

Colouring Agents

Colouring agents have long been used in foods and cosmetics in an attempt to improve the appearance of the product or subject. They are also used in medicinal preparations for several reasons. These include improving their acceptability to patients, giving drug formulations a distinctive appearance to help identification and prevent counterfeiting, and increasing the stability of light-sensitive drugs. This chapter describes colouring agents used in medicines and some used in foods, cosmetics, and some medical devices including contact lenses. Most countries restrict the nature and extent of colouring agents used for such purposes. Matters of concern that have received considerable publicity include sensitivity reactions (see Tartrazine, p.1473) and hyperactive behaviour in children (see below).

Colouring agents can be broadly categorised into synthetic dyes and into natural agents (such as canthaxanthin, caramel, carmine, chlorophyll, cochineal, saffron, and turmeric, all of which are described in this chapter). Other compounds that may be used as cosmetic colours or food colours (and which are themselves natural pigments of foodstuffs) are anthocyanins (E163) and carotenoids. In this latter group are included bixin and norbixin which are obtained from annatto, capsanthin (E160c) which is an extract of paprika, carotenes (E160a) (see Betacarotene, p.1930), lycopene (E160d), beta-apo-8'-carotenal (E160e), and the ethyl ester of beta-apo-8'-carotenoic acid (E160f); lutein (E161b), like canthaxanthin, can be classified either as a carotenoid or as a xanthophyll.

Other agents described elsewhere in *Martindale* that may be used as food colours include aluminium (p.2254), gold (p.2316), indigo carmine (p.2324), patent blue V (p.2363), riboflavin (p.1977), silver (p.2387), and titanium dioxide (p.1617).

Hyperactivity. The role of foods and food additives in hyperactive behaviour (p.2148) has been debated for many years.

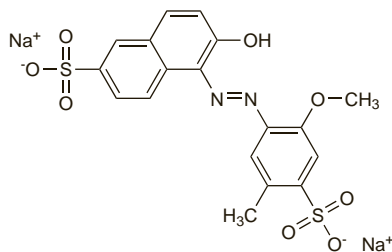
A meta-analysis¹ sought to evaluate whether artificial food colours (including carmoisine, sunset yellow, and tartrazine) contribute to the symptomatology of childhood hyperactivity in children already diagnosed with hyperactive syndromes. For the primary analysis only double-blind placebo-controlled trials were evaluated. Overall, the results supported the hypothesis that such food colours promote hyperactivity in hyperactive children as measured on behavioural ratings. However, caution was advised about making any clinical recommendations. The restrictions needed for a colour-free diet may be too much of a burden on the children and their families. Also, there is a need to find out more about the biology of artificial food colours and to ascertain whether responses depend on an allergic or pharmacological mechanism. A further study² in a more general population of children also found that mixtures of food additives including food colourings were associated with an increase in hyperactivity, although the European Food Safety Authority considered³ that the results of the study were not conclusive enough to necessitate a change in the approved daily intakes for the additives involved.

- Schab DW, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. *J Dev Behav Pediatr* 2004; **25**: 423-34.
- McCann D, et al. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. *Lancet* 2007; **370**: 1560-7. Correction. *ibid*; 1542.
- European Food Safety Authority. Assessment of the results of the study by McCann et al. (2007) on the effect of some colours and sodium benzoate on children's behaviour: scientific opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC). Available at: http://www.efsa.europa.eu/EFSA/Scientific_Opinion/afc_ej660_McCann_study_sum_en.pdf (accessed 04/07/08)

Allura Red AC

CI Food Red 17; Colour Index No. 16035; E129; FD & C Red No. 40; Rojo allura AC. Disodium 6-hydroxy-5-(6-methoxy-4-sulphonato-*m*-tolylazo)naphthalene-2-sulphonate.

Красный Очарователь
C₁₈H₁₄N₂Na₂O₈S₂ = 496.4.
CAS — 25956-17-6.



