0.1 g substance or 0.1 ml of a 20% aqueous suspension was negative.

Daily stomach intubation of rats (5 days/week) of 1 or 2 g/kg body weight for 13 weeks was reported to evoke no deleterious effects.

The available data do not suggest high toxicity. A detailed report on the 13-week oral study is requested and information on possible mutagenic and sensitizing properties.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier

CI 24790 [4-(2',4'-dihydroxy-8'-sulfonaphthylazo)phenyl]-[4-(2'-hydroxy-4'-sulfophenyl-8'-sulfonaphthylazo)phenyl]-1,1-cyclohexane

$C_{44}H_{36}N_4O_{12}S_3 2Na$ CAS N° 13421-53-9
MW : 908.98

Synonyms : - Acid Red 163
- C-WR Rot 18

Highly soluble in water, soluble in ethanol, slightly soluble in acetone.

Used in rinsed off cosmetics up to 0.1%.

The oral LD_{50} was > 5 g/kg in female rats, and > 10 g/kg in female mice.

In a primary skin irritation test in guinea pigs a 1% aqueous solution was applied to the intact skin three times on day one and three times on each of two successive days without producing any changes.

In an eye irritation test in guinea pigs 0.1 ml of a 1% aqueous solution was found to be practically non irritating.

A sensitization test in guinea pigs was conducted by an induction treatment with 0.1 ml of a 1% aqueous solution applied intracutaneously three times per day on 5 days in week one, and epicutaneously once daily in week 2. After 2 weeks a challenge treatment by intracutaneous injections of 0.1 ml of 1%, 0.1% and 0.01% aqueous solution did not produce any sensitization reaction.

A short-term oral toxicity test and information on genotoxicity is needed to enable an evaluation.

No opinion can be expressed because a lack of data.

Information : Colipa dossier, December 1983

CI 26100 1-[4-phenylazo phenylazo]-2-hydroxynaphthalene

$C_{22}H_{16}N_4O$ CAS N° 85-86-9
MW : 352.40

Synonyms : - Solvent Red 23
- Sudan III
- C-Ext. Rot 56
- DC Red 17

Insoluble in water, sparingly (0.2%) soluble in ethanol, soluble in acetone and fats.

Used in cosmetics for all types of applications up to 0.5%.

The oral LD_{50} in rats was > 16 g/kg, in dogs > 1 g/kg. An LD_{50} of c. 0.5 g/kg was found in rabbits and rats upon intraperitoneal administration. In rabbits the intrapleural and subcutaneous LD_{50} was > 1 g/kg.

In an irritation test in rabbits on the intact and abraded skin under occlusion 0.5 g in 0.2 ml 1,2-propanol was slightly irritating.

Upon application of 0.1 g with 2 drops of propanediol to the rabbit eye the substance was classified as slightly irritant.

In a patch test with 8 patients suffering from pigmented contact dermatitis induced by azodyes, 1% of the colourant in petrolatum did not induce any positive reaction. Sensitizing properties were observed with commercial samples in human subjects (1) and in guinea pigs (2), but with purified samples no positive reactions were obtained.

Short-term dermal treatment of rabbits with 0.1 and 1.0% in USP white ointment and hydrophilic ointment daily for 21 days on intact and abraded skin, and for 90 days on intact skin resulted in mild dermal inflammation, thickening and hyperkeratosis (summary report only).

A chronic (18-month) skin painting study in mice with 0.1 ml of a 1% solution in aqueous sodium lauryl sulfate solution, applied once weekly, did not reveal changes in growth rate, behaviour or survival, and no gross or microscopic changes were seen in type or incidence of spontaneous abnormalities.

No indications of carcinogenic properties were obtained upon long term feeding to mice and rats in amounts of respectively 40 and 200 mg/kg b.w./day, but the studies are considered inadequate (3).

An oral dose of 50 mg/rat was excreted mainly ($>$ 80%) in the faeces. After a single i.p. dose of 2.72 mg ^{3}H-labelled colourant, only 5.1% was found in the faeces while 15.8% appeared in the urine, 0.3% in the bile and 27.8% remained in the body, leaving 51% unaccounted for. In the urine, most of the activity was present in the form of p-aminophenol (3).
The substance is an active inducer of enzymes which metabolize 7,12-dimethylbenz(a)anthracene.

No mutagenic properties were detected in an Ames test (4).

Approval of this colourant for foods has been withdrawn in several countries, but in some it is permitted for non-food applications. IARC considered all experiments examined inadequate for an evaluation.

A short-term oral toxicity study to examine systemic effects and further information on mutagenicity is requested.

However the Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier
(1) Chem.Abstr. 92: 70577 s
(2) Chem.Abstr. 98: 59724 r
(3) IARC Monograph 8 (1974) 241-247
(4) Chem.Abstr. 91: 84714

CI 26105 1-[[2-methyl-4-[(2-methylphenyl)-azo]phenyl]azo]-2-naphthalenol

$C_{24}H_{20}N_4O$ CAS N° 85-83-6
MW : 380.48

Synonyms : - CI Solvent Red 24
- Scarlet Red
- Sudan IV

Practically insoluble in water, moderately soluble in chloroform, soluble in fats and paraffin.

Used up to 0.005% in rinsed off cosmetics.

The oral LD_{50} in rats was $>$ 5 g/kg.

In a skin irritation test in rabbits with 500 mg in 0.5 ml 1,2-propanediol, the irritation index was found to be 2.3. Therefore the substance is considered slightly irritating to the skin.

In an eye irritation test in rabbits with 100 mg, made into a paste with 8 drops of 1,2-propanediol, the dye was classified as slightly irritating to the mucous membranes.

In a carcinogenicity study in mice 12 food colours were examined. One group of 81 males and 25 females received CI 26105 in the diet as a 1% solution in vegetable oil in an amount providing 2 mg/mouse/day (c. 40 mg/kg b.w.) for a periode of 500 - 700 days. Absence of carcinogenicity was considered doubtful because of multiple liver adenoma in one test animal.

A carcinogenicity study was conducted with one group of 20 rats which were fed 0.1% in the diet for their lifetime. Three rats survived one year and only one survived 2 years. The colourant induced liver damage. The author considered the dye (6942) a liver carcinogen.

In another carcinogenicity study 5 rats/sex were fed 4% in the diet for 18 months. One out of 4 rats living up to 12 months showed liver damage. The author considered the dye (6942) a liver carcinogen.

Subcutaneous injection of 24 rats with 0.2 ml of a 2% solution in Tween 80 once a week resulted in sarcomas at the injection site in 4 out of 8 rats surviving more than 400 days.

Upon intraperitoneal injection of rats with 1 ml 0.15% solution in DMSO, or of 1 ml of a 1% suspension in olive oil, a small amount of the dye was recovered from the faeces, whereas the urine did not contain any detectable amounts.

In an Ames test with up to 500 µg/plate the dye was not found to be mutagenic in TA 1537, 1538 and 98.

Although the studies were inadequate, the Committee found that there were indications of carcinogenic potential as indicated by several studies.

The use of this colouring agent in cosmetic products should not be permitted.

Information : - Colipa dossier, November 26, 1984
- IARC, 8 (1974) 217-224

CI 27290 1(bis-phenylazo)-2-hydroxy naphthalene-6,8-disulfonic acid, sodium salt

$C_{22}H_{16}N_4O_7S_2.2Na$ CAS N° 5413-75-2
MW : 556

Synonyms : - Acid red 73
- Ext Rot 24

Soluble in water, very slightly soluble in acetone, insoluble in other organic solvents.

Use level up to 0.2% in rinsed off cosmetics.

The oral LD_{50} in rats was $>$ 5 g/kg. The rats treated with 5 g/kg showed lethargy, piloerection, increased salivation and diarrhoea.

No signs of skin irritation were observed by single application of 0.5 g of the colourant mixed with water (1:1) to the intact and abraded skin of rabbits under occlusion.

An eye irritation test in rabbits with 100 mg undiluted colourant produced only a temporary mild conjunctival reaction in one animal.

A sensitization test is not available, but no cases of allergy due to the colourant have been reported.

An adequate short-term oral toxicity study is required and information on genotoxic properties.

However the Committee sees no objection to maintaining the use of this colouring agent only in rinsed off cosmetic products for the time being.

Information : Colipa dossier, February 1984

CI 27755 Tetrasodium salt of [(sulfo-4-phenyl-1-azo)-4-sulfo-7'-naphthylazo-1]-hydroxy-1-amino-7-naphthalene-disulphonic-3-6-acid

$C_{26}H_{19}N_5O_{13}S_4.4NA$ CAS N° 2118-39-0
MW : 825.6

Synonyms : - Food Black 2
- Schwarzfarbstoff 7984
- Black 7984

Soluble in water.

Used up to 0.1% in rinsed off products, up to 0.5% in non-rinsed off products, and up to 0.1% in contact with mucous membranes.

The oral LD_{50} in rats was > 5 g/kg; the intravenous LD_{50} in mice was > 1.0 g/kg.

Application of 50 mg undiluted substance into the eye of two rabbits induced slight erythema of the conjunctivae which disappeared within 24 hours. No corneal damage was observed.

Intracutaneous injection of 0.1 ml 5% solution into the back skin of rabbits did not induce any skin damage. The black spot in the skin disappeared largely during the second day and completely after 2 days.

Guina pigs given s.c. 10 doses of 1 ml of 0.05-0.1% in isotonic saline during 21 days showed no intolerance. A challenge test after 14 days was negative.

Two male and two female pigs were daily dosed by gavage with 1000 mg/kg during the days 1 - 21 and with 1500 mg/kg during days 22 - 69. Haematology, serum enzymes, and microscopy of the liver, spleen, lymphnodes and kidneys were not affected.
Rats given 1.5 g/kg orally for 19 days and cats given 100 mg/kg for 8 days, and 5 mg/kg for 31 days showed no increase in Heinz bodies.

Rats fed 0.1% in the diet for 200 days showed normal growth and no toxic effects were noted.

Chronic administration of 0.5% in the drinking water of 10 male rats during 543 days did not induce signs of intoxication. The treated rats showed no tumours. There were no controls (Summary report only).

In a second study, groups of 25 rats/sex received 0 or 0.5% in drinking water for 337 days and were observed for 1184 days. Mortality of males was greater in the test group than in controls. At 30 months 6 test females and 1 control female survived. Nine mammary febroadenomas and one ovarium tumour occurred in test females, one sarcoma and five mammary fibroadenomas in control females. No extensive pathology was done (Summary report only).

