7. Of these, 4 developed neurotoxicity immediately; in the other 3 it did not develop for between 6 and 48 hours. The duration varied. One patient did not improve, one made a partial recovery, a third took 6 weeks to recover, another took 5 days; yet 2 patients recovered within 1⁄ to 2⁄ hours while the final patient experienced only transient effects.

1. Hahn AF, *et al.* Paraparesis following intrathecal chemotherapy. *Neurology* 1983; **33:** 1032–8.

Hypersensitivity. Hypersensitivity reactions to benzyl alcohol have been reported.[1-3]

1. Grant JA, *et al.* Unsuspected benzyl alcohol hypersensitivity. *N Engl J Med* 1982; **306:** 108.
2. Shmunes E. Allergic dermatitis to benzyl alcohol in an injectable solution. *Arch Dermatol* 1984; **120:** 1200–1.
3. Wilson JP, *et al.* Parenteral benzyl alcohol-induced hypersensitivity reaction. *Drug Intell Clin Pharm* 1986; **20:** 689–91.

Neonates. During 1981 and 1982 reports were published from 2 centres in the USA[1-3] of 20 deaths in low-birth-weight neonates attributed to the use of benzyl alcohol as a preservative in solutions used to flush their umbilical catheters and in some cases also to dilute their medication. The neonates suffered a toxic syndrome whose features included metabolic acidosis, symptoms of progressive encephalopathy, intracranial haemorrhage, and respiratory depression with gasping.

These deaths prompted the FDA[4] to recommend that benzyl alcohol should not be used in such flushing solutions; sodium chloride injection 0.9% without preservative should be used instead. The FDA had also advised against the use of benzyl alcohol or any preservative in fluids being used for the dilution or reconstitution of medicines for the newborn.

Those reporting the deaths[2,3] considered that the toxic syndrome could have been caused by the accumulation of the benzoic acid metabolite of benzyl alcohol, which could not be handled effectively by the immature liver; given the very low weight of the neonates they would have been receiving a comparatively high dose of benzyl alcohol. In commenting on the problem, the American Academy of Pediatrics[5] agreed that the FDA's warning was warranted, but pointed out that there was no evidence from controlled studies to confirm that benzyl alcohol was responsible.

1. Gershanik JJ, *et al.* The gasping syndrome: benzyl alcohol (BA) poisoning? *Clin Res* 1981; **29:** 895A.
2. Brown WJ, *et al.* Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet* 1982; **i:** 1250.
3. Gershanik J, *et al.* The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med* 1982; **307:** 1384–8.
4. Anonymous. Benzyl alcohol may be toxic to newborns. *FDA Drug Bull* 1982; **12:** 10–11.
5. American Academy of Pediatrics. Benzyl alcohol: toxic agent in neonatal use. *Pediatrics* 1983; **72:** 356–7.

Pharmacokinetics

Benzyl alcohol is metabolised to benzoic acid. This is conjugated with glycine in the liver to form hippuric acid which is excreted in the urine. Benzaldehyde and benzoic acid are degradation products *in vitro*.

Uses

Benzyl alcohol is used as an antimicrobial preservative. It is bacteriostatic mainly against Gram-positive organisms and some fungi. It is used in a range of pharmaceutical preparations in concentrations up to 2%. Concentrations of 5% or more are employed when it is used as a solubiliser. Benzyl alcohol is used as a preservative in foods and cosmetics. It is also used as a disinfectant at a concentration of 10%.

In addition to its antiseptic properties, concentrations of benzyl alcohol of up to 10% possess weak local anaesthetic and antipruritic activity.

Preparations

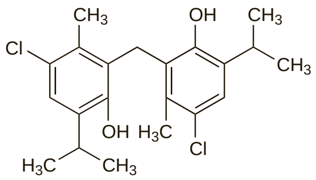
Proprietary Preparations (details are given in Part 3)
Canad.: Babys Own Teething Gel†; Zilactin Cold Sore Gel; ***USA:*** Zilactin.