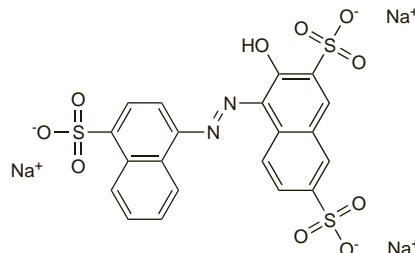
Profile

Allura red AC is used as a colouring agent in drugs, cosmetics, and foodstuffs.

Amaranth

Amarant; Amaranto; Bordeaux S; CI Acid Red 27; CI Food Red 9; Colour Index No. 16185; E123; formerly FD & C Red No. 2; Naphtol Rot S. It consists mainly of trisodium 3-hydroxy-4-(4-sulphonato-1-naphthylazo)naphthalene-2,7-disulphonate.

Амарант
C₂₀H₁₁N₂Na₃O₁₀S₃ = 604.5.
CAS — 915-67-3.



NOTE. The name amaranth is also used to refer to a number of species of plant in the genus *Amaranthus*, some of which have been used as a source of dyes.

Profile

Amaranth is used as a colouring agent in medicines, foodstuffs, and cosmetics.

Carcinogenicity. Although some evidence of carcinogenicity was found in early *animal* studies, subsequent work failed to confirm these findings and in the UK amaranth is considered suitable for use as a food colour.¹

- MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.

Annatto

CI Natural Orange 4; Colour Index No. 75120; E160(b).

Аннато
CAS — 1393-63-1.

Bixin

E160(b). Methyl (9-*cis*)-hydrogen-6,6'-diapo- ψ , ψ -carotenedioate.

Биксин
C₂₅H₃₀O₄ = 394.5.
CAS — 6983-79-5.

Norbixin

E160(b). 6,6'-Diapo- ψ , ψ -carotenedioic acid.

Норбиксин
C₂₄H₂₈O₄ = 380.5.
CAS — 542-40-5.

Profile

Annatto is a colouring agent extracted from the seeds of *Bixa orellana*. It and its derivatives, the carotenoids bixin and norbixin, are used to colour foods, drugs, and cosmetics.

Bixin and norbixin exist in both *cis*- and *trans*- forms, with the *cis*- forms being the major colouring components.

Hypersensitivity. Hypersensitivity reactions to annatto have been reported rarely. A single case of anaphylaxis has been reported in a male patient, after consumption of cereal coloured with annatto.¹ Sensitivity was confirmed with a skin test. The design of several oral challenge studies using annatto has been criticised in a literature review.² However, the authors of the review acknowledge that annatto may cause rare but severe reactions in some patients, and may worsen the symptoms of patients with recurrent urticaria.

- Nish WA et al. Anaphylaxis to annatto dye: a case report. *Ann Allergy* 1991; **66**: 129-31.
- Lucas CD et al. The role of natural color additives in food allergy. *Adv Food Nutr Res* 2001; **43**: 195-216.

Beetroot Red

Beet Red; E162; Rojo de remolacha.

Свекловый Красный
CAS — 7659-95-2 (*betanine*).

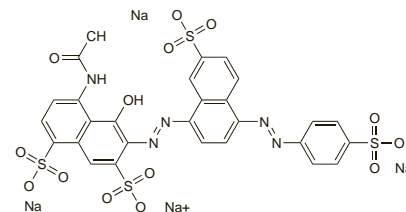
Profile

Beetroot red is obtained from the roots of red beets, *Beta vulgaris* var. *rubra* (Chenopodiaceae). The main colouring principle consists of betacyanins of which betanine is the main constituent. Beetroot red is used as a colouring agent for drugs, foodstuffs, and cosmetics.

Black PN

Brilliant Black BN; Brilliant Black PN; CI Food Black 1; Colour Index No. 28440; E151; Negro brillante BN; Negro PN; Noir Brilliant BN. It consists mainly of tetrasodium 4-acetamido-5-hydroxy-6-[7-sulphonato-4-(4-sulphonatophenylazo)-1-naphthylazo]naphthalene-1,7-disulphonate.

Бриллиантовый Чёрный PN; Чёрный Блестящий PN
C₂₈H₁₇N₅Na₄O₁₄S₄ = 867.7.
CAS — 2519-30-4.