One male and 4 female rats fed 0.5% colourant in the drinking water for 8 months were mated. The progeny was kept on 0.5% in drinking water for 110 days. From 19 F_1 females, an F_2 generation was bred. Twenty three F_2 females were kept on 0.5% in drinking water for 360 days and then continued on unsupplemented drinking water up to 800 days. A similar group of 18 F_2 male and 25 F_2 female controls were observed also for 28 months. No abnormalities were noted regarding growth, reproduction or any other effects (Summary report only).

Repeated s.c. injection of 10 male rats with 0.5 ml 1% solution twice weekly for one year did not induce tumours at the injection site.

In a similar study 25 male rats received 0.5 ml of a 2% solution s.c. twice weekly. After 40 injections treatment was discontinued because of swelling at the injection site. The local changes disappeared slowly.

An oral dose of the colourant is excreted in the faeces. When given parenterally to mice the whole animal is coloured intensely, this being fully reversible after 12 hours. After i.v. injection of 50 mg/kg b.w. into dogs, 10% was excreted unchanged in urine and 13% as a colourend metabolite while 80% were not accounted for.

High oral exposure was well tolerated by pigs and rats but only summary reports are available of most studies.

Information on possible genotoxicity should be provided.

JECFA has not established an ADI for use as a food colour, because it considered the long-term studies inadequately conducted, and the reproduction study insufficiently reported. The Scientific Committee for Food (1975) endorsed this decision but was of the opinion that the colourant is not acceptable for use in food.

However the Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information :
- Colipa dossier, 19th June 1984
- 21st Report of the JECFA, Geneva 1977. WHO Techn. Report Series No. 617.
- Report of the Scientific Committee for Food. First Series 31 December 1975.

CI 40215 (Aniline-p-phenylazo)sulfonic acid, sodium salt

$C_{12}H_{10}N_3O_3NaS$ CAS N° 1325-54-8

M_M : 299

Synonym : C.I. Direct Orange 34, 39, 44, 46, 60

Soluble in water, slightly soluble in alcohol.

Use level up to 0.1% in rinsed off cosmetics.

The oral LD_{50} was 5300 mg/kg for male rats, 5100 mg/kg for female rats and 7500 mg/kg for female mice.

Skin irritation was examined in male guinea pigs with a 2% aqueous solution on the intact skin without occlusion during an exposure period of 20 minutes. No signs of irritation were observed.

An eye irritation test in guinea pigs with 0.1 ml of a 2% aqueous solution was likewise negative.

Sensitizing properties were examined in 15 guinea pigs by daily intracutaneous injection of a 0.1 ml of a 1% aqueous solution at three sites on the flank on 5 consecutive days. After a rest period of 4 weeks the treated animals and 10 control animals received as challenge treatment four injections of different dilutions of the 1% solution, viz. 1:10, 1:100, 1:500 and 1:1000. No signs of sensitization were observed. The chemical structure of the compound suggests the possibility of photosensitizing properties.

A short-term oral toxicity study, and information on genotoxicity are requested.

No opinion can be expressed because a lack of data.

Information : Belgium (Belgium)

CI 40850 Trans Canthaxanthin

$C_{40}H_{52}O_2$ CAS N° 514-78-3
MW : 564.9

Synonyms : - Food Orange G
- C-Orange 15 g
- L-Orange 7 g

Insoluble in water, poorly soluble in ethanol and vegetable oils.

Used at a level of 5% in cosmetics intended for contact with the skin and mucous membranes.

The oral LD_{50} in mice was $>$ 10 g/kg.

Dermal treatment of guinea pigs in an open epicutaneous test with 0.1 ml of a 5% syrup for 3 weeks did not induce irritation.

In an eye irritation test in rabbits with 0.1 ml of a 1% aqueous suspension minimal irritation of the conjunctivae occurred.

A sensitization test in guinea pigs with a 0.1% suspension was negative.

In an oral 90-day study in dogs with 100 and 400 mg/kg, administered daily by capsule, no effect was noted on body weight or general health.

A 3 generation study in rats with 0.1% in the diet revealed no adverse effect.

In a chronic rat study 0, 0.5, 2 and 5% was fed in the diet for 93 - 98 weeks. No adverse effects were seen on growth, food intake, mortality or tumour incidence.

This substance has been evaluated for food use and an ADI of 25 mg/kg b.w. was allocated by JECFA. The substance is also used in medical practice as a photoprotective agent.

The available information justifies the use of this colouring agent in cosmetic products.

Information : - Colipa dossier
- FAO Nutrition Meetings Rept. Series 38 B, WHO Food Add./6625

CI 42045 4,4'-bis(N-diethylamino)-2",4"-disulfotriphenyl methane, sodium salt

$C_{27}H_{32}N_2O_6S_2.Na$ CAS N° 129-17-9
MW : 567

Synonyms : - Acid Blue 1
- C-ext Blau 13
- Blue VRS

Soluble in water and ethanol.

Use level 0.1% both for rinsed off-, and for non rinsed off products.

The oral LD_{50} in rats was $>$ 10 g/kg, in mice $>$ 5 g/kg; the i.p. LD_{50} in mice was 3.0 g/kg in males and 3.2 g/kg in females.

A skin irritation test in rabbits with 0.5 ml of a saturated solution in saline was negative.

No eye irritation was observed in rabbits with 0.25 ml of a saturated solution in saline.

A 90-day oral study in rats fed 0, 1 or 5% in the diet did not reveal any changes in growth rate, haematology, results of urine examinations, gross pathology or microscopy of 5 different organs.
In a more detailed 90-day rat feeding study with dietary levels varying from 0.3 to 3.0% slight growth depression occurred in males fed 1.5 and 3.0%. No overt signs of toxicity occurred in haematology, urine analyses, kidney function, or organ weights. Microscopically, fatty changes were observed in the liver and an increased incidence of active acini in the thyroids of rats of the two high dose groups. The no toxic effect level was established at 0.75% in the diet (c. 375 mg/kg b.w./day).

In a subcutaneous injection study in rats the administration of 20 mg/rat, once weekly, for 45 weeks resulted in ulceration and abscess formation at the injection site, and 2 out of 20 treated rats developed rhabdomyosarcomas in the area of the injection site.

From another study with subcutaneous injections of 0.5 ml 2% aqueous solution twice weekly in rats and mice, and detailed microscopy of the skin at the site of injection, indications were obtained suggesting that sarcoma production results from derangement of connective tissue repair rather than from induction by a process of chemical carcinogenesis.
In a bladder implantation test in mice no significant increase in incidence of tumours was observed.

The results of several Ames tests and of a mitotic cross over gene conversion test in yeast was negative.

According to IARC this substance is carcinogenic in rats following subcutaneous or intramuscular injection, because it produced sarcomas at the site of repeated injections. This finding may be of little relevance for its use in cosmetics. However, further information on genotoxicity is needed. Moreover a sensitization test should be conducted, and a short-term dermal toxicity study is needed to examine local skin changes as well as systemic effects.

However the Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : - Colipa dossier, August 1983
- Combes, R.D. and R.D. Haveland-Smith, Mut. Res. 98 (1982) 101-168
- IARC Monograph vol. 1a (1978) 163-170

CI 42080 4,4'-bis[(N-ethyl-N-benzyl)amino]-2",4"-disulfotriphenylmethane, monosodiumsalt

$C_{37}H_{36}N_2O_6S_2.Na$ CAS N° 3486-30-4
MW : 697

Synonyms : - CI Acid Blue 7
- C-Ext. Blau 1
- DC Blue no. 3
- Ext. DC Blue N° 3

Highly soluble in water, soluble in ethanol.

Used at levels up to 0.1% in rinsed off products.

Oral LD_{50} values in rats are (in mg/kg) 11440, > 10000, > 5000, > 5000 and > 2000.

Two skin irritation tests in mice with 10% aqueous solutions which were applied either once, or twice daily for 5 days did not produce any [illegible]. A skin irritation test in rabbits with 0.5 g of the undiluted substance and with 0.5 g aqueous suspension applied to the intact and abraded skin under occlusion was negative. Two other skin irritation tests in rabbits were also negative.

In two eye irritation tests in rabbits with 0.1 g colourant only minimal irritation of conjunctivae was observed. In another test in rabbits the undiluted colourant and suspensions of 33 and 10% in saline induced slight redness and chemosis, while a 5% suspension in saline did not produce changes.

An adequate short-term oral toxicity study is requested and information on possible genotoxic and sensitising properties.

However the Committee sees no objection to maintaining the use of this colouring agent only in rinsed off cosmetic products for the time being.

Information : Colipa dossier, February 1984

CI 42100 4,4'-Bis (N-ethyl-m-sulfobenzylamino)-2"-chloro triphenylmethane sodium salt

$C_{37}H_{35}ClN_2O_6S_2.Na$ CAS N° 4857-81-2
MW : 724

Synonym : Acid Green 9

Soluble in water and ethanol.

Used in rinsed off products up to 0.02%.

The oral LD_{50} in rats was 11.5 g/kg.

Application to the rabbit skin of 0.5 g moistened with water was very slightly irritating both to the intact skin and to the abraded skin.

In an eye irritation test in rabbits the undiluted substance produced slight irritation. Rinsing the eye after one minute resulted in less changes.

The Committee requests an adequate short-term oral toxicity study, and information on genotoxicity and sensitization.

However the Committee sees no objection to maintaining the use of this colouring agent only in rinsed off cosmetic products for the time being.

Information : Colipa dossier Dec. 1983

CI 42170 4,4'-bis(N-ethyl-m-sulfobenzylamino)-2,2-dimethyl-2"-chloro-triphenylmethane, monosodium salt

$C_{39}H_{39}ClN_2O_6S_2Na$ CAS N° 5863-51-4
MW :753

Synonyms : - Acid Green 22
- L-ext. Grün 2
- C-ext. Grün 10

CI 42170 without Cl is CI 42160
CI 42170 without $2CH_3$ is CI 42100
CI 42170 without $2CH_3$ and Cl is CI 42085 (C grün 3)

The toxicity studies reported were conducted with CI 42085 (see data sheet on this colour).

No information is available on CI 42170, CI 42160 or CI 42100. Therefore these colours cannot be evaluated.

