

Thimerosal

1 Nonproprietary Names

BP: Thiomersal
PhEur: Thiomersalum
USP: Thimerosal

2 Synonyms

[(*o*-Carboxyphenyl)thio]ethylmercury sodium salt; ethyl (2-mercaptobenzoato-*S*)-mercury, sodium salt; ethyl (sodium *o*-mercaptobenzoato)mercury; mercuriothiolate; sodium ethylmercurithiosalicylate; *Thimerosal Sigmaultra*; thiomersalate.

3 Chemical Name and CAS Registry Number

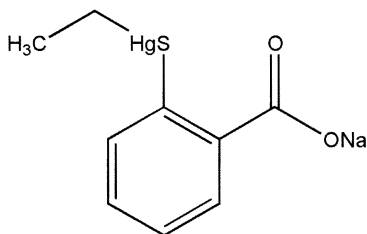
Ethyl[2-mercaptobenzoato(2-)-*O,S*]-mercurate(1-) sodium [54-64-8]

4 Empirical Formula Molecular Weight

C₉H₉HgNaO₂S

404.81

5 Structural Formula



6 Functional Category

Antimicrobial preservative; antiseptic.

7 Applications in Pharmaceutical Formulation or Technology

Thimerosal has been used as an antimicrobial preservative in biological and pharmaceutical preparations since the 1930s;⁽¹⁾ see Table I.

It is used as an alternative to benzalkonium chloride and other phenylmercuric preservatives and has both bacteriostatic and fungistatic activity. Increasing concerns over its safety have, however, led to questions regarding its continued use in formulations; see Section 14.

Thimerosal is also used in cosmetics (see Section 16) and to preserve soft contact lens solutions.

Therapeutically, thimerosal is occasionally used as a bacteriostatic and fungistatic mercurial antiseptic, which is usually applied topically at a concentration of 0.1% w/w.⁽²⁾ However, its use is declining owing to its toxicity and effects on the environment.

Table I: Uses of thimerosal.

Use	Concentration (%)
IM, IV, SC injections	0.01
Ophthalmic solutions	0.001–0.15
Ophthalmic suspensions	0.001–0.004
Otic preparations	0.001–0.01
Topical preparations	0.01

8 Description

Thimerosal is a light cream-colored crystalline powder with a slight, characteristic odor.

9 Pharmacopeial Specifications

See Table II.

Table II: Pharmacopeial specifications for thimerosal.

Test	PhEur 2002	USP 25
Identification	+	+
Characters	+	—
Appearance of solution	+	—
pH	6.0–8.0	—
Inorganic mercury compounds	≤0.7%	—
Loss of drying	≤0.5%	≤0.5%
Ether-soluble substances	—	≤0.8%
Mercury ions	—	+
Readily carbonizable substances	—	+
Assay	97.0–101.0%	97.0–101.0%

10 Typical Properties

Acidity/alkalinity: pH = 6.7 for a 1% w/v aqueous solution at 20°C.

Antimicrobial activity: thimerosal is bactericidal at acidic pH, bacteriostatic and fungistatic at alkaline or neutral pH. Thimerosal is not effective against spore-forming organisms. See also Section 12. For reported minimum inhibitory concentrations (MICs), see Table III.⁽³⁾

Table III: Reported minimum inhibitory concentrations (MICs) for thimerosal.⁽³⁾

Microorganism	MIC (μg/ml)
<i>Aspergillus niger</i>	128.0
<i>Candida albicans</i>	32.0
<i>Escherichia coli</i>	4.0
<i>Klebsiella pneumoniae</i>	4.0
<i>Penicillium notatum</i>	128.0
<i>Pseudomonas aeruginosa</i>	8.0
<i>Pseudomonas cepacia</i>	8.0
<i>Pseudomonas fluorescens</i>	4.0
<i>Staphylococcus aureus</i>	0.2

Density (bulk): $<0.33 \text{ g/cm}^3$

Dissociation constant: $\text{p}K_a = 3.05$ at 25°C .

Melting point: $232\text{--}233^\circ\text{C}$ with decomposition.

Solubility: soluble 1 in 8 of ethanol (95%), 1 in 1 of water; practically insoluble in benzene and ether.

11 Stability and Storage Conditions

Thimerosal is stable at normal temperatures and pressures; exposure to light may cause discoloration.

Aqueous solutions may be sterilized by autoclaving but are sensitive to light. The rate of oxidation in solutions is increased by the presence of trace amounts of copper and other metals. Edetic acid or edetates may be used to stabilize solutions but have been reported to reduce the antimicrobial efficacy of thimerosal solutions; *see* Section 12.