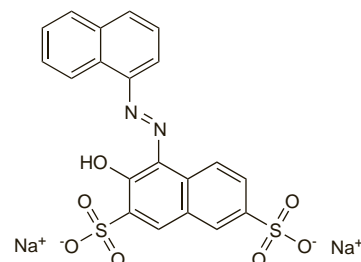
Profile

Black PN is used as a colouring agent in medicines, cosmetics, and foods.

Bordeaux B

Azorubrum; Burdeos B; CI Acid Red 17; Colour Index No. 16180. It consists mainly of disodium 3-hydroxy-4-(1-naphthylazo)naphthalene-2,7-disulphonate.

Кислотный Бордо
C₂₀H₁₂N₂Na₂O₇S₂ = 502.4.
CAS — 5858-33-3.



Profile

Bordeaux B was formerly used as a colouring agent for medicines and foods but has been replaced by other colours.

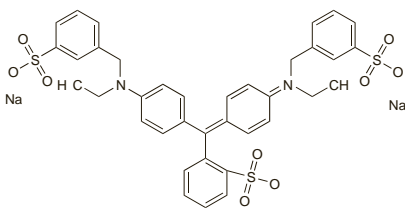
Brilliant Blue FCF

Azul brillante FCF; Blue EGS; CI Acid Blue 9; CI Food Blue 2; Colour Index No. 42090; E133; FD & C Blue No. 1; Patent Blue AC. Disodium 4,4'-bis(N-ethyl-3-sulphonatobenzylamino)triphenylmethylum-2-sulphonate.

Бриллиантовый Голубой FCF; Синий Блестящий FCF

$C_{37}H_{34}N_2Na_2O_9S_3 = 792.8$.

CAS — 3844-45-9.

**Profile**

Brilliant blue FCF is used as a colouring agent in medicines, cosmetics, and foodstuffs. The parent compound, brilliant blue, is under investigation as a stain in ophthalmology.

Enteral feeds. Blue colourings such as brilliant blue FCF have been added to enteral feeds to aid the detection of pulmonary aspiration but such use has been associated with toxic effects. Blue discoloration of the skin, initially attributed to cyanosis, has been reported¹ in a child who received a large quantity of brilliant blue FCF as a colouring in an enteral feed. Abnormal systemic absorption of the dye has also been reported² in 2 critically ill patients, both of whom subsequently died. As of September 2003 the FDA was aware of 20 cases of blue discoloration of body fluids and skin associated with the use of blue dyes, including 12 fatalities.³ Most cases occurred in patients with a history of sepsis, suggesting that altered intestinal permeability could be a factor.

1. Zillich AJ, *et al.* Skin discoloration with blue food colouring. *Ann Pharmacother* 2000; **34**: 868–70.
2. Lucarelli MR, *et al.* Toxicity of Food Drug and Cosmetic Blue No. 1 dye in critically ill patients. *Chest* 2004; **125**: 793–5.
3. Anonymous. Blue discoloration and death from FD&C Blue No. 1. *WHO Drug Inf* 2003; **17**: 239–40.

Brown FK

Chocolate Brown FK; CI Food Brown 1; E154; Marrón FK. A mixture of 6 azo dyes: sodium 2',4'-diaminoazobenzene-4-sulphonate; sodium 2',4'-diamino-5'-methylazobenzene-4-sulphonate; disodium 4,4'-(4,6-diamino-1,3-phenylenebisazo) dibenzenesulphonate; disodium 4,4'-(2,4-diamino-1,3-phenylenebisazo) dibenzenesulphonate; disodium 4,4'-(2,4-diamino-5-methyl-1,3-phenylenebisazo) dibenzenesulphonate; trisodium 4,4'-(2,4-diaminobenzene-1,3,5-triazo)tribenzenesulphonate.

Коричневый FK

CAS — 8062-14-4.

Profile

Brown FK is used as a colouring agent for foodstuffs.