CI 42510 4,4',4"-triamino-3-methyl-triphenyl carbenium chloride

$C_{20}H_{20}ClN_3$
MW : 337.8

CAS N° 632-99-5

Synonyms : - Basic Violet 14
- Fuchsine
- Magenta I
- Rosaniline

This colourant is the main constituent of Magenta, which is a mixture of three closely related monohydrochlorides of 4,4',4"-triamino-triaryl methane dyes. The other 2 compounds are :
4,4',4"-triamino-triphenylcarbenium chloride (paramagenta = parafuchsine = pararosaniline = CI 42500) and
4,4',4"-triamino-2,2'-dimethyl-triphenylcarbenium chloride (Magenta II).

Slightly soluble in water, soluble in alcohols and acids, almost insoluble in ether.

Used up to 0.01% in non rinsed off cosmetics, 0.3% in rinsed off products and hair dye preparations.

The oral LD_{50} of a 40% suspension in carboxymethylcellulose in rats was > 12 g/kg b.w.

A skin irritation test in rabbits with 0.5% in propylene glycol did not produce oedema or microscopic changes of the treated skin sites. A similar test in guinea pigs with 0.2% in a 1% aqueous Tylose solution likewise failed to induce oedema. Erythema could not be judged due to colouration of the skin.

An eye irritation test in guinea pigs with 0.1 ml of a 0.2% aqueous solution showed practically no reaction of the treated eyes.

In a sensitization test, guinea pigs were treated topically with 5% in a 25% aqueous solution of gum arabic, daily for 5 days. On the following 5 days they received daily intracutaneous injections of 0.1 ml 0.1% in saline.

After 2 weeks rest period the challenge treatment consisted of an intracutaneous injection of 0.1 ml 0.01, 0.001, and 0.001% in saline. No signs of an allergic response were observed.

In an Ames test Magenta was positive in TA 1538 with a metabolic activation system. In a second test positive results were obtained with TA 98 and TA 1538 and metabolic activation. An Ames test with parafuchsine (= pararosaniline) was negative. Magenta was negative in an in vitro chromosome aberration test in Chinese hamster cells and a mitotic recombination assay in yeast (Simon et al. J. Nat. Cancer Inst. 62 (1979). Parafuchsine was both negative in in vitro transformation tests with hamster cells and in a host mediated assay in mice in a mitotic recombination test and using Salmonella (Envir. Mutagenesis 1 (1979) 27-35).

In a long term oral study, mice received 12 mg Magenta in arachis oil by stomach tube once weekly for 52 weeks. They were then observed till death. The incidence of subcutaneous sarcomas, hepatomas, intestinal polyps and carcinomas was not increased.

Hamsters treated with Magenta (400 mg/kg) by gavage twice weekly during their lifetime showed no increased incidence of tumours.

Life-time administration of Magenta to rats by stomach tube twice weekly in maximum tolerated doses of 300 and 200 mg/kg b.w. did not affect the type or multiplicity of tumours.

In a skin painting study, mice were treated three times weekly for 18 months with 0.05 ml of a formulation containing 6, 73 or 140 ppm Fuchsine. This is equivalent with 0.003, 0.0037, and 0.007 mg Fuchsine/mouse, or with 0.006, 0.0074 and 0.14 mg Fuchsine/kg b.w. There were no indications of a carcinogenic effect. (The report on this recent study is incomplete).

From long-term studies it appeared that oral toxicity is low, because doses of more than 100 mg/kg b.w./day are well tolerated by different mammalian species.

The available information justifies the use of this colouring agent in cosmetic products.

Information : - Colipa dossier, 19th June 1984
- IARC 4 (1973) 57-64

CI 42520 4,4',4"-triamino-3,3',3"-methyl-triphenyl-carbenium chloride

$C_{22}H_{23}N_3.HCl$ CAS N° 3248-91-7
MW : 366

Synonyms : - Basic Violet 2
- New Magenta

Very soluble in water and ethanol.

Used up to 0.0005% in rinsed off cosmetics.

The oral LD_{50} in rats was > 200 mg/kg.

A skin irritation test in rabbits with 0.5 ml 10% aqueous solution under occlusion dit not induce any skin changes. A repeated skin application test in hairless mice with a 10% aqueous solution, applied twice daily for 5 days did not produce any skin reaction.

An eye irritation test in rabbits with 0.1 ml 1% aqueous solution produced weak corneal opacity and weak to moderate conjunctival irritation.

In a maximization test, guinea pigs were treated with 0.1 ml 1% aqueous solution by intradermal injection and 5% in vaseline by topical application for induction treatment. The challenge treatment after 14 days with 0.1 ml 0.1% aqueous solution did not induce any reaction.

An Ames test with up to 2500 µg/plate showed positive results with TA 1538 and TA 98 in the presence of a metabolic activation system.

An adequate short-term oral study is required. A chromosome aberration test in mammalian cells is necessary to evaluate potential genotoxic properties.

The Committee sees no objection to maintaining the use of this colouring agent for rinsed off products only, taking into account the very low level of use.

Information : Colipa dossier, 19th June 1984

CI 42535 Bis-4,4'-dimethylamino-4"-methylamino-triphenyl-carbenium chloride

$C_{23}H_{26}N_3$ / $C_{24}H_{28}N_3$ / $C_{25}H_{30}N_3$ CAS N° 8004-87-3
MW : 344 MW : 358 MW : 372

Synonyms : - Basic Violet 1
- Methyl Violet

Soluble in water.

This colour has been called Methyl Violet but it is actually a poorly defined combination of violet rosanilins comprising a series of dyes including Crystal Violet (Mut. Res. 98 (1982) p. 157).

Use level up to 0.1% in rinsed off and non rinsed off cosmetics, and up to 2.5% in hair setting lotions.

Oral LD_{50} values are 2.6 g/kg and 1.0 g/kg in rats.

A skin irritation test in rabbits with a 2.5% aqueous solution was negative.

In an eye irritation test in rabbits a 2.5% aqueous solution was found to be an irritant, but a 0.1% aqueous solution was negative.

A maximization test in guinea pigs was conducted with a 1% aqueous solution for intradermal injection and 75% in liquid paraffin for topical application in the induction phase. A 10% aqueous solution used as a challenge, produced weak signs of sensitization in 3/10 animals.

In a repeated insult patch test with 22 volunteers the solution examined (concentration not mentioned) did not induce signs of sensitizing potency.

In a 13 weeks feeding study in rats, 500 ppm in the diet induced slight growth retardation but no significant changes in blood, urine, liver function or in the results of the pathological examinations (a detailed report is not available).

An Ames test with the strains TA 1535, 1537 and 1538 and up to 1000 µg/plate was negative. A second Ames test with the 5 tester strains and up to 10 µg/plate was also negative. In a third Ames test, however, TA 1535 gave a positive result in the absence of metabolic activation. A spot test in two strains of Neurospora Crassa with up to 400 µg/plate was negative.
In a micronucleus test in rats, oral administration of 2000, 4000 and 8000 mg/kg b.w. did not increase the number of micronucleated polychromatic erythrocytes.

Positive results have been reported in chromosome aberration tests conducted with different samples of Gentian Violet and Crystal Violet. The degree of the effects depended on the source of the sample (Mut. Research 58 (1978) and 89 (1981).

In an in vivo screening test for measuring dermal absorption (by the stripping method with Tesafilm), no absorption was detectable after a 24-hr contact period with the arm skin of 10 male volunteers.

Little information is available on systemic toxicity. Dermal absorption seems to be unimportant. Because this dye is not clearly defined, and the results of the genotoxicity test depend on the source of the sample an evaluation is not possible.

An opinion can not be given until information is available on the level of CI 42555 in CI 42535

Information :
- Colipa dossier, 19th June 1984
- Mutation Research 58 (1978) 269-276
- Mutation Research 89 (1981) 21-34
- Mutation Research 98 (19982) 101-243

CI 42555 4,4',4"-ter(N-dimethylamino)triphenylmethane chloride

$C_{25}H_{30}N_3.Cl$ CAS N° 548-62-9
MW : 408

Synonyms : - Basic Violet 3
- C-ext. Violett 6
- Crystal Violet
- Gentian Violet

Soluble in water, ethanol and glycerine.

This dye is the major component of Methyl Violet 2 B (CI 42535) which is a mixture of dyes. Specifications have recently been described by JECFA (1984).

Used up to 0.1% in rinsed off and non rinsed off cosmetics and up to 0.5% in hair colourants.

Oral LD_{50} values (in mg/kg) varied between 180 and 920 in rats, between 96 and 800 in mice, and between 125 and 250 in rabbits. The intraperitoneal LD_{50} (in mg/kg) was 5.10 in mice, 8.90 in rats and 5.00 in rabbits. A minimal lethal dose of 25 mg/kg was found in mice upon rectal administration.

A skin irritation test in rabbits with 0.5 g undiluted substance or 0.5 g of a 50% aqueous suspension was negative. Aqueous solutions of 1% or 2% may induce necrotic changes of stripped skin of humans and guinea pigs.

Application of a 0.25% suspension in saline to the eye of the rabbit induced corneal turbidity and swelling of the iris and conjunctivae. With higher concentrations necrosis of the iris and severe swelling of conjunctivae was observed. No changes were seen with a 0.025% suspension in saline.

In a maximization test in guinea pigs a 10% aqueous solution showed weak sensitizing potency.

A 90-day, oral toxicity study in rats with 75 and 150 mg/kg b.w./day showed considerable mortality, severe degeneration in the liver and kidneys and haemorrhages in the lungs, airways and trachea (summary report only).

Chronic (20-month) skin painting of mice, 3 times weekly, with 0.05 ml of 0.01 g % in a semi-permanent hair dye formulation (0.005 mg colourant/mouse) did not induce a clear toxic or carcinogenic effect.

A teratogenicity study in rats with oral dosing of 2.5, 5.0 or 10.0 mg/kg/day showed maternal mortality in the high dose group and clinical signs in all dose groups. The incidence of major visceral malformations (hydroureter and hydronephrosis) and of skeletal malformations (ribs) was higher in the treated groups than in controls. The incidence of malformations increased with dose but was not significant in the low dose group.
In a teratogenicity study in rabbits dose levels of 0.5, 1.0 and 2.0 mg/kg/day were intubated. All treated groups showed mortality and considerable reduction in maternal weight gain. These changes were dose-realted. The incidence of foetal resorptions increased and foetal weight decreased in a dose-related way. Malformations, however, showed no relationship with treatment.

