

Chlorocresol

1 Nonproprietary Names

BP: Chlorocresol
PhEur: Chlorocresolom
USPNF: Chlorocresol

2 Synonyms

4-Chloro-*m*-cresol; *p*-chloro-*m*-cresol; 2-chloro-5-hydroxytoluene; 6-chloro-3-hydroxytoluene; 3-methyl-4-chlorophenol; *Nipacide PC*; parachlorometacresol; PCMC.

3 Chemical Name and CAS Registry Number

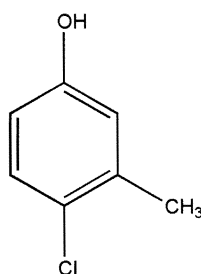
4-Chloro-3-methylphenol [59-50-7]

4 Empirical Formula Molecular Weight

C₇H₇ClO

142.58

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Chlorocresol is used as an antimicrobial preservative in cosmetics and pharmaceutical formulations. It is generally used in concentrations up to 0.2% in a variety of preparations except those intended for oral administration. Chlorocresol is effective against bacteria, spores, molds, and yeasts; it is most active in acidic media. Preservative efficacy may be reduced in the presence of some other excipients, particularly nonionic surfactants, *see* Sections 10 and 12.

In higher concentrations, chlorocresol is an effective disinfectant. *See* Table I.

Table I: Uses of chlorocresol.

Use	Concentration (%)
Eye drops	0.05
Injections	0.1
Shampoos and other cosmetics	0.1–0.2
Topical creams and emulsions	0.075–0.12

8 Description

Colorless or almost colorless, dimorphous crystals or crystalline powder with a characteristic phenolic odor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for chlorocresol.

Test	PhEur 2002	USPNF 20
Identification	+	+
Characters	+	—
Appearance of solution	+	+
Melting range	64–67 °C	63–66 °C
Nonvolatile matter	≤0.1%	≤0.1%
Acidity or alkalinity	+	—
Related substances	≤1.0%	—
Assay	98.0–101.0%	99.0–101.0%

10 Typical Properties

Antimicrobial activity: chlorocresol has bactericidal activity against both Gram-positive and Gram-negative organisms (including *Pseudomonas aeruginosa*), spores, molds, and yeasts. It is most active in acidic solutions, with antimicrobial effectiveness decreasing with increasing pH; it is inactive above pH 9. Antimicrobial activity may also be reduced by loss of chlorocresol from a formulation due to incompatibilities with packaging materials or other excipients, such as nonionic surfactants, *see* Section 12. Synergistic antimicrobial effects between chlorocresol and other antimicrobial preservatives, such as 2-phenylethanol, have been reported.^(1,2) Reported minimum inhibitory concentrations (MICs) for chlorocresol are shown in Table III.⁽³⁾

Bacteria: concentrations of approximately 0.08%, with a contact time of 10 minutes, are bactericidal. A typical MIC is 0.02%.

Fungi: chlorocresol is active against molds and yeasts. Fungicidal concentrations (after 24 hours of contact) range 0.01–0.04%.

Spores: at temperatures of 80 °C or above and in concentrations greater than 0.012%, chlorocresol is active against spores. It is much less active at room temperature. Heating at 98–100 °C for 30 minutes in the presence of 0.2% chlorocresol has previously been used as a compendial

Table III: Minimum inhibitory concentrations (MICs) for chlorocresol.⁽³⁾

Microorganism	MIC ($\mu\text{g}/\text{mL}$)
<i>Aspergillus niger</i>	2500
<i>Candida albicans</i>	2500
<i>Escherichia coli</i>	1250
<i>Klebsiella pneumoniae</i>	625
<i>Pseudomonas aeruginosa</i>	1250
<i>Pseudomonas fluorescens</i>	1250
<i>Staphylococcus aureus</i>	625

method for the sterilization of solutions of substances that would not withstand autoclaving.

Boiling point: 235 °C

Dissociation constant: $pK_a = 9.2$

Flash point: 110 °C (open cup)

Melting point: dimorphous crystals with a melting point of 55.5 °C and 65 °C.

Partition coefficients: at 25 °C

Liquid paraffin : water = 1.53

Peanut oil : water = 117

Solubility: see Table IV.

Table IV: Solubility of chlorocresol.