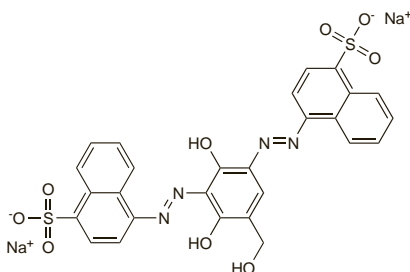
Brown HT

Chocolate Brown HT; CI Food Brown 3; Colour Index No. 20285; E155; Marrón HT. Disodium 4,4'-(2,4-dihydroxy-5-hydroxymethyl-1,3-phenylenebisazo)di(naphthalene-1-sulphonate).

Коричневый HT

$C_{27}H_{18}N_4Na_2O_9S_2 = 652.6$.

CAS — 4553-89-3.

**Profile**

Brown HT is used as a colouring agent for drugs and foodstuffs.

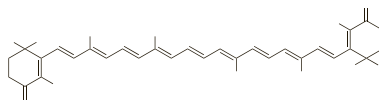
Canthaxanthin

Canthaxantina; Canthaxantinum; CI Food Orange 8; Colour Index No. 40850; E161(g); Kantaksantiini; Kantaxantin. β,β -Carotene-4,4'-dione.

Кантаксантин

$C_{40}H_{52}O_2 = 564.8$.

CAS — 514-78-3.

**Profile**

Canthaxanthin is a carotenoid but unlike beta-carotene or β -apo-8'-carotenal it has no vitamin A activity. It has selected uses as a food colouring and is given to salmon, trout, and poultry to colour their flesh, and to laying hens to colour the yolks of their eggs. It is also used to colour drugs and cosmetics.

Canthaxanthin has also been given orally to produce an artificial suntan, and as an adjunct to beta-carotene in the management of erythropoietic protoporphyria (see Porphyrias under Haem Derivatives, p.1448). Such use has led to retinal deposits and in some cases to impairment of vision.

Adverse effects. Canthaxanthin has been associated with retinal changes involving accumulation of bright yellow particles around the macula ('gold speck' maculopathy), and alterations in eye function and visual deterioration have occurred.^{1,2} Although these reports have related to oral use either for the production of an artificial tan by means of pigment deposition in the skin or for the medical treatment of erythropoietic protoporphyria, there has been concern about the use of canthaxanthin as a food colouring, and it was suggested that it should be restricted to use as a feed additive for farmed salmon and trout in order to produce a coloration of the fish flesh.¹ The results of long-term toxicity studies in animals have led to concern² about the potential for hepatotoxicity. However, subsequent studies failed to confirm hepatotoxicity in humans and it is now allowed as a food colouring,³ although its uses are restricted in some countries.

There has also been a report of fatal aplastic anaemia in a patient who took canthaxanthin in order to produce an artificial tan.⁴

1. MAFF. Food advisory committee: final report on the review of the colouring matter in food regulations 1973. *FdAC/REP/4*. London: HMSO, 1987.
2. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-fifth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 789 1990. Also available at: http://libdoc.who.int/trs/WHO_TRS_789.pdf (accessed 25/05/07)
3. FAO/WHO. Evaluation of certain food additives and contaminants: forty-fourth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser* 859 1995. Also available at: http://libdoc.who.int/trs/WHO_TRS_859.pdf (accessed 25/05/07)
4. Bluhm R, *et al.* Aplastic anemia associated with canthaxanthin ingested for 'tanning' purposes. *JAMA* 1990; **264**: 1141–2.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg: Bronzearte.

Multi-ingredient Arg: Bronsul; Sol Bronze Vital.

Caramel

Burnt Sugar; Caramelo; Sacch. Ust.; Saccharum Ustum.

Жжёный Сахар; Сахарный Колер

CAS — 8028-89-5.

Pharmacopoeias. In *USNF*.

USNF 26 (Caramel). A concentrated solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark brown mass results, a small amount of alkali or of alkaline carbonate or a trace of mineral acid being added while heating. It is a thick, dark brown liquid, having the characteristic odour of burnt sugar, and a pleasant bitter taste. One part dissolved in 1000 parts of water yields a clear solution having a distinct yellowish-orange colour. The colour of this solution is not changed and no precipitate is formed after exposure to sunlight for 6 hours. When spread as a thin layer on a glass plate, it appears homogeneous, reddish-brown, and transparent. Miscible with water; immiscible with ether, with chloroform, with acetone, with petroleum spirit, and with benzene; soluble in dilute alcohol up to 55%. Store in airtight containers.

