

Cresol

1 Nonproprietary Names

BP: Cresol
JP: Cresol
USPNF: Cresol

2 Synonyms

Cresylic acid; cresylol; hydroxytoluene; tricresol.

3 Chemical Name and CAS Registry Number

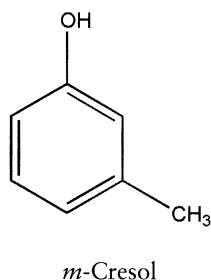
Methylphenol [1319-77-3]

4 Empirical Formula Molecular Weight

C₇H₈O

108.14

5 Structural Formula



6 Functional Category

Antimicrobial preservative; disinfectant.

7 Applications in Pharmaceutical Formulation or Technology

Cresol is used at 0.15–0.3% concentration as an antimicrobial preservative for intramuscular, intradermal, and subcutaneous injectable pharmaceutical formulations. It is also used as a preservative in some topical formulations and as a disinfectant. Cresol is not suitable as a preservative for preparations that are to be freeze-dried.⁽¹⁾

8 Description

Cresol consists of a mixture of cresol isomers predominantly *m*-cresol and other phenols obtained from coal tar or petroleum. It is a colorless, yellowish to pale brownish-yellow, or pink-colored liquid, with a characteristic odor similar to phenol but more tarlike. An aqueous solution has a pungent taste.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for cresol.

Test	BP 2001	JP 2001	USPNF 20
Identification	+	+	+
Characters	+	—	—
Specific gravity	1.029–1.044	1.032–1.041	1.030–1.038
Distilling range	+	+	195–205 °C
Acidity	+	—	—
Hydrocarbons	≤0.15%	+	+
Volatile bases	≤0.15%	—	—
Hydrocarbons and volatile bases combined	≤0.25%	—	—
Phenol	—	—	≤5.0%
Sulfur compounds	+	+	—
Nonvolatile matter	≤0.1%	—	—

10 Typical Properties

Acidity/alkalinity: a saturated aqueous solution is neutral or slightly acidic to litmus.

Antimicrobial activity: cresol is similar to phenol but has slightly more antimicrobial activity. It is moderately active against Gram-positive bacteria, less active against Gram-negative bacteria, yeasts, and molds. Cresol is active below pH 9; optimum activity is obtained in acidic conditions. Synergistic effects between cresol and other preservatives have been reported.^(2,3) When used as a disinfectant most common pathogens are killed within 10 minutes by 0.3–0.6% solutions. Cresol has no significant activity against bacterial spores.

Solubility: see Table II.

Table II: Solubility of cresol.

Solvent	Solubility at 20 °C
Benzene	Miscible
Chloroform	Freely soluble
Ethanol (95%)	Freely soluble
Ether	Freely soluble
Fixed alkali hydroxides	Freely soluble
Fixed and volatile oils	Freely soluble
Glycerin	Miscible
Water	1 in 50

11 Stability and Storage Conditions

Cresol and aqueous cresol solutions darken in color with age and on exposure to air and light.

Cresol should be stored in a well-closed container, protected from light, in a cool, dry place.

12 Incompatibilities

Cresol has been reported to be incompatible with chlorpromazine.⁽⁴⁾ Antimicrobial activity is reduced in the presence of nonionic surfactants.

13 Method of Manufacture

Cresol may be obtained from coal tar or prepared synthetically by either sulfonation or oxidation of toluene.

14 Safety

Reports of adverse reactions to cresol are generally associated with the use of either the bulk material or cresol-based disinfectants, which may contain up to 50% cresol, rather than for its use as a preservative.

Cresol is similar to phenol although it is less caustic and toxic. However, cresol is sufficiently caustic to be unsuitable for skin and wound disinfection. In studies in rabbits, cresol was found to be metabolized and excreted primarily as the glucuronide.⁽⁵⁾

A patient has survived ingestion of 12 g of cresol though with severe adverse effects.⁽⁶⁾

LD₅₀ (mouse, oral): 0.76 g/kg⁽⁷⁾

LD₅₀ (rabbit, skin): 2 g/kg

LD₅₀ (rat, oral): 1.45 g/kg

See also Sections 17 and 18.

