Profile

Trimedoxime bromide is a cholinesterase reactivator given with atropine in the treatment of organophosphorus poisoning.

◊ References.

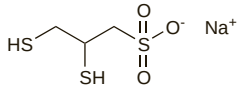
1. Kozer E, *et al.* Pediatric poisoning from trimedoxime (TMB4) and atropine automatic injectors. *J Pediatr* 2005; **146**: 41–4.

Unithiol

DMPS; Unithiolum; Unitiol; Unitioli. Sodium 2,3-dimercaptopropanesulfonate .

$C_3H_7NaO_3S_3$ = 210.3.

CAS — 4076-02-2.



Profile

Unithiol is a chelator structurally related to dimercaprol (p.1444). It is water soluble and reported to be less toxic than dimercaprol. Unithiol is used in the treatment of poisoning by heavy metals including arsenic, lead, and inorganic and organic mercury compounds; it has also been used in poisoning with chromium or cadmium, although its efficacy is not established.

Unithiol is given orally in doses of 100 mg three or four times daily in chronic poisoning. In acute poisoning, a dose of 1.2 to 2.4 g by mouth, in divided doses over 24 hours, has been suggested. It may also be given parenterally in patients with severe toxicity; a suggested intravenous dose is 3 to 5 mg/kg every 4 hours, reducing the frequency after 1 to 2 days and then changing to oral therapy.

◊ Reviews.

1. Hruby K, Donner A. 2,3-Dimercapto-1-propanesulphonate in heavy metal poisoning. *Med Toxicol* 1987; **2:** 317–23.
2. Aposhian HV, *et al.* Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology* 1995; **97:** 23–38.

Arsenic poisoning. Complete recovery, without renal or neurological sequelae, has been reported[1,2] following the use of unithiol in patients with potentially lethal acute arsenic poisoning; haemodialysis was also used in 1 patient.[2] Increased urinary arsenic excretion, with some improvement in clinical symptoms, has also been reported[3,4] with unithiol in chronic arsenic toxicity.

1. Moore DF, *et al.* Acute arsenic poisoning: absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulphonate (DMPS). *J Neurol Neurosurg Psychiatry* 1994; **57:** 1133–5.
2. Kruszewska S, *et al.* The use of haemodialysis and 2,3 propanesulphonate (DMPS) to manage acute oral poisoning by lethal dose of arsenic trioxide. *Int J Occup Med Environ Health* 1996; **9:** 111–115.
3. Wax PM, Thornton CA. Recovery from severe arsenic-induced peripheral neuropathy with 2,3-dimercapto-1-propanesulphonic acid. *J Toxicol Clin Toxicol* 2000; **38:** 777–80.
4. Guha Mazumder DN, *et al.* Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water. *J Toxicol Clin Toxicol* 2001; **39:** 665–74.

Lead poisoning. Unithiol may be used in lead poisoning, although other chelators are generally preferred (see Treatment of Adverse Effects under Lead, p.2332). In a study of 12 children[1] it reduced lead concentrations in blood but did not affect the concentrations of copper or zinc in plasma, although the urinary excretion of lead, copper, and zinc was increased during treatment.

1. Chisolm JJ, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children. *J Pharmacol Exp Ther* 1985; **235:** 665–9.

Mercury poisoning. Unithiol is used in poisoning with mercury and mercury salts (see Treatment of Adverse Effects under Mercury, p.2342) and has been given by various routes. In 7 patients with poisoning due to mercury vapour or mercuric oxide, unithiol 100 mg given twice daily by mouth for up to 15 days enhanced urinary elimination of mercury;[1] the urinary elimination of copper and zinc was also increased in most patients and 2 developed skin rashes. A dose of 5 mg/kg intramuscularly three times daily, reduced to once daily by the third day of treatment, effectively reduced the half-life of mercury in the blood after poisoning with methylmercury.[2] A patient with severe mercuric chloride poisoning was treated successfully with unithiol given intravenously for 4 weeks, then orally for 3 weeks.[3] Unithiol has also been used with haemofiltration in patients with inorganic mercury poisoning and acute renal failure.[4,5]