Multi-ingredient: ***Arg.:*** Standard XXI; ***Austral.:*** Coso; Soothe'n Heal; ***Austria:*** Dermaspray; ***Belg.:*** Dermaspray†; Purigel Crisp; Purigel NF; ***Chile:*** Aucusik; Medikem†; Medisept†; ***Denm.:*** Doloproct Comp; ***Fr.:*** Biseptine; Codotussyl Maux de Gorge; Dermaspraid Antiseptique; Pastilles Medicinales Vicks; ***Ger.:*** Autoderm Extra; Gelipur; Spitacid; ***India:*** Dicloran MS; ***Israel:*** Otomycin; ***Ital.:*** Borocaina; Foille Scottature; Foille Sole; Pitiren; Prurex; Skab 2; ***Singapore:*** Saak†; ***Spain:*** Acerbiol; Pastillas Antisep Garg M; ***UK:*** Sudocrem; ***USA:*** Itch-X; MouthKote O/R; Oragesic; Super Ivy Dry; Topic; Tucks.

Used as an adjunct in: ***Jpn:*** Panpurol†.

Biclotymol *(rINN)*

Biclotimol; Biclotymolum. 2,2′-Methylenebis(6-chlorothymole).
Биклотимол
$C_{21}H_{26}Cl_2O_2$ = 381.3.
CAS — 15686-33-6.



Profile

Biclotymol is a phenolic antiseptic that is used in lozenges and sprays for mouth and throat infections. It is also an ingredient of cough preparations.

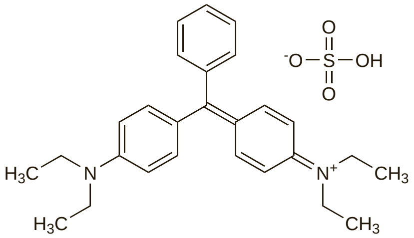
Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Hexaspray†; ***Fr.:*** Hexaspray; Humex; Rhinathiol maux de gorge†; Sagadreps†; Sagaspray; Solutricine Maux de Gorge; ***Hong Kong:*** Hexaspray; ***Port.:*** Hexaspray; ***Rus.:*** Hexaspray (Гексаспрей).

Multi-ingredient: ***Fr.:*** Hexalyse; Hexapneumine; Hexarhume; ***Hong Kong:*** Hexalyse; Hexapneumine; ***Rus.:*** Hexalyse (Гексализ).

Brilliant Green

CI Basic Green 1; Colour Index No. 42040; Diamond Green G; Emerald Green; Ethyl Green; Malachite Green G; Solid Green; Verde brillante; Viride Nitens. 4-(4-Diethylaminobenzhydrylidene)cyclohexa-2,5-dien-1-ylidenediethylammonium hydrogen sulphate.
$C_{27}H_{34}N_2O_4S$ = 482.6.
CAS — 633-03-4.



NOTE. The name Emerald Green has also been used for copper acetoarsenite.

Profile

Brilliant green is a triphenylmethane antiseptic dye with actions similar to those of methylrosanilinium chloride (p.1653). Its activity is greatly reduced in the presence of serum.

A gel containing brilliant green 0.5% with lactic acid was formerly used in the treatment of skin ulcers.

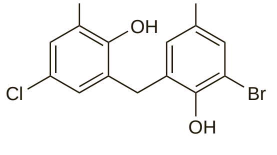
An alcoholic solution of brilliant green 0.5% and methylrosanilinium chloride 0.5% (Bonney's Blue) was formerly used for disinfecting the skin, but concern over evidence of *animal* carcinogenicity with methylrosanilinium chloride has led to a decline in its use. A solution of the two disinfectants has been used for marking incisions before surgery.

There have been occasional reports of sensitivity to brilliant green.

Adverse effects. For a report of necrotic skin reactions after application of a 1% solution of brilliant green to stripped skin, see under the Adverse Effects of Methylrosanilinium Chloride, p.1653.

Bromchlorophen

Bromchlorophene; Bromochlorophane; Bromoclorofeno. 2,2′-Methylenebis[6-bromo-4-chlorophenol].
$C_{13}H_8Br_2Cl_2O_2$ = 426.9.
CAS — 15435-29-7.



Profile

Bromchlorophen is a halogenated bisphenol antiseptic more active against Gram-positive than Gram-negative bacteria. It is used for disinfection of the hands and skin. It has also been used in deodorants and toothpastes.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Ger.:*** Dibromol.

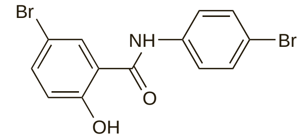
Bromsalans

Bromosalicilanilidas.
CAS — 55830-61-0.

Description. Bromsalans are a series of brominated salicylanilides that possess antimicrobial activity.