The colourant was found to be mutagenic to Bacillus subtilis, Escherichia coli and Salmonella typhimurium, to damage bacterial DNA in vitro, and to inhibit DNA syntheses by E. coli B polymerase. Negative results with S. typhimurium have been reported also. The substance is cytotoxic to mammalian cells and produces chromosomal aberrations in Chinese hamster ovary cells. it is also a human clastogen in vitro. Chromosomal anomalies were, however, not found in a chick embryo assay and in vivo mouse bone marrow assay.

No information on dermal absorption is available.

This dye (CI 42555, CAS Reg. no 548-62-9, called Gentian Violet) is now being examined in metabolism studies, an oral rat multigeneration study, and oral sub-chronic and chronic studies in rats and mice in the framework of the U.S. National Toxicology Program.

An extensive literature review is available on this substance. Excellent teratogenicity studies have been made and reported.

This substance is highly toxic; the non-toxic daily oral dose is not known, but is less than 0.5 mg/kg b.w. Mutagenic and teratogenic properties have been established. There are indications of teratogenicity in humans. It has been used as an antibacterial and anthelmintic and it has been reported as a cause of epidemic occupational nosebleeds in apple pickers. Certain triphenylmethane-classed dyes, of which this colourant is a member, are animal and human carcinogens. Although Gentian Violet is used extensively in medical practice the Committee came to the conclusion that this substance should not be used as a colourant in cosmetics.

However, the Committee noted that Gentian Violet has therapeutic uses. Industry is to be asked to define the extent to which the toxic compound is present in the mixtures.

Information : - Colipa dossier, April 1984
- NTP 1983
- JECFA (1984) WHO Technical Report Series 710

CI 42735 4,4'Bis (N-ethyl-m-sulfobenzylamino) - 2,2'-dimethyl-4"-(N-diethylamino) triphenylmethane

$C_{43}H_{49}N_3O_6S_2.Na$ CAS N° 6605-30-2
MW : 789

Synonyms : - Acid Blue 104
- C-ext. Blau 14

Very soluble in water and ethanol.

Use level in rinsed off products 0.3%, in non rinsed off products 0.1%.

The oral LD_{50} in rats was $>$ 8 g/kg.

No irritation of the rabbit skin occurred upon treatment with 0.5 g of a 20% aqueous suspension, or with 0.5 g of the undiluted substance.

No irritation of the rabbit eye was seen after application of 0.1 ml of a 20% aqueous suspension, or 0.1 g of the undiluted substance.

A 90-day oral toxicity study in rats, treated with 1 or 2 g/kg b.w./day on 5 days/week by gavage, failed to reveal deleterious effects.

The Committee wishes to see the detailed report of the 90-day study, and to obtain information on possible mutagenic and sensitizing properties.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products.

Information : Colipa dossier

CI 44025 Ethanamium, N-[-4[[4-(diethylamino)-phenyl]-(3,6-disulfo-1-naphthalenyl)-methylene]-2,5-cyclohexadiene-1-yliden]-N-ethyl-hydroxide, inner salt

$C_{31}H_{33}N_2O_6S_2Na$ CAS N° 12768-78-4
MW : 616

Synonym : - Acid Green 16

Moderately soluble in water.

Use level in cosmetics up to 0.01%.

The oral LD_{50} in rats was $>$ 5 g/kg.

A skin irritation test in rabbits with a 50% paste in olive oil produced slight erythema and oedema after a contact period of 24 hours under occlusion both on the intact and abraded skin (mean score 0.8).

In an eye irritation test in rabbits 100 mg of the undiluted substance induced slight redness of the conjunctivae and slight opacity of the cornea (mean score 1).

Results of a well conducted short-term oral toxicity study, a sensitization test and information on genotoxicity are needed to enable an evaluation of the substance.

Information : Colipa dossier

CI 44045 Bis-4,4'-dimethylaminophenyl-4"-phenylaminonaphthyl-carbenium chloride

$C_{33}H_{32}H_3.Cl$ CAS N° 2580-56-5
MW : 506

Synonyms : - Basic Blue 26
- L-ext. Blau 2
- C-WR Blau 8

Soluble in water and ethanol.

Use level 0.1% in rinsed off and non rinsed off cosmetics, and up to 0.5% in hair dye formulations.

Oral LD_{50} values in rats are 1037 and 542 mg/kg.

A primary skin irritation test in rabbits with 100 mg substance applied as a 50% aqueous paste under occlusion induced very slight oedema in 5/6 rabbits which rapidly disappeared. Erythema could not be judged due to the colour of the test substance. Based on oedema only, the substance was considered non irritant. Another primary irritation test on the rabbit skin, with 0.5 ml of a 5% dilution in propylene glycol, did not show any oedema. The treated site of the skin was examined microscopically. No changes were observed.

Application of 100 mg undiluted substance to the rabbit eye produced severe irritation. Dilutions were not examined.

A sensitization test in guinea pigs with 10 topical induction treatments of a 25% aqueous solution and 2 intradermal injections of 0.1 ml Freund's complete adjuvant in a period of 3 weeks, followed (after a 12-day rest period) by a challenge treatment with 0.5 ml of the 25% aqueous solution, did not provoke any sign of sensitization as judged from oedema formation and histopathological examination. Erythema could not be examined due to the colourant.

An adequate short-term oral toxicity study, an Ames test and a chromosomal aberration test should be made.

No opinion can be expressed because a lack of data.

Information : Colipa dossier, April 1984

CI 45100 3,6-di-(N-diethylamino)9-(2',4'-disulfophenyl) xanthyl immonium, inner salt

$C_{27}H_{30}N_2O_7S_2.Na$ CAS N° 3520-42-1
MW : 580

Synonym : Acid Red 52

Soluble in water and ethanol.

Used in rinsed off products up to 0.1%.

The oral LD_{50} in female rats was $>$ 10 g/kg.

Application of 500 mg undiluted substance under occlusion to the intact and abraded skin of rabbits did not induce any skin reaction.

In an eye irritation test in rabbits the undiluted substance was found to be slightly irritating.

Because no information is available on sensitization, genotoxicity or on systemic effects upon oral exposure, evaluation is not possible.

Information : Colipa dossier

CI 45190 3-(2'-methylphenylamino)-6-(2"-methyl-4"-sulfophenyl-amino-9-(2"'-carboxyphenyl)-xanthylimmonium, sodium salt

$C_{34}H_{26}N_2O_6S.Na$ CAS N° 6252-76-2
MW : 613

Synonyms : - Acid Violet 9
- L-ext Violett 2
- C-WR Violett 5
- Ext DC Red no. 3

Soluble in water and ethanol.

Use level : 0.1% in rinsed off and non rinsed off cosmetics.

The oral LD_{50} in rats was $>$ 5 g/kg.

In a skin irritation test in rabbits with 0.75 ml of a 50% aqueous solution, the colourant was found to be slightly irritating. In guinea pigs a 1% aqueous solution was not irritating.

An eye irritation test in rabbits with 100 mg undiluted substance showed moderate irritation. In guinea pigs 0.1 ml of a 1% aqueous solution turned out to be slightly irritating.

In a sensitization test, guinea pigs were treated intracutaneously with 0.1 ml of a 0.1% concentration on 5 consecutive days; The challenge treatment with 0.1 ml of the same concentration four weeks later did not provide evidence of sensitizing properties.

An Ames test, a chromosomal aberration test and an adequate, short-term oral toxicity study are needed for an evaluation. Moreover it is recommended to conduct a maximization test in guinea pigs to demonstrate absence of sensitizing properties.

No opinion can be expressed because a lack of data.

Information : Colipa dossier, August 1983

CI 45220 2,7-Dimethyl-3,6-di (N-ethyl amino) 9-(2',4' disulfophenyl) xanthyl immoniun, innersalt

$C_{25}H_{26}N_2O_7S_2Na$ CAS N° 5873-16-5
MW : 570

Synonyms :
- Acid Red 50
- Amido Rhodamine G Extra
- Sulfo Rhodamine G
- C-wr Rot 16

Soluble in water and ethanol.

Used in rinsed off products up to 0.1%.

The oral LD_{50} in female rats was found to be $>$ 10 g/kg.

Application of 500 mg of undiluted dye to the abraded and non-abraded skin of rabbits did not induce signs of irritation.

Slight irritation of the rabbit eye was observed after application of 100 mg of the undiluted product.

Information is requested on short-term oral toxicity, sensitization and mutagenicity.

No opinion can be expressed because a lack of data.

Information : Colipa dossier

CI 46500 Linear trans quinacridone

$C_{20}H_{12}N_2O_2$ CAS N° 1047-16-1
MW : 238

Synonym : Pigment Violet 19

Insoluble in water, ethanol, oils, ketones and esters.

Use level 0.4% in rinsed off products and 0.003% in non rinsed off products.

Oral LD_{50} values reported for female rats are $>$ 10 g/kg and $>$ 5 g/kg.

A skin irritation test in rabbits with 0.5 g of a slurry of the powder with water under occlusion resulted in only slight irritation, whereas no irritation was reported from a similar rabbit test conducted with 0.5 g of the substance made into a paste with polyethylene glycol 400.

In two eye irritation tests in rabbits, one with 100 mg of the substance as a powder, the other with 100 mg made into a paste with 6 drops polyethylene glycol 400, only minimal changes were observed, which allowed the substance to be classified as not irritating to the eye.

In a short-term oral study, groups of 10 male rats were treated with 500 mg/kg by gavage 14 times in 18 days with various colourants, including CI 46500. No overt signs of toxicity were noticed by examining haematology, urine composition, gross pathology and histopathology of 5 major organs (summary report only).

An Ames test with up to 1 mg/plate was negative.

Information on possible sensitizing properties, and a detailed report on the short-term oral study and a chromosome aberration test are required.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier, August 1983

CI 47000 2-(2-quinolyl)-1,3-indandione

$C_{18}H_{11}NO_2$ CAS N° 8003-22-3
MW : 273

Synonyms : - CI Solvent Yellow 33
- D and C Yellow N° 11
- C-ext Gelb 23

Insoluble in water, soluble in acetone and toluene.

Used up to 0.1% in rinsed off products, 0.05% in products for mucous membranes and 0.5% in non rinsed off products.

Oral LD_{50} in rats $>$ 10 g/kg, in dogs $>$ 1 g/kg, in mice $>$ 20 g/kg.