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Cresol may be irritant to the skin, eyes, and mucous membranes. Eye protection, gloves, and a respirator are recommended. In the UK, the occupational exposure limit for cresol is 22 mg/m³ (5 ppm) long-term (8-hour TWA).⁽⁸⁾ In the USA, the permissible and recommended exposure limits are 22 mg/m³ long-term and 10 mg/m³ long-term respectively.⁽⁹⁾

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, intradermal, and SC injections). Included in parenteral medicines licensed in the UK.

17 Related Substances

Chlorocresol; m-cresol; o-cresol; p-cresol; phenol.

m-Cresol

Empirical formula: C₇H₈O

Molecular weight: 108.14

CAS number: [108-39-4]

Synonyms: *m*-cresylic acid; 3-hydroxytoluene; *meta*-cresol; 3-methylphenol.

Appearance: colorless or yellowish liquid with a characteristic phenolic odor.

Boiling point: 202 °C

Density: 1.034 g/cm³ at 20 °C

Flash point: 86 °C (closed cup)

Melting point: 11–12 °C

Refractive index: $n_D^{20} = 1.5398$

Solubility: soluble in organic solvents; soluble 1 in 40 parts of water.

Safety:

LD₅₀ (cat, SC): 0.15 g/kg^(7,10)

LD₅₀ (mouse, IP): 0.17 g/kg

LD₅₀ (mouse, oral): 0.83 g/kg

LD₅₀ (mouse, SC): 0.45 g/kg

LD₅₀ (rabbit, IV): 0.28 g/kg

LD₅₀ (rabbit, oral): 1.1 g/kg

LD₅₀ (rabbit, SC): 0.5 g/kg

LD₅₀ (rabbit, skin): 2.05 g/kg

LD₅₀ (rat, oral): 2.02 g/kg

LD₅₀ (rat, skin): 1.1 g/kg

o-Cresol

Empirical formula: C₇H₈O

Molecular weight: 108.14

CAS number: [95-48-7]

Synonyms: *o*-cresylic acid; 2-hydroxytoluene; 2-methylphenol; *ortho*-cresol.

Appearance: colorless deliquescent solid with a characteristic odor; it becomes yellow on storage.

Boiling point: 191–192 °C

Density: 1.047 g/cm³ at 20 °C

Flash point: 81–83 °C (closed cup)

Melting point: 30 °C

Refractive index: $n_D^{20} = 1.553$

Safety:

LD₅₀ (cat, SC): 0.6 g/kg^(7,10)

LD₅₀ (mouse, oral): 0.34 g/kg

LD₅₀ (mouse, SC): 0.35 g/kg

LD₅₀ (mouse, skin): 0.62 g/kg

LD₅₀ (rabbit, IV): 0.2 g/kg

LD₅₀ (rabbit, oral): 0.8 g/kg

LD₅₀ (rabbit, SC): 0.45 g/kg

LD₅₀ (rat, oral): 1.35 g/kg

LD₅₀ (rat, skin): 0.62 g/kg

p-Cresol

Empirical formula: C₇H₈O

Molecular weight: 108.14

CAS number: [106-44-5]

Synonyms: *p*-cresylic acid; 4-hydroxytoluene; 4-methylphenol; *para*-cresol.

Appearance: crystalline solid.

Boiling point: 201.8 °C

Density: 1.0341 g/cm³ at 20 °C

Flash point: 86 °C (closed cup)

Melting point: 35.5 °C

Refractive index: $n_D^{20} = 1.5395$

Solubility: soluble in ethanol (95%) and ether; very slightly soluble in water.

Safety:

LD₅₀ (cat, SC): 0.08 g/kg^(7,10)

LD₅₀ (mouse, IP): 0.03 g/kg

LD₅₀ (mouse, oral): 0.34 g/kg

LD₅₀ (mouse, SC): 0.15 g/kg

LD₅₀ (rabbit, IV): 0.16 g/kg

LD₅₀ (rabbit, oral): 1.1 g/kg

LD₅₀ (rabbit, SC): 0.3 g/kg

LD₅₀ (rabbit, skin): 0.3 g/kg

LD₅₀ (rat, oral): 1.80 g/kg

LD₅₀ (rat, skin): 0.75 g/kg

18 Comments

m-Cresol is generally considered the least toxic of the three cresol isomers.⁽¹⁰⁾ Inhalation of aerosolized *m*-cresol in pulmonary insulin delivery formulations has been shown to be safe in animal models.⁽¹¹⁾

19 Specific References

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20 General References

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21 Author

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22 Date of Revision

13 March 2002.