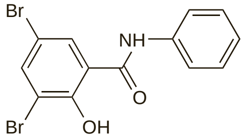
Dibromsalan *(USAN, pINN)*

Dibromsalán; Dibromsalanum; NSC-20527. 4′,5-Dibromosalicylanilide; 5-Bromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.
Дибромсалан
$C_{13}H_9Br_2NO_2$ = 371.0.
CAS — 87-12-7.



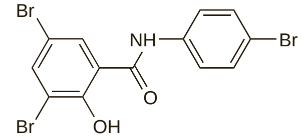
Metabromsalan *(USAN, pINN)*

Métabromsalan; Metabromsalán; Metabromsalanum; NSC-526280. 3,5-Dibromosalicylanilide; 3,5-Dibromo-2-hydroxy-*N*-phenylbenzamide.
Метабромсалан
$C_{13}H_9Br_2NO_2$ = 371.0.
CAS — 2577-72-2.



Tribromsalan *(BAN, USAN, rINN)*

ET-394; NSC-20526; TBS; Tribromsalán; Tribromsalanum. 3,4′,5-Tribromosalicylanilide; 3,5-Dibromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.
Трибромсалан
$C_{13}H_8Br_3NO_2$ = 449.9.
CAS — 87-10-5.



Profile

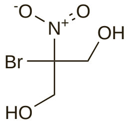
Bromsalans have antibacterial and antifungal activity and have been used in medicated soaps, but there have been many reports of photosensitivity arising from this use.

Preparations

Proprietary Preparations (details are given in Part 3)
Ital.: Bergamon Sapone.

Bronopol *(BAN, rINN)*

Bronopolum. 2-Bromo-2-nitropropane-1,3-diol.
Бронопол
$C_3H_6BrNO_4$ = 200.0.
CAS — 52-51-7.
ATC Vet — QD01AE91.



Pharmacopoeias. In *Br.* and *Pol.*

BP 2008 (Bronopol). White or almost white crystals or crystalline powder, odourless or almost odourless. Freely soluble in water and in alcohol; slightly soluble in glycerol and in liquid paraffin. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

Incompatibility. The activity of bronopol can be reduced by sodium metabisulfite, sodium thiosulfate, cysteine hydrochloride, and compounds with a thiol group. Incompatibility with unprotected aluminium affects packaging.

Stability. The stability of bronopol is affected by increases in temperature and by increases in pH above 8.

Creams and shampoos containing bronopol 0.01% as a preservative were found to contain free nitrite and, as a result of amines present in the preparations, nitrosamines.[1] It was recommended that nitrosamine formation could be reduced in preparations containing amines and bronopol by limiting the bronopol concentration to 0.01% and inclusion of alpha tocopherol 0.2% or butylated hydroxytoluene 0.05%.

1. Dunnett PC, Telling GM. Study of the fate of bronopol and the effects of antioxidants on N-nitrosamine formation in shampoos and skin creams. *Int J Cosmet Sci* 1984; **6:** 241–7.

Adverse Effects

Bronopol may be irritant when applied topically and cases of contact dermatitis have been reported.

Pharmacokinetics

Bronopol is absorbed following topical use.

Uses

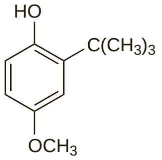
Bronopol is active against a wide range of bacteria, including *Pseudomonas aeruginosa*, but is less active against moulds and yeasts. Bronopol is used as a preservative in shampoos, cosmetics, and both topical and oral pharmaceutical preparations; concentrations in pharmaceutical preparations range from 0.01 to 0.1%, with the usual concentration being 0.02%. It is also used for its antimicrobial properties in various industrial applications, including in air conditioning systems.

Butylated Hydroxyanisole *(BAN)*

BHA; Butilhidroksianizolas; Butilhidroxianisol; Butil-hidroxianizol; Butilidrossianisolo; Butylhydroxianisol; Butylhydroxyanisol; Butylhydroxyanisole; Butylhydroxyanisolum; Butylohydroksyanizol; Butyylihydroksianisoli; E320. 2-*tert*-Butyl-4-methoxyphenol; 2-(1,1-dimethylethyl)-4-methoxyphenol.

$C_{11}H_{16}O_2$ = 180.2.

CAS — 25013-16-5.



Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Butylhydroxyanisole; Butylated Hydroxyanisole BP 2008). A white, yellowish, or slightly pinkish, crystalline powder. It contains not more than 10% of 3-(1,1-dimethylethyl)-4-methoxyphenol. Practically insoluble in water; freely soluble in alcohol and in fatty oils; very soluble in dichloromethane; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 26 (Butylated Hydroxyanisole). A white, or slightly yellow, waxy solid with a faint characteristic odour. Insoluble in water; soluble 1 in 4 of alcohol, 1 in 2 of chloroform, and 1 in 1.2 of ether; freely soluble in propylene glycol.

Incompatibility. Butylated hydroxyanisole is incompatible with oxidising agents and ferric salts. Traces of metals can cause loss of activity.

Adverse Effects

Butylated hydroxyanisole can be irritant to the eyes, skin, and mucous membranes and can cause depigmentation. There are also reports of contact urticaria.

Carcinogenicity. There has been concern as to whether butylated hydroxyanisole may be a carcinogen.[1,2] These concerns stem from a study in which *rodents* given food containing 1 to 2% butylated hydroxyanisole developed squamous cell carcinoma of the forestomach. No similar malignancies were found in studies with *animals* that do not have a forestomach. The International Agency for Research on Cancer has concluded[2] that there is sufficient evidence for the carcinogenicity of butylated hydroxyanisole in *animals* but that there is no data on its carcinogenicity in humans.

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 776* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_776.pdf (accessed 27/08/08)
2. IARC/WHO. Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 40* 1986. Available at: http://monographs.iarc.fr/ENG/Monographs/vol40/volume40.pdf (accessed 23/05/06)

Effects on the blood. For a report of methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed, see under Adverse Effects in Alkyl Gallates (p.1628).

Pharmacokinetics

Butylated hydroxyanisole is absorbed from the gastrointestinal tract, then metabolised and conjugated, and excreted in the urine; less than 1% is excreted in the urine as unchanged drug within 24 hours of ingestion.

Uses

Butylated hydroxyanisole is an antoxidant with some antimicrobial activity. It is used as a preservative in cosmetics and foods as well as pharmaceutical preparations, particularly to delay or prevent oxidative rancidity of fats and oils in concentrations of up to 0.02%; higher concentrations have been used for essential oils. It is also used to prevent the loss of activity of oil-soluble vitamins. To improve efficacy, butylated hydroxyanisole is frequently used with other antoxidants such as butylated hydroxytoluene or an alkyl gallate and with sequestrants or synergists such as citric acid.

Commercial supplies of butylated hydroxyanisole used in food technology consist of mixtures of the 2-*tert* and 3-*tert* isomers.

Use in food. In the UK the Food Advisory Committee has recommended that the use of butylated hydroxyanisole and butylated hydroxytoluene should no longer be permitted as additives for infant formulas as they are no longer required for the economic manufacture of vitamin A and vitamin A esters.[1]

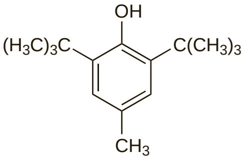
1. MAFF. Food Advisory Committee: report on the review of the use of additives in foods specially prepared for infants and young children. *FdAC/REP/12*. London: HMSO, 1992.

Butylated Hydroxytoluene *(BAN)*

BHT; Butilhidroksitoluenas; Butilhidroxitolueno; Butil-hidroxitoluol; Butylhydroxitoluen; Butylhydroxitoluenum; Butylhydroxytoluen; Butylhydroxytoluène; Butylhydroxytoluene; Butylhydroxytoluenum; Butylohydroksytoluen; Butyylihydroksitolueeni; E321. 2,6-Di-*tert*-butyl-*p*-cresol.

$C_{15}H_{24}O$ = 220.4.

CAS — 128-37-0.



Pharmacopoeias. In *Eur.* (see p.vii) and *Int.* Also in *USNF.*

Ph. Eur. 6.2 (Butylhydroxytoluene; Butylated Hydroxytoluene BP 2008). A white or yellowish-white, crystalline powder. F.p. 69° to 70°. Practically insoluble in water; freely soluble in alcohol and in vegetable oils; very soluble in acetone.

USNF 26 (Butylated Hydroxytoluene). A white crystalline solid with a faint characteristic odour. Insoluble in water and in propylene glycol; soluble 1 in 4 of alcohol and 1 in 1.1 of chloroform and of ether.

Incompatibility. Butylated hydroxytoluene is incompatible with oxidising agents and ferric salts. Traces of metals can cause loss of activity.

Adverse Effects

As for Butylated Hydroxyanisole, p.1633.