Profile

Caramels are used in foods, drugs, and cosmetics to produce pale yellow to dark brown colours. They have no calorific value. They are complex mixtures of compounds prepared by heating carbohydrates (food-grade sweeteners consisting of glucose, fructose, or polymers of these) either alone or in the presence of acids or alkalis (food-grade citric or sulfuric acids or calcium,

potassium, or sodium hydroxides, or mixtures of these). The caramels can be classified according to the reactants used in the manufacturing process:

Class I (E150a, plain caramel, spirit caramel, or caustic caramel); no ammonium or sulfite compounds are used.

Class II (E150b or caustic sulfite caramel); sulfite compounds used but not ammonium compounds.

Class III (E150c, ammonia caramel, or beer caramel); ammonium compounds used but not sulfite compounds

Class IV (E150d, sulfite ammonium caramel, or soft-drink caramel); both ammonium and sulfite compounds used.

Some caramels also have flavouring properties.

Carbazole Violet

Colour Index No. 51319; Pigment Violet 23. 8,18-Dichloro-5,15-diethyl-5,15-dihydrodiindolo(3,2-b:3',2'-m)triphenodioxazine.

Фиолетовый Карбазол

$C_{34}H_{22}Cl_2N_4O_2 = 589.5$.

CAS — 6358-30-1.

Profile

Carbazole violet is a colouring agent used in cosmetics and contact lenses.

Carmine

Carmín; CI Natural Red 4; Cochineal Carmine; Colour Index No. 75470; E120.

Кармин

CAS — 1390-65-4.

Profile

Carmine is an aluminium lake of the colouring matter of cochineal (p.1471). It contains carminic acid, an anthraquinone glycoside. Unless precautions are taken during manufacture and transport to prevent contamination, carmine may be infected with salmonella micro-organisms.

Carmine and some of its salts are used as colouring agents in medicines, foodstuffs, and cosmetics.

Carmine passes through the gastrointestinal tract unchanged and has been used as a faecal 'marker'.

Hypersensitivity. By February 2004 the FDA was aware of 35 cases of hypersensitivity to carmine, carminic acid, or cochineal extract published in the scientific and medical literature and/or reported directly to the FDA. Hypersensitivity reactions to carmine, carminic acid, or cochineal extract included contact dermatitis (4 cases), urticaria/angioedema (9), occupational asthma (10), and systemic anaphylaxis (12). In more than half of these reports, there was evidence of an IgE-mediated diagnostic response. The adverse effects included allergic reactions to foods containing carmine and cochineal extract, occupational asthma from exposure to carmine, and allergic reactions to topically applied cosmetics containing carmine.

The FDA concluded that carmine and cochineal extract may cause potentially severe allergic responses and proposed that food and cosmetic labelling be enhanced; a declaration of inactive ingredients in drugs was already in force.¹

1. *Fed Regist* 2006; **71**: 4839–51. Available at: <http://www.cfsan.fda.gov/~lrd/fr060130.html> (accessed 16/11/06)

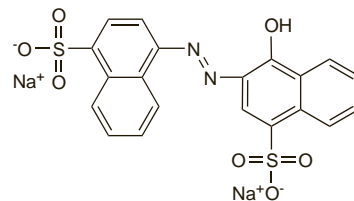
Carmoisine

Azorubina; Azorubine; Carmoisina; CI Food Red 3; Colour Index No. 14720; E122. It consists mainly of disodium 4-hydroxy-3-(4-sulphonato-1-naphthylazo)naphthalene-1-sulphonate.

Кармуазин

$C_{20}H_{12}N_2Na_2O_7S_2 = 502.4$.

CAS — 3567-69-9.

**Profile**

Carmoisine is used as a colouring agent in foods, medicines, and cosmetics. It has also been investigated clinically as a stain, to aid visualisation of malignant neoplasms of the skin during surgery.