A skin irritation test in rabbits with 0.2 g dry colour for 4 hours produced only marginal erythema.
Repeated application of 0.1 and 1.0% in white petrolatum or hydrophylic ointment up to 64 applications did not produce more changes than those observed with the vehicles alone.

Application of 50 mg dry colour to the eye of rabbits resulted in slight conjunctivitis in 3/6 animals.

A sensitization test in guinea pigs by 10 intracutaneous injections of 0.1 ml 1.0% suspension in saline, followed by two challenge treatments with the same suspension after 14 and 28 days did not elicit signs of sensitization. However, strong sensitizing properties in guinea pigs have been reported recently (Sato et al. 1984).
In a patch test with one application of 1% in polyethylene glycol conducted in 88 humans, four of them reacted positively. These persons were also known to react positively to a number of other substances.

In a sensitization test in 29 human subjects, 0.0005, 0.001 and 0.002% in 0.5% aqueous soap solution was applied three times weekly for 3 weeks. After a two weeks rest period patches with the same test solutions provoked positive reactions in two subjects with 0.002%, in one with 0.001% and in none of the subjects with 0.0005%.

In a 90-day oral study, the feeding of rats with 0.25, 05, 1.0, 2.0 and 5.0% in the diet resulted in liver enlargement at all feeding levels.

The feeding of one male and one female dog with 2% in the diet for the major part of a 90-day period resulted in slight liver changes including proliferation of bile duct epithelium.

In a 6-week study male rats were fed 0.1-3.0% in the diet. The 3.0% level caused growth depression. Liver enlargement occurred with 0.55, 1.29 and 3.0%. In the top-dose group microscopical changes were seen in the liver, kidneys, spleen, bone marrow and thyroid.

Feeding 0.03, 0.1, 0.3 or 1.0% in the diet of rats for one year resulted in growth depression in males at all levels and in females at 1.0%. Increased liver weights occurred at 0.3 and 1.0%. Microscopic changes, mainly pigment deposition, was seen in the liver with 0.1% and above, in the renal tubules with 0.3 and 1.0%, and in the spleen with 1.0%.

A skin painting study was conducted in mice with a 1% solution in benzene by applying 1 mg of pure dye/mouse/week for 95 weeks.
In males mortality was higher in the test animals than in the vehicle controls. Microscopically the skin showed signs of an irritative effect (epidermal thickening and acanthosis). Tissue masses in the test group were similar to the control group.

Although several feeding studies have been conducted, a no-effect level for systemic toxicity has not been established. This could be lower than 15 mg/kg b.w. Indications of sensitizing effects in humans have been obtained.

The Committee wants information on genotoxic properties, dermal absorption and the establishment of a definitive no effect level.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being in rinsed off products only. The Committee observed that the same substance could be used also in other cosmetic products provided that the microscopic changes associated with pigment deposition were shown to be reversible.

Information : - Colipa dossier, Dec. 1983
- Sato et al., Contact Dermatitis 10 (1984) 30 - 38

CI 50325 1-Methoxy-3-amino-4-sulpho-5-phenyl-7-phenylamino-8,9-(3'-sulphobenzo-1',2') phenazine, sodium salt

$C_{29}H_{22}N_4O_7S_2.Na$ CAS N° 6837-46-3
MW : 624,6

Synonym : Acid violet 50

Soluble in water and ethanol.

Used at levels up to 0.01% in rinsed off products.

The oral LD_{50} in male rats was 10 g/kg.

Application of a 1% aqueous solution to the skin of rabbits did not induce any changes. A similar application to the skin of 5 humans was also negative.
Repeated local application to the rabbit skin of the 1% aqueous solution each 30 seconds for half an hour did not induce any skin reaction.

An eye irritation test in rabbits with 0.05 ml of a 1% aqueous solution rinsed after 30 seconds resulted in slight irritation of the conjunctivae.

No toxicological judgement can be made on the basis of the available data. Information is needed on short-term oral toxicity, genotoxicity and sensitization.

The Committee sees no objection to maintaining the use of this colouring agent for for the time being in rinsed off products only.

Information : Colipa dossier Dec. 1983

CI 50420 Nigrosine

CAS N° 8005-03-6

Synonym : Acid Black 2

Chemical configuration : Sodium salts of sulfonated Nigrosine Spirit soluble (CI 50415)

Soluble in water, and in water/ethanol (50:50), and insoluble in ethanol and acetone.

Used in rinsed off cosmetics 0.3%, in non rinsed off products 0.01%, and in hair colourants up to 2.0%.

The oral LD_{50} in rats was $>$ 4 g/kg body weight. The rats only showed decreased activity and rapid respiration.

In a skin irritation test in rabbits a 5% aqueous solution was not irritating.

An eye irritation test in rabbits with a 5% solution showed only slight reactions of the iris and the conjunctivae which recovered in 3 days. The substance was not considered an eye irritant.

A sensitization test in guinea pigs with 7 topical induction treatments (0.5 ml 2% aqueous solution) and 1 intradermal injection of Freund's adjuvant followed (after 12 days rest) by a challenge treatment with 0.5 ml 2% aqueous solution did not induce oedema or microscopic skin changes (Erythema could not be examined due to the black colour). It was concluded that no sensitization occurred.

Chronic (20-month) skin painting of mice, 3 times weekly with 0.05 ml of 0.15 g % in a semi-permanent hair dye formulation (0.075 mg colourant/mouse) did not induce significant changes in the type or incidence of tumours.

No mutagenic activity was observed in a plate incorporation assay and in a liquid preincubation assay with S.typhimurium strains at concentrations up to 5 mg/plate and 0.5 mg/plate respectively. In a chromosome aberration test on Chinese hamster ovary cells no significant increase in the number of breaks per metaphase were observed.

No information on systemic toxicity is available. A short-term oral study is, therefore, needed.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier, April 1984

CI 51319 8,18-Dichloro-5,15-diethyl-5,15-dihydro-di-indolo-(3,2-B:3',2'-M-triphenodioxazine)

$C_{34}H_{22}Cl_2N_4O_2$ CAS N° 6358-30-1
MW : 589

Synonym : Pigment Violet 23

Insoluble in water, oils, fats and waxes.

Used up to 0.1% in rinsed off products.

The oral LD_{50} in rats and mice was $>$ 10 g/kg.
The dermal LD_{50} in rats was $>$ 5 g/kg.

A skin irritation test in rabbits with 0.5 g undiluted pigment did not induce any skin changes.

In an eye irritation test in rabbits with 100 mg undiluted colourant, only redness of the conjunctivae occurred in 2/6 rabbits if the eye was not washed, and also in 2/6 rabbits if the eye was washed.

In a short-term oral study rats received 0.5 g/kg b.w. by gavage 28 times in 43 days. There were no changes in haematology, urine examination or in the results of gross and microscopic examination (Summary report only).

Information on sensitization and genotoxicity is needed. In addition more detailed results of a short-term oral toxicity study should be provided.

No opinion can be expressed.

Information : Colipa dossier, 19th June 1984

CI 59040 4-Hydroxy-1,6,9-trisulfopyrene trisodium salt

$C_{16}H_{10}O_{10}S_3.3Na$ CAS N° 6358-69-6
MW : 524

Synonyms : - D & C Green 8
- Solvent Green 7
- C-ext Gelb 24

Soluble in water, slightly soluble in ethanol.

Use level : 0.2% for rinsed off and not rinsed off products.

The oral LD_{50} in rats was 16 g/kg, in mice 10.5 g/kg.
The intravenous LD_{50} in mice was 1.05 g/kg.

Skin irritation tests in rabbits with 0.5 g powder, 0.5 ml of a 30% aqueous solution or 0.5 ml of a 3% aqueous solution were negative.

Eye irritation tests in rabbits with 0.1 g powder, 0.1 ml of a 30% aqueous solution, or 0.1 ml of a 3% aqueous solution did not reveal any irritation.

In a two year study 50 male mice were skin painted twice a week with 2.5 mg substance (0.05 ml of a 5% solution) for 1 1/2 year. After 2 years no skin tumours were observed nor other symptoms of toxicity. In another mouse study 3.5 mg (0.05 ml of a 7% aqueous solution) was applied to the skin once weekly for 2 years. One mouse out of 60 developed a benign skin tumour (fibroma) near the application site. No control group was used in this study (summary only).

A 90 day toxicity study was conducted in rats with 3-hydroxy-5,8,10 trisulfopyrene trisodium salt (Pyrene) fed at dietary levels of 100, 1000 and 10.000 ppm. Growth was slightly retarded in males of the high-dose group. There were no treatment-related changes in haematology, clinical chemistry of blood and urine, organ weights, or in the gross and microscopic pathology. The level of 50 mg/kg body weight/day was considered a no-toxic effect level.

No information is available on possible sensitizing properties.

The available data may justify the use of this colouring agent in cosmetic products, if information on the absence of sensitizing properties is available.

Information : Colipa dossier and Chemline

CI 60724 1-Hydroxy-4-N-phenylamino-anthraquinone

$C_{20}H_{13}NO_3$ CAS N° 19286-75-0
MW : 315

Synonym : Disperse Violet 23.27

Insoluble in water.

The commercial colour contains about 60% of the pure substance. The remaining 40% are dispersing agents, binders and protective colloids. The substance is used in rinsed off cosmetics up to 0.20%, i.e. 0.35% of the commercial product.

The oral LD_{50} of the commercial product in rats was $>$ 5 g/kg.

An irritation test in rabbits with 0.5 g mixed with water on the intact and abraded skin under occlusion showed slight to very slight oedema in 3/6 animals. The substance was classified "non-irritant".

An eye irritation test in rabbits with 61 mg of the product only evoked some redness of the conjunctivae in all test animals. The substance was classified as "non-irritant".

Because no information is available on sensitization, genotoxicity and systemic effects upon oral exposure no evaluation is possible.

Information : Colipa dossier

CI 60730 1-N-(2'-sulfo-4'-methylphenylamino)-4-hydroxy-anthraquinone, sodium salt

$C_{21}H_{15}NO_6S.Na$ CAS N° 4430-18-6
MW : 431

Synonyms : - Acid Violet 43
- Ext. D and C Violet N° 2

Soluble in water and ethanol.

Use level 0.3% in rinsed off cosmetics, 0.1% in non rinsed off products, and up to 0.2% in temporary hair colourants.

Oral LD_{50} values are $>$ 4640 mg/kg for male rats, and $>$ 2000 mg/kg in dogs.