1. Mant TGK. Clinical studies with dimercaptopropane sulphonate in mercury poisoning. *Hum Toxicol* 1985; **4:** 346.
2. Clarkson TW, *et al.* Tests of efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak. *J Pharmacol Exp Ther* 1981; **218:** 74–83.
3. Toet AE, *et al.* Mercury kinetics in a case of severe mercuric chloride poisoning treated with dimercapto-1-propane sulphonate (DMPS). *Hum Exp Toxicol* 1994; **13:** 11–16.
4. Pai P, *et al.* Treatment of a case of severe mercuric salt overdose with DMPS (dimercapo-1-propane sulphonate [sic]) and continuous haemofiltration. *Nephrol Dial Transplant* 2000; **15:** 1889–90.
5. Dargan PI, *et al.* Case report: severe mercuric sulphate poisoning treated with 2,3-dimercaptopropane-1-sulphonate and haemodiafiltration. *Crit Care* 2003; **7:** R1–R6.

Wilson's disease. Unithiol 200 mg twice daily[1] was used successfully to maintain cupriuresis in a 13-year-old boy with Wilson's disease (p.1459) after he developed systemic lupus during treatment with penicillamine and with trientine dihydrochloride. Unithiol was started in 2 similar patients[1] but both withdrew from treatment, one because of fever and a fall in leucocyte count after a test dose and the other because of intense nausea and taste impairment.

1. Walshe JM. Unithiol in Wilson's disease. *BMJ* 1985; **290:** 673–4.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Dimaval; ***Ger.:*** Dimaval; Mercuval.

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-analysis[1] 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 study[2] 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 considered[3] that the results of the study were not conclusive enough to necessitate a change in the approved daily intakes for the additives involved.

1. 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.
2. 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.
3. 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)

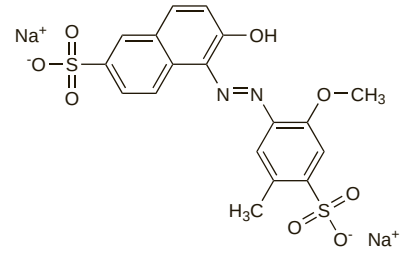
Allura Red AC

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

$C_{18}H_{14}N_2Na_2O_8S_2$ = 496.4.

CAS — 25956-17-6.



Profile

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

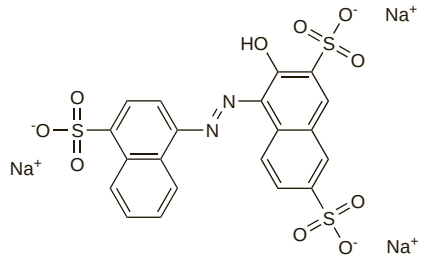
Amaranth

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

$C_{20}H_{11}N_2Na_3O_{10}S_3$ = 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]

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

$C_{25}H_{30}O_4$ = 394.5.

CAS — 6983-79-5.

Norbixin

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

Норбиксин

$C_{24}H_{28}O_4$ = 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.

1. Nish WA *et al*. Anaphylaxis to annatto dye: a case report. *Ann Allergy* 1991; **66:** 129–31.
2. 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.

Свекольный 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.

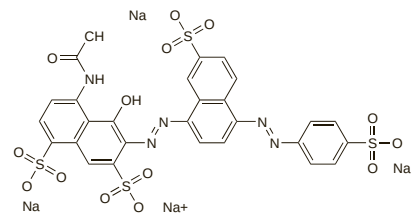
Black PN

Brilliant Black BN; Brilliant Black PN; CI Food Black 1; Colour Index No. 28440; E151; Negro brillante BN; Negro PN; Noir Brillant 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

$C_{28}H_{17}N_5Na_4O_{14}S_4$ = 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

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

CAS — 5858-33-3.