Solvent	Solubility at 20 °C unless otherwise stated
Acetone	Soluble
Alkali hydroxide solutions	Soluble
Chloroform	Soluble
Ethanol	1 in 0.4
Ether	Soluble
Fixed oils	Soluble
Glycerin	Soluble
Terpenes	Soluble
Water	1 in 260 ^(a) 1 in 50 at 100 °C ^(a)

^(a) Aqueous solubility is decreased in the presence of electrolytes, particularly sodium chloride, potassium chloride, and potassium sulfonate.⁽⁴⁾

Vapor pressure: 0.67 kPa at 100 °C

11 Stability and Storage Conditions

Chlorocresol is stable at room temperature but is volatile in steam. Aqueous solutions may be sterilized by autoclaving. On exposure to air and light, aqueous solutions may become yellow colored. Solutions in oil or glycerin may be sterilized by heating at 160 °C for 1 hour. The bulk material should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Chlorocresol can decompose on contact with strong alkalis, evolving heat and fumes that ignite explosively. It is also incompatible with solutions of calcium chloride, codeine phosphate, diamorphine hydrochloride, papaveretum, and quinine hydrochloride.⁽⁵⁾ Discoloration also occurs with iron salts. Chlorocresol additionally exhibits strong sorption or binding tendencies to organic materials such as rubber, certain plastics, and nonionic surfactants.⁽⁶⁻⁹⁾

Chlorocresol may be lost from solutions to rubber closures, and in contact with polyethylene may initially be rapidly removed by sorption and then by permeation, the uptake being temperature dependent. Presoaking of components may reduce losses due to sorption, but not those by permeation.^(10,11) Chlorocresol may also be taken up by polymethylmethacrylate and by cellulose acetate. Losses to polypropylene or rigid polyvinyl chloride are usually small.⁽¹²⁾

At a concentration of 0.1%, chlorocresol may be completely inactivated in the presence of nonionic surfactants, such as polysorbate 80.⁽⁷⁾ Bactericidal activity is also reduced, due to binding, by cetomacrogol or methylcellulose.^(7,9) In emulsified or solubilized systems, chlorocresol readily partitions into the oil phase, particularly into vegetable oils.⁽⁸⁾

13 Method of Manufacture

Chlorocresol is prepared by the chlorination of *m*-cresol.

14 Safety

Chlorocresol is used primarily as a preservative in topical pharmaceutical formulations but has also been used in nebulized solutions⁽¹³⁾ and ophthalmic and parenteral preparations. It should not, however, be used in formulations for intrathecal, intracisternal, or peridural injection.

Chlorocresol is metabolized by conjugation with glucuronic acid and sulfate and is excreted in the urine, mainly as the conjugate, with little chlorocresol being excreted unchanged.

Although less toxic than phenol, chlorocresol may be irritant to the skin, eyes, and mucous membranes and has been reported to cause some adverse reactions when used as an excipient.⁽¹⁴⁾

Sensitization reactions may follow the prolonged application of strong solutions to the skin, although patch tests have shown that chlorocresol is not a primary irritant at concentrations up to 0.2%. Cross sensitization with the related preservative chloroxylenol has also been reported.^(15,16)

When used systemically, notably in a heparin injection preserved with chlorocresol 0.15%, delayed irritant and hypersensitivity reactions attributed to chlorocresol have been reported.^(17,18) See also Section 19.

LD₅₀ (mouse, IV): 0.07 g/kg⁽¹⁹⁾

LD₅₀ (mouse, oral): 0.6 g/kg

LD₅₀ (mouse, SC): 0.36 g/kg

LD₅₀ (rat, oral): 1.83 g/kg

LD₅₀ (rat, SC): 0.4 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Chlorocresol can be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and protective clothing are recommended. Chlorocresol presents a slight fire hazard when exposed to heat or flame. It burns to produce highly toxic fumes containing phosgene and hydrogen chloride.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (topical creams and emulsions). Included in nonparenteral and parenteral medicines licensed in the UK.

17 Related Substances

Cresol; chloroxylenol.

18 Comments

Chlorocresol has a characteristic odor which is difficult to mask in formulations, even at concentrations of 0.05–0.1%.

Although used in Europe, chlorocresol is not used in the USA in parenteral formulations.

The EINECS number for chlorocresol is 200-431-6.

19 Specific References

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20 General References

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21 Author

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22 Date of Revision

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