In a skin irritation test in rabbits with 0.5 ml 1% solution in propylene glycol erythema could not be judged due to the colourant. Microscopically no pathological dermal changes were observed.

In an eye irritation test in rabbits 0.2 ml of a 1% dilution in water/propylene glycol (50:50) was slightly irritating.

A sensitization test in guinea pigs was carried out by an induction treatment with 7 successive topical applications of 0.5 ml 1% in propylene glycol in 2 weeks and 0.1 ml Freund's complete adjuvant injected intradermally on day 0. The challenge treatment was made after a 12 days rest, by topical application of 0.5 ml 1% solution in propylene glycol for 48 hours. No sensitization reactions were observed grossly or microscopically.

In a 3-week dermal test, guinea pigs received daily 0.5 g/kg b.w. of a 0.1% or a 1.0% preparation in USP hydrophilic ointment (up to 5 mg/kg b.w.), 5 times/week. No significant changes were observed in appearance of the application sites or in survival, weight gain, weights of liver and kidneys, or in the histology of skin, kidneys and liver.

In a 13-week dermal study, rabbits were treated with 0.5 g 0.1%, or 1.0% in USP hydrophylic ointment (or $\leq$ 2 mg/kg b.w.) on 5 days/week. No skin erythema or oedema developed. There were no significant effects on weight gain or on the weights of the liver or kidneys, and no changes were observed microscopically in the skin, kidneys or liver.

Mice were skin painted with c. 27 mg colourant/kg b.w. as 1% in propylene glycol once weekly for 102 weeks. No adverse effects were observed on survival, or on incidence of tumours or leukaemia.
In a second chronic dermal study, mice were skin painted three times weekly with 50 mg of 0.15% in a hair dye formulation (1.5 mg/kg/b.w.). No treatment related effects were observed.

An Ames test conducted as a plate incorporation assay and as a spot test (with up to 400 µg/plate) was negative. Another Ames test was also negative.

Information is required on short-term oral toxicity to determine the no-effect level. Genotoxicity information from a chromosomal aberration study is needed.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier, March 1984

CI 61554 1,4-Bis(N-n-butylamino)anthraquinone

$C_{22}H_{26}N_2O_2$ CAS N° 12769-17-4
MW : 350

Syonyms : - Solvent Blue 35
- C-ext Blau 12

Soluble in organic solvents, insoluble in water.

Use level up to 0.1% in rinsed off and non rinsed off products.

The oral LD_{50} in rats was 4.35 g/kg b.w.

No skin irritation was seen in rabbits treated on the intact and abraded skin with 0.5 g of a 50% aqueous suspension, or with 0.5 g of the undiluted product.

An eye irritation test in rabbits was negative.

In a 90 day toxicity study, rats received first 0, 1000 or 2000 mg/kg b.w. and later 0, 25, 50 or 100 mg/kg b.w./day by gavage on 5 days/week. With 100 and 50 mg/kg high mortality occurred. There was growth depression, decreased food intake and anaemia in alle treatment groups. At autopsy increased weights of liver and kidneys were found.
Histopathological changes occurred in liver, kidneys, intestine, lungs and heart. The no-effect level was lower than 25 mg/kg. The authors of the summary report (Ivankovic and Preussman) discourage the use of this colouring owing to its toxic properties.

In a skin penetration test in human volunteers no diffusion or absorption of the colouring could be established.

In view of the high systemic toxicity and the absence of a no toxic effect level the Committee recommends not to use this colouring for cosmetics.

Information : Colipa dossier

CI 61585 1,4-Bis-(2',4',6'-trimethyl-3'-sulfophenylamino)-anthraquinone

$C_{32}H_{30}N_2O_8S_2.2\ Na$ CAS N° 4474-24-2
MW : 678

Synonyms : - Acid Blue 80
- Iragon Blau L-UD

Soluble in water and ethanol.

Used up to 0.02% in rinsed off products.

The oral LD_{50} in rats was $>$ 15 g/kg.

Application to the skin of rabbits under occlusion in an amount of 500 mg moistened with water produced minimal irritation.

An eye irritation test in rabbits with 100 mg undiluted substance resulted in moderate irritation. Rinsing the eyes hardly affected the results.

Information is needed on short-term oral toxicity, sensitization, and genotoxicity.

The Commitee sees no objection to maintaining the use of this colouring agent for the time being in rinsed off products only.

Information : Colipa dossier Dec 1983

CI 62045 1-Amino-4-cyclohexylaminoanthraquinone-2-sulfonic acid, sodium salt

$C_{20}H_{19}N_2O_5S.Na$ CAS N° 4368-56-3
MW : 422

Synonym : Acid Blue 62

Soluble in water (50 g/l).

Use level 0.01% in rinsed off cosmetics, and up to 0.5% in semi-permanent and temporary hair colouring products.

Oral LD_{50} values are $>$ 5 g/kg in rats in two studies and 11.7 g/kg in a third rat study.

Skin irritation tests in rabbits with 0.5 g suspended in olive oil induced oedema; with 0.75 ml of a 1:1 mixture with water slight erythema and slight oedema occurred, but with 0.5 ml of a 1.5% aqueous solution no changes were observed microscopically.

In an eye irritation test in rabbits 100 mg of the substance caused moderate irritation. In another eye irritation test a 1.5% aqueous solution was found to be slightly irritating.

In a sensitization test, guinea pigs were injected intradermally with 0.1 ml 5% concentration in saline at 4 sites for induction. The challenge treatment after 14 days with a 2% concentration in saline was negative in all animals. Then the induction treatment was repeated and the challenge applied again after 14 days. No positive reactions were obtained.

A modified maximization test was conducted by topical application of 0.3 g colourant as such 10 times in 3 weeks. Two weeks later, the challenge with 0.5 ml 25% aqueous solution did not evoke any positive reaction as observed grossly and microscopically.

A 90-day oral study was conducted in rats by daily intubation of 150 mg/kg b.w. There were statistically significant differences in haematological values between test and control animals. In males SGPT was increased and bilirubin and SAP were decreased. All values were stated to be within the range published for the species. The relative weights of the ovaries, adrenals and pituitary were decreased in females. It is stated that the test animals did not show any gross or microscopic abnormality.

In a 20 months skin painting study in mice 0.05 ml 0.2% in a formulation (2 mg colourant/kg b.w.) was applied three times weekly. About 75% of the test and control animals died before week 88. The examinations included weight gain, urinalysis, haematology, organ weights and histopathology. There were no effects which were attributed to treatment.

An Ames test and a chromosomal abberration test should be made. A short term oral toxicity test should be made at doses sufficiently high to demonstrate a possible effect.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Colipa dossier, March 1984

CI 71105 (Trans)-naphthyl-1,5-dicarbonyl-4,8-dibenzimidazole

$C_{26}H_{12}N_4O_2$ CAS N° 4424-06-0
MW : 412

Synonyms : - C-ext Orange 14
- Vat Orange 7
- Pigment Orange 43

Insoluble in water, acetone, or ethanol.

Use level : 0.5% in rinsed off products; 0.02% in non rinsed off products.

The oral LD_{50} in rats and mice was $>$ 10 g/kg.

A skin irritation test with the pure colour applied to the intact and abraded rabbit skin showed only very slight irritation.

An eye irritation test in rabbits with 100 mg of dry colour was negative.

In a 90-day feeding study in rats with 1.0 and 5.0% of the colouring in the diet no changes were observed in growth rate or in blood and urine examinations, or in gross and microscopic pathology of 5 organs (summary report only).

In view of its low systemic toxicity upon oral administration it seems justified for the time being to accept the use of this colouring agent. However, information is requested on possible sensitizing and mutagenic properties. In addition the Committee wants to examine the detailed report on the 90-day study.

Information : Colipa dossier

CI 73312 Benzo(b)thiophen-3(2H)-one,4,7-dichloro-2-(4,7-dichloro-3-oxobenzo(B)thien-2(3H)-ylidene

$C_{16}H_4Cl_4O_2S_2$ CAS N° 14295-43-3
MW : 434

Synonym : Pigment Red 88

Insoluble in water.

Used in soaps up to 0.002%.

The oral LD_{50} in rats is $>$ 5 g/kg.

In a skin irritation test in rabbits 0.5 g of pigment in 2 ml olive oil applied under occlusion to the intact and abraded skin for 24 hours induced slight oedema but no erythema.

An eye irritation test in rabbits with 100 mg of the undiluted colour revealed slight to moderate redness and slight swelling of the conjunctivae.

Information is requested on short-term oral toxicity, sensitization and genotoxicity.

No opinion can be expressed because a lack of data.

Information : Colipa dossier

CI 73905 Liniary trans 3,10-dichlorochinacridon

$C_{20}H_{10}O_2N_2Cl_2$ CAS N°
MW : 381

Synonym : PV-Echt-Rot EG

Insoluble in water and organic solvents.

Used in soaps at 0.01 - 0.03%.

The oral LD_{50} was $>$ 15 g/kg if administered as a 25% suspension in sesame oil.

Topical treatment of rabbits with 0.5 ml of a 10% dilution, daily for 5 days, did not cause skin irritation. Intracutaneous injection of rabbits with 0.02 ml of a 10% suspension induced necrosis at the injection site. This effect did not occur with concentrations of 5% or less.

Eye irritation did not occur in rabbits by applying 0.1 ml of 10% or 5% dilutions.

A sub-acute (30-day) feeding study was conducted in rats with 0, 0.2, 1.0 or 5% in the diet. There were no adverse effects on growth rate, food intake, haematology or urine composition. Organ weights and microscopical examination revealed no treatment-related changes.

Information on possible mutagenic and sensitizing properties is requested.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : Report Farbwerke Hoechst AG 1971

CI 73915 2,9, Dimethyl-7,14-dioxo-5,7,12,14-tetrahydroquino-2,3,6-acridine

$C_{22}H_{16}N_2O_2$ CAS N° 980-26-7
MW : 340

Synonyms : - Pigment Red 122
- trans-Quinacridone

Insoluble in most common solvents.

Use level 0.1% in rinsed off products.

The oral LD_{50} in female rats was $>$ 5 g/kg. No mortality or signs of intoxication were noted in female rats after stomach intubation of 25% soap solution with 0.015% of the colour at a dose of 10 g soap/kg. The acute dermal toxicity (LD_{50}) in guinea pigs was $>$ 3 g/kg.