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

12 Incompatibilities

Incompatible with aluminum and other metals, strong oxidizing agents, strong acids and bases, sodium chloride solutions,⁽⁴⁾ lecithin, phenylmercuric compounds, quaternary ammonium compounds, thioglycolate, and proteins. The presence of sodium metabisulfite, edetic acid, and edetates in solutions can reduce the preservative efficacy of thimerosal.⁽⁵⁾

In solution, thimerosal may be adsorbed by plastic packaging materials, particularly polyethylene. It is strongly adsorbed by treated or untreated rubber caps that are in contact with solutions.^(6,7)

When it was used with cyclodextrin, the effectiveness of thimerosal was reduced; however, this was related to the lipid nature of the other ingredients in the preparation.⁽⁸⁾

13 Method of Manufacture

Thimerosal is prepared by the interaction of ethylmercuric chloride, or hydroxide, with thiosalicylic acid and sodium hydroxide, in ethanol (95%).

14 Safety

Thimerosal is widely used as an antimicrobial preservative in parenteral and topical pharmaceutical formulations. However, concern over the use of thimerosal in pharmaceuticals has increased as a result of a greater awareness of the toxicity of mercury and other associated mercury compounds.^(9,10) The increasing number of reports of adverse reactions, particularly hypersensitivity,^(11,12) to thimerosal and doubts as to its effectiveness as a preservative have led to suggestions that it should not be used as a preservative in eye drops⁽¹³⁾ or vaccines.^(14–16) In both Europe and the USA, regulatory bodies have recommended that thimerosal in vaccines be phased out.^(17–19)

The most frequently reported adverse reaction to thimerosal, particularly in vaccines,^(14–21) is hypersensitivity, usually with erythema and papular or vesicular eruptions. Although not all thimerosal-sensitive patients develop adverse reactions to vaccines containing thimerosal, there is potential risk. Patch testing in humans and animal experiments have suggested that 0.1% w/v thimerosal can sensitize children.⁽²²⁾ The incidence of sensitivity to thimerosal appears to be increasing; a study of 256 healthy subjects showed approximately 6% with positive sensitivity.⁽²³⁾

Adverse reactions to thimerosal used to preserve contact lens solutions have also been reported. Reactions include ocular redness, irritation, reduced lens tolerance, and conjunctivitis.^(24–26) One estimate suggests that approximately 10% of contact lens wearers may be sensitive to thimerosal.⁽²⁷⁾

Thimerosal has also been associated with false positive reactions to old tuberculin,⁽²⁸⁾ ototoxicity,⁽²⁹⁾ and an unusual reaction to aluminum⁽³⁰⁾ in which a patient suffered a burn 5 cm in diameter at the site of an aluminum foil diathermy electrode after preoperative preparation of the skin with a 0.1% w/v thimerosal solution in ethanol (50%). Investigation showed that considerable heat was generated when such a solution came into contact with aluminum.

An interaction between orally administered tetracyclines and thimerosal, which resulted in varying extents of ocular irritation, has been reported in patients using a contact lens solution preserved with thimerosal.⁽³¹⁾

Controversially, some have claimed a connection between the use of thimerosal in vaccines and the apparent rise in the incidence of autism in recent years. However, in the UK, the Department of Health has stated that there is no link between thimerosal exposure and autism.⁽³²⁾

LD₅₀ (mouse, oral): 91 mg/kg⁽³³⁾

LD₅₀ (rat, oral): 75 mg/kg

LD₅₀ (rat, SC): 98 mg/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Thimerosal is irritant to the skin and mucous membranes and may be systemically absorbed through the skin and upper respiratory tract. Thimerosal should be handled in a well-ventilated environment. Eye protection, gloves, and a respirator are recommended.

Chemical decomposition may cause the release of toxic fumes containing oxides of carbon, sulfur, and mercury in addition to mercury vapor. In the UK, the occupational exposure limit for mercury-containing compounds, calculated as mercury, is 0.01 mg/m³ long-term (8-hour TWA) and 0.03 mg/m³ short-term.⁽³⁴⁾

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (IM, IV, and SC injections; ophthalmic, otic, and topical preparations). Included in nonparenteral and parenteral medicines licensed in the UK. In the UK, the use of thimerosal in cosmetics is limited to 0.003% w/w (calculated as mercury) as a preservative in shampoos and hair-creams, which contain non-ionic emulsifiers that would render other preservatives ineffective. The total permitted concentration (calculated as mercury) when mixed with other mercury compounds is 0.007% w/w.⁽³⁵⁾

17 Related Substances

Phenylmercuric acetate; phenylmercuric borate; phenylmercuric nitrate.

18 Comments

Some variation between the results obtained when comparing different thimerosal assay methods has been reported.⁽³⁶⁾

The EINECS number for thimerosal is 200-210-4.

19 Specific References

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21 Authors

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22 Date of Revision

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