Effects on the blood. For a report of methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed formula, see under Adverse Effects in Alkyl Gallates, p.1628.

Poisoning. A 22-year-old woman experienced severe epigastric cramping, nausea and vomiting, and generalised weakness, followed by dizziness, confusion, and a brief loss of consciousness after ingesting 4 g of butylated hydroxytoluene. She recovered after conservative treatment, which was given 2 days later. The antoxidant had been taken as an unauthorised remedy for genital herpes simplex.[1]

1. Shlian DM, Goldstone J. Toxicity of butylated hydroxytoluene. *N Engl J Med* 1986; **314:** 648–9.

Pharmacokinetics

Butylated hydroxytoluene is readily absorbed from the gastrointestinal tract. It is excreted in the urine mainly as glucuronide conjugates of oxidation products.

Uses

Butylated hydroxytoluene is an antoxidant with uses similar to those of Butylated Hydroxyanisole, p.1633.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Proseptine-Plus.

Multi-ingredient: ***Fr.:*** Cinq sur Cinq.

Cadexomer-Iodine *(BAN)*

Cadexomer Iodine *(USAN)*; Cadexomerjod; Cadexómero yodado; Cadexomerum Iodum; Kadeksomeerijodi. 2-Hydroxymethylene cross-linked (1→4)-α-D-glucan carboxymethyl ether containing iodine.

CAS — 94820-09-4.
ATC — D03AX01.
ATC Vet — QD03AX01.

Adverse Effects and Precautions

As for Povidone-Iodine, p.1659. Some patients have experienced stinging and erythema on application of cadexomer-iodine to their ulcers. Free iodine is released during exposure of cadexomer-iodine preparations to wound exudate and absorption of iodine may occur. Prolonged treatment with cadexomer-iodine should be given with caution in patients with thyroid disorders.

Uses and Administration

Cadexomer-iodine, like povidone-iodine (p.1659), is an iodophore that releases iodine. It is used for its absorbent and antiseptic properties in the management of venous leg ulcers and pressure sores. It is applied as a powder, ointment, or paste containing iodine 0.9%; sufficient powder or ointment should be applied to form a layer about 3 mm thick. Treatment should not usually be continued for more than 3 months.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Iodosorb†; ***Austria:*** Iodosorb; ***Canad.:*** Iodosorb; ***Denm.:*** Iodosorb; ***Fin.:*** Iodosorb; ***Fr.:*** Iodosorb†; ***Ger.:*** Iodosorb†; ***Gr.:*** Iodosorb; ***Irl.:*** Iodoflex; ***Ital.:*** Iodosorb; ***Neth.:*** Iodosorb; ***Singapore:*** Iodoflex; Iodosorb; ***Spain:*** Iodosorb†; ***Swed.:*** Iodosorb; ***Switz.:*** Iodosorb; ***UK:*** Iodoflex; Iodosorb.

Calcium Peroxide

Calcium Dioxide; E930.

Пероксид Кальция

CaO_2 = 72.08.

CAS — 1305-79-9;.

Profile

The action of calcium peroxide is similar to that of hydrogen peroxide (p.1647). Calcium peroxide is used in dental products for tooth whitening. It is also used as a flour bleaching and improving agent.

Preparations

Proprietary Preparations (details are given in Part 3)

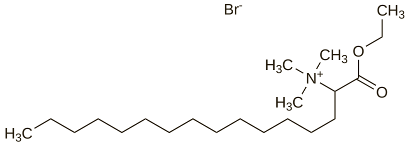
Multi-ingredient: ***Arg.:*** Hexiben.

Carbaethopendecinium Bromide

Carbethopendecinii Bromidum; Carbethoxypentadecyltrimethylammonium Bromide; Karbethopendecinium bromid. 1-Ethoxy-*N,N,N*-trimethyl-1-oxo-2-hexadecanaminium bromide.

$C_{21}H_{44}NO_2Br$ = 422.5.

CAS — 10567-02-9.



Profile

Carbaethopendecinium bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p.1634). It is used in topical preparations for disinfection of skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Part 3)
Cz.: Mukoseptonex; Ophthalmo-Septonex; Septonex.

Multi-ingredient: ***Cz.:*** Mesocain; Mukoseptonex E; N-Septonex†; Ophthalmo-Septonex; Paradentol†; Septonex; Septonex Plus; Triamcinolon-Ivax.