Rabbits topically treated with 0.5 ml of an aqueous slurry of the colour showed slight skin irritation. No adverse dermal effect occurred in guinea pigs after daily immersion in a 0.5% aqueous solution for 3 days.

No eye irritation was noted in rabbits upon treatment with 100 mg powder. The minimal irritation observed with 0.1 ml of an 8% soap solution containing 0.015% of the colour was attributed to the alkaline properties of the soap.

A maximization test in guinea pigs, with 33% in petrolatum for induction, and 2 and 1% concentrations for the challenge treatment, did not provide evidence of sensitization.

An Ames test with up to 1000 µg/plate was negative.

Because no information on systemic effects is available an evaluation is not possible. Results of a short-term oral toxicity study are requested as well as further information on the solubility of this subsance.

Information : Colipa dossier

CI 74100 Phthalocyanine, metal free

$C_{32}H_{18}N_8$
MW : 512

CAS N° 574-93-6

Synonyms : - C-ext Blau 10
- L-ext Blau 5

Insoluble in water, ethanol and ether.

Used in rinsed off cosmetics at 0.5%.

The oral LD_{50} in rats was > 6 g/kg.

A skin irritation test in rabbits with 0.5 g on the intact and abraded skin under occlusion did not induce any local reaction.

In an eye irritation test with 0.1 g of the test substance slight to moderate changes of the cornea and conjunctivae were observed in 2/3 rabbits. No changes were seen, however, in 3 other rabbits which had the treated eye rinsed with water 30 seconds after application of the colourant. The results indicate slight eye irritating properties.

Information is needed on short-term oral toxicity, sensitization and genotoxicity.

Long-term oral studies in rats and mice were started by NCI.

No opinion can be expressed because a lack of data.

Information : Colipa dossier

CI 74160 Copper ($_{29}H,_{31}H$-phthalocyaninato(2-)$N_{29},N_{30},N_{31},N_{32}$)

$C_{32}H_{16}CuN_8$ CAS N° 147-14-8
MW : 576

Synonyms : - Pigment Blue 15
- C ext Blue 10

Insoluble in water, alcohol and most conventional solvents; soluble in dimethyl formamide + 2% phosphoric acid.

Use level 0.6% both in rinsed off, and non rinsed off cosmetics, and 1.0% in temporary hair preparations.

Oral LD_{50} values for rats are $\geq$ 4.6, $\geq$ 5.6 and $\geq$ 10 g/kg.

Skin irritation tests in rabbits with 0.5 g, or with 0.5 ml of a 46% dispersion produced slight, or slight to moderate erythema and oedema. With 100 mg undiluted dye, or with 0.1 ml 25% or 50% in physiological saline solution no irritation occurred.

An eye irritation test in rabbits with 100 mg of a 46% dispersion (vehicle not mentioned) produced slight opacity with damage to the surface epithelium in 2/6 rabbits. In another test with 100 mg dye, or 100 mg 25 or 50% suspension in water no changes were observed. In a third test with the dye (applied as Viscoblau BL Teig) dulling of the cornea and mild conjunctival reactions were seen in 3/6 rabbits; the total score resulted in the classification : "non irritant".

A sensitization test in guinea pigs with induction treatment by intracutaneous injections of a 0.1 ml 1% aqueous solution 3 times/day for 5 days, and topical challenge treatment with 0.1 ml 1% aqueous solution after 4 weeks was negative.

In a sensitization test, guinea pigs received intracutaneous injections of 0.1 ml 1% aqueous solution, 3 times daily for 5 consecutive days. After a rest period of 4 weeks 0.1 ml 1% aqueous solution administered again intracutaneously produced a slight positive reaction in 5/15 test animals.

In a 90-day oral study groups of 10 rats/sex were treated by gavage with 0, 1 or 2 g/kg b.w./day, 5 times a week. No changes were observed in condition and behaviour, growth rate, haematology, urinalysis and serum biochemistry. No gross abnormalities were observed at autopsy. Microscopic examination of c. 10 internal organs was negative. (Only a 2-page summary report is available).

A repeated s.c. injection test was conducted in 20 mice which received 0.5 mg of the dye once a week for 34 weeks. No tumours developed at the injection site.

In an Ames test with the S.typhimurium strains TA 1538 and 1535, 1 µg of the dye/plate did not increase the number of revertants. Chalks containing copper phthalocyanine exhibited marked mutagenic activity in the Ames test. This property could be removed by purification.

Further information is needed on sensitization and genotoxicity. The necessity of purity criteria is clear from the positive results with impure material in the Ames test.

The Committee sees no objection to maintaining the use of this colouring agent in cosmetic products for the time being.

Information : - Colipa dossier, June 19th, 1984
- Mutation Research 12 (1983) 1 - 7

CI 74180 Di-sodium sulfonate of copper phthalocyanine

$C_{32}H_{14}CuN_8O_6S_2.2Na$ CAS N° 1330-38-7
MW : 780

Synonyms : - C-ext Blau 10
- Direct Blue 86

Soluble in water; slightly soluble in ethanol.

Use level 0.1% both in rinsed off-, and non rinsed off cosmetics.

Oral LD_{50} values in rats were > 5000 mg/kg in two tests.

Repeated application of a 10% aqueous suspension to the skin of mice (twice daily for 5 days) did not evoke any signs of irritation.

An eye irritant test in rabbits with 0.05 ml of a 5% aqueous suspension produced only slight redness of the conjunctivae.

In a sub-acute study in rats 1000 mg/kg b.w. was administered by gavage daily on 22 days during a 30-day period. From the green-blue discolouration of the urine it appeared that intestinal absorption occurred. There were no changes in haematological or blood biochemical parameters. Urine composition remained normal. The kidneys showed blue discolouration and increased weights, not accompanied by microscopical changes.

The Committee wishes to see the results of a sensitization test, and information on genotoxic properties.

The Committee sees no objection to maintaining the use of this colouring agent for the time being in rinsed off products only. For non rinsed off products, no opinion can be expressed. In this case, the Committee requires a dermal penetration test in vitro or in vivo. If penetration is considerable, a short-term oral study is required to establish the no effect level.

Information : - Colipa dossier, February 1984

CI 75660 3,5,7,2',4'-pentahydroxyflavone

$C_{15}H_{10}O_7$ + 1 or $2H_2$ CAS N° 480-16-0
MW : 302 (anhydrous)

Synonyms : - C-WR Gelb 15
- Natural Yellow 8

Slightly soluble in water (0.025%), highly soluble in ethanol.

Use level 0.01% in rinsed off products.

The oral LD_{50} in male mice was 6.3 g/kg.

A skin irritation test in 2 rabbits with repeated application of a 5% mixture with water (each 30 seconds for 1/2 hour at the same site) did not induce any skin reaction. A similar test in 5 humans was likewise negative. A patch test in 5 humans was conducted also with a 5% mixture with water during 24 hours. No changes were seen.

An eye irritation test in rabbits was conducted with 50 µl of a 5% aqueous suspension. After 30 seconds the eye was washed with water. There were no changes up to 24 h after treatment.

Because no information is available on sensitization, mutagenicity or systemic effects, an evaluation is not possible.

Information : Colipa dossier, August 1983

CI 77019 Aluminium Potassium Silicate

$KAl_2(AlSi_3O_{10})(OH)_2$ CAS N° 12001-26-2

MW : 399

Synonyms : - CI Pigment White 20
- CI Pigment White 26
- Mica
- Punice Muscovite Mica

Insoluble in all liquids used in cosmetics.

Use level in cosmetics for mucous membrane areas 50%, for non-rinsed products 67%, for rinsed off products 2%.

The oral LD_{50} in rats was $>$ 5 g/kg when administered as a 20% suspension in corn oil. The LC_{50} in an acute inhalation toxicity study for 1 hour was $>$ 200 mg/litre.

A skin irritation test in rabbits with 0.5 g of the undiluted product did not elicit any skin reactions.

When applied as such to the eye of rabbits no changes were observed.

Because no information is available on short term oral toxicity, sensitization and mutagenicity the substance cannot be evaluated.

Information : Colipa dossier

CI 77163 Bismuthoxychloride

Cl-Bi = 0 CAS N° 7787-59-9

MW : 260

Synonyms : - C-Weiss 10
- Pearl White 14

Insoluble in water.

Use level in contact with the eyes 80%, in contact with mucous membranes 30%, in rinsed off products 50%, in non rinsed off products 20%.

Reported values for the oral LD_{50} in rats are $>$ 37.5 g/kg, $>$ 21.5 g/kg, and $>$ 10 g/kg.

Treatment of abraded and intact rabbit skin with 0.5, 1.0, or 2.0 ml of a 50% aqueous slurry/kg body weight for 24 hours produced slight erythema and desquamation in some animals but no tissue alterations.

In an eye irritation test in rabbits with 100 mg of the compound only very slight reactions were seen, while with 0.1 ml of a 1% aqueous suspension applied daily for 10 days no irritation was observed.

No sensitization occurred in guinea pigs with 0.5 ml of a 0.1% suspension in saline. In a repeated insult patch test with 60 human subjects no irritation or sensitization was observed after 9 applications followed by a challenge treatment.

In a 90-day oral study in rats daily dosing by gavage with 0.25, 1.0 or 5 g/kg b.w. as an aqueous suspension did not result in deleterious effects.

Rats have been fed on diets with 0, 1, 2 or 5% of the colouring for 2 years. Neither carcinogenic activity nor other toxic effects due to treatment were observed (1).

In view of the very high concentrations in cosmetics, the Committee wants to know whether repeated use of such products is well tolerated.

The available data justifies the use of this colouring agent in cosmetic products.

Information : Colipa dossier
(1) Fd. Cosmet. Toxicol. 13 (1975) 543-544

CI 77288 Chromic oxide

Cr_2O_3 CAS N° 1308-38-9

MW : 152.02

Synonyms : - Pigment Green 17
- Chromium sesquioxide

Insoluble in water and organic solvents.

Use level up to 50%.

The oral LD_{50} for male rats was $>$ 5 g/kg.

The acute dermal LD_{50} in rabbits was $>$ 3.5 g/kg.

Slight skin irritation occurred in rabbits upon treatment of the abraded and non-abraded skin with the pure substance moistened with water to a paste.

Slight eye irritation was found in rabbits with 100 mg of the dry powder or 0.1 ml of a 50% aqueous suspension. Daily treatment of the rabbit eye with 0.02 ml 5% suspension (5 times/week for 4 weeks) did not induce significant irritation.

No-sensitizing properties were observed with 0.1 ml of a 0.1% aqueous suspension tested in guinea pigs by the Landsteiner method.

A 90-day rat feeding study with 2 and 5% in the diet revealed no pathological changes although there was a dose-related decrease in the weights of the liver and spleen.

In a 2 year feeding study with 1.0, 2.0 and 5.0% chromic (III) oxide in the diet of groups of 60 male and female rats no toxic or carcinogenic effects were observed. During the study a few females were mated with males of the same diet group. Fertility, gestation period and litter size were normal and the pups showed no malformations.

Chromium (III) compounds are much less toxic than chromium (VI) compounds. While several chromium (VI) compounds have been shown to be mutagenic, carcinogenic and teratogenic, no such evidence exists for chromic oxide. Chromium (III) compounds are not mutagenic, which agrees with the negative findings in the long-term rat study with very high feeding levels.

In an epidemiological study of employees of a ferrochromium plant exposed simultaneously to Cr (III) and Cr (VI) in an average ratio 10:1 no increased risk of cancer mortality or incidence was observed.

It seems justified to accept the continued use of this colouring agent provided that contamination of Cr (III) by Cr (VI) is prevented. Therefore the purity of the colouring used should meet te requirements of the existing specifications.

Information : - Colipa dossier
- IARC Monograph Vol. 23(1980) 205-323

CI 77289 Chromium oxide hydrated

$Cr_2O_3.2H_2O$ or $Cr_2O(OH)_4$ CAS N° 12001-99-9

MW : 188

Synonyms : - Pigment Green 18
- Chromium Hydrate Green
- Permanent Green
- Hydrated chromium sesquioxide

Insoluble in water.

This substance is an inner hydrate of chromium oxide CI 77288. The water of hydration may be removed by temperatures above 200 - 300 °C. It is therefore less heat resistant than the chromium oxide (CI 77288). Both products differ in colour properties.

Since it may be expected that the toxicological properties of the hydrated and non-hydrated form of chromium oxide are very similar.

The Committee sees no objection to maintaining the use of this substance in cosmetic products.

Acid red 195 4-(2'-oxo-4'sulphonaphthylazo)-1-phenyl-3-methyl-5-oxo-pyrazole, chromiumcomplex(1/1)monosodiumsalt

$C_{20}H_{13}CrN_4O_5.SNa$ CAS N° 12220-24-5
MW : 496

Soluble in water (30 g/l).

Used up to 0.03% in rinsed off cosmetics and up to 0.02% in non rinsed off products.

The oral LD_{50} in rats was > 7 g/kg.

A primary skin irritation test with a 50% concentration in a mixture of propylene glycol and saline (70:30) did not evoke any erythema or oedema. Application of 0.1% in yellow soft paraffin to the skin of 50 dermatitis prone subjects in a 48 hour-closed patch test did not induce any degree of positive reaction.

In an eye irritation test in rabbits with 0.1 g of the colourant no changes of the cornea, iris or conjunctivae were observed.

Information is required on sensitization, on genotoxicity and on short term oral toxicity. The Committee also requests information on the incidence of deleterious effects (Stevens-Johnson syndrome) in patients using pyrazole containing drugs which are also exposed to cosmetics containing this colourant (cf. CI 18820, 19120, 21110, 21115).

No opinion can be expressed because a lack of data.

Information : Colipa dossier, April 1984

Bromothymol blue 3,3'-dibromothymolsulfophthalein

$C_{27}H_{28}Br_2O_5S$ CAS N° 76-59-5
MW : 624

Sparingly soluble in water, soluble in ethanol.

Use level 0.1% in rinsed off products.

The oral LD_{50} in male mice was $>$ 19.9 g/kg.

No skin irritation was observed in 5 test persons patch tested with a 1% suspension in carboxymethylcellulose.

In an eye irritation test in rabbits with 1% aqueous suspension slight redness of the conjunctivae was the only reaction observed.

Information is requested on short-term oral toxicity, genotoxicty and sensitization.

The Committee sees no objection to maintaining the use of this colouring agent, for rinsed off products only.

Information : Colipa dossier, February 1984

Bromocresol Green 3,3'5,5'-Tetrabromo-m-cresolsulfonphthaleine

$C_{21}H_{14}Br_4O_5S$ CAS N° 76-60-8
MW : 724

Soluble in ethanol, sparingly soluble in water.

Used in rinsed off products up to 0.05%.

The oral LD_{50} in male mice was > 17.9 g/kg body weight.

A 1% aqueous suspension did not cause eye irritation in rabbits.

No skin irritation occurred in an occlusive patch test in 5 persons with 1% suspension in aqueous CMC solution.

An Ames test with and without metabolic activation was negative.

Further information is requested on genotoxic properties. In addition a sensitization test should be conducted and a short-term oral toxicity study in which also possible accumulation of Br in the tissues is examined.

No opinion can be expressed.

Information : - Colipa dossier, March 1982
- Submission II by Colipa, August, 1983

PART 2

LIST OF COLOURING AGENTS PROVISIONALLY ALLOWED WHICH MAY BE CONTAINED IN COSMETIC PRODUCTS INTENDED TO COME INTO CONTACT WITH THE MUCOUS MEMBRANES IN ACCORDANCE WITH ARTICLE 5 (1) (2) (3)

(a) Reds

Reference number	Colour index number	Colouring agent number according to the EEC Directives of 1962 concerning food colouring matters or other indications (4)	Restrictions		
			Field of application	Maximum concentration authorized	Purity conditions (4)
1	12 120				
2	12 350				
3	12 385				
4	14 700		r		
5	15 500 15 500(Ba)		Use of Basalts prohibited in lipsticks		
6	15 585(Ba)				
7	15 620				
8	15 800				
9	16 035				
10	26 100				
11	27 290				
12	45 160				
13	75 480				
14	75 580				

(b) Oranges and yellows

1	18 965				
2	45 340				
3	47 000		r		

(1) These colouring agents may also be used in cosmetics coming into contact with other parts of the body.

(2) For certain colouring agents, restrictions are provided which may relate to the field of application of the colouring agent (the letter 'r' in the column of restrictions relating to the field of application signifies that the colouring agent is prohibited in the manufacture of cosmetic products which can come into contact with the mucous membranes of the eye, especially eye make up and eye make-up removers) or to the maximum authorized concentration.

(3) Lakes or salts of these colouring agents using substances not prohibited under Annex II or not excluded under Annex V from the scope of the Directive are equally allowed.

(4) Colouring agents whose number is preceded by the letter 'E' in accordance with the EEC Directives of 1962 concerning foodstuffs and colouring matters must fulfil the purity requirements laid down in those Directives.

(c) **Greens and blues**

Reference number	Colour index number	Colouring agent number according to the EEC Directives of 1962 concerning food colouring matters or other indications	Restrictions		
			Field of application	Maximum concentration authorized	Purity conditions
1	42 040				
2	42 140				
3	42 170				
4	42 735				
5	44 040				
6	44 045				
7	59 040				
8	61 554				
9	62 085				
10	77 288				Free from chromate ions
11	77 289				Ditto
12	77 520				
13	74 160				

(d) **Violets, browns, blacks and whites**

1	20 170				
2	27 755	E 152			E 152
3	42 580				
4	45 190				
5	77 019				
6	77 163	Bismuth chloride oxide (and its mixtures with mica)			
7	77 265				
8	77 718				

PART 3

(A) LIST OF COLOURING AGENTS PROVISIONALLY ALLOWED FOR COSMETIC PRODUCTS WHICH DO NOT COME INTO CONTACT WITH THE MUCOUS MEMBRANES

Reds

12310, 12335, 12420, 12430, 12440, 16140, 16155, 16250, 17200, 18000, 18050, 18055, 18065, 26105, 45100, 50240, E121

Oranges and yellows

11680, 11710, 13065, 15575, 16230, 18690, 18736, 18745, 19120, 19130, 21230, 71105

Blues and greens

10006, 10020, 42045, 42050, 42080, 42755, 44025, 62095, 62550, 63000, 71255, 74100, 74220, 74350, αα-bis(5-bromo-4-hydroxy-6-methyl-*m*-cumenyl)toluene-2, α-sultone, ααbis(3,5-dibromo-4-hydroxy-*o*-tolyl)toluene-2, α-sultone, 1,4-bis(butylamino)anthraquinone

Violets, browns, blacks and whites

12010, 12196, 12480, 16580, 27905, 42555, 42571, 43625, 46500, 51319, 61710, 61800, sodium 2,4-diamino-azobenzenesulphonate and five related colouring agents (Brown FK), α-(5-bromo-6-hydroxy-*m*-tolyl)-α-(3-bromo-5-methyl-4-oxocyclohexa-2,5-dienylidene)toluene-2-sulphonic acid

(B) LIST OF COLOURING AGENTS PROVISIONALLY ALLOWED FOR COSMETIC PRODUCTS WHICH COME INTO CONTACT ONLY BRIEFLY WITH THE SKIN

Reds

11210, 12090, 12155, 12170, 12315, 12370, 12459, 12460, 13020, 14895, 14905, 16045, 16180, 18125, 18130, 24790, 27300, 27306, 28160, 45220, 60505, 60710, 62015, 73300

Yellows and oranges

11720, 11725, 11730, 11765, 11850, 11855, 11860, 11870, 12055, 12140, 12700, 12740, 12770, 12790, 13900, 14600, 15970, 15975, 18820, 18900, 19555, 21090, 21096, 21100, 21108, 21110, 21115, 22910, 25135, 25220, 26090, 29020, 40215, 40640, 41000, 45376, 47035, 48040, 48055, 56205, 4-(3-chlorphenylazo)-3-hydroxy-2 naphth-*O*-anisidide, trisodium 3-hydroxypyren-5,8,10-trisulphonate

Blues and greens

10025, 26360, 42052, 42085, 42095, 42100, 50315, 50320, 50400, 50405, 51175, 52015, 52020, 52030, 61505, 61585, 62045, 62100, 62105, 62125, 62130, 62500, 62560, 63010, 64500, 74180

Violets, browns, blacks and whites

12145, 14805, 15685, 17580, 20285, 20470, 21010, 25410, 30045, 30235, 40625, 42510, 42520, 42525, 42535, 42650, 48013, 57020, 60730, 61100, 61105, 61705, 62030, 63165, 63615

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