Erythromycin

Document History
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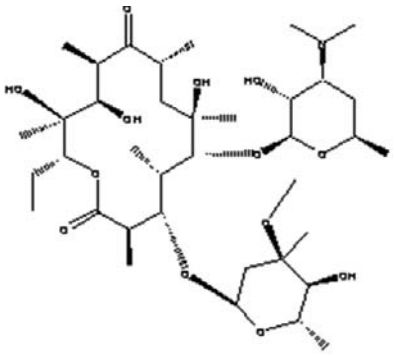
I. IDENTIFICATION

Chemical Name: Erythromycin
Synonyms: Erythromycin base
CAS Number: 114-07-8
Molecular Formula: $C_{37}H_{67}NO_{13}$
Structural Formula:



Note: Derivatives such as erythromycin estolate, and other esters and salts of erythromycin have different physical, chemical, and toxicological properties than erythromycin base and are not covered by this OEL.

II. CHEMICAL AND PHYSICAL PROPERTIES[1,2]

Physical State and Appearance: White, crystalline solid
Odor Description: Odorless
Molecular Weight: 733.94
Melting Point: 135-140°C (275-284°F) as hydrate, 190-193°C (374-379°F) anhydrous
Solubility in Water: about 2 mg/mL, hygroscopic
Stability: Unstable in acid solutions. Erythromycin is a weak base (pKa=8.8) which readily forms salts and esters with carboxylic acids (eg. erythromycin stearate, erythromycin ethyl succinate).

III. USES

Erythromycin is a macrolide antibiotic, which exhibits both bactericidal and bacteriostatic action against a broad spectrum of microorganisms, particularly gram-positive cocci and several strains of mycobacteria.[3] It is an isolated fermentation product of *Streptomyces erythreus*. Erythromycin is also an approved animal drug.[4]

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. *Oral Toxicity*

Rat LD_{50}: >3000 mg/kg[5]

Mouse LD_{50}: 3112mg/kg[5], 4600 mg/kg[6]

Hamster LD_{50}: 3018 mg/kg[5]

2. *Eye Irritation*

An ointment of 0.5% erythromycin was instilled in one eye of each of four rabbits three times a day for four days in a modified Draize procedure. The other eye was treated with control. Mild conjunctival redness was observed in both eyes; ointment results were not different than control.[7]

3. *Skin Absorption*

Not available.

4. *Skin Irritation*

Solutions of 1% and 5% erythromycin in 95% ethanol were applied to the shaved skin of New Zealand white rabbits. An application of 0.5 mL was applied daily for 4 days. Irritation indices, indicating slight irritation, were 0.86 and 1.03 for the 1% and 5% solution, respectively, out of a maximum index of 8.0.[8]

5. *Skin Sensitization*

Female albino guinea pigs (10/group) were treated with 0.5 mL solution of 25% erythromycin in ethanol using the Buehler and Griffith method. The test solution was applied once a week for three weeks, then once again two weeks later to a previously untreated area of skin. Application sites were occluded for 24 hours. Scores for erythema and edema

indicated there was no evidence of contact allergenicity.[9]

6. Inhalation Toxicity

Not available.

7. Other Toxicity

Subcutaneous toxicity — Rat LD_{50}: >2000 mg/kg[5]; Mouse LD_{50}: >2500 mg/kg[5]

Intravenous toxicity —Mouse LD_{50}: 650 mg/kg[6]

B. Subacute Toxicity

Not available.

C. Subchronic Toxicity

Rats were fed diets containing 0, or 0.05-0.2% (45-185 mg/kg/day) erythromycin for three months. No adverse effects were found.[5]

D. Chronic Toxicity/Carcinogenicity

A one-year study in which six dogs were fed erythromycin at daily doses of 0 or 50–100 mg/kg for the first three months and 100 mg/kg for the subsequent nine months showed no systemic or hematopoietic effects.[10]

Erythromycin, as the stearate salt, was tested in a two-year study in F344/N rats and B6C3F1 mice. Male and female rats were given erythromycin stearate in the feed at 0, 5000, or 10,000 ppm. There was no evidence of carcinogenic activity in any test group. Effects associated with chronic exposure in the high-dose rats (about 370 mg/kg and 435 mg/kg for males and females, respectively) were granulomas of the liver. There was an increased incidence of bone marrow hyperplasia in high-dose female rats.[11]

Male and female mice received feed with 0, 2500, or 5000 ppm erythromycin stearate. No adverse effects were observed in mice at any dose.[11]

E. Reproductive/Developmental Toxicity

There was no apparent effect on male or female fertility in rats fed erythromycin at levels up to 0.25% of diet. There was no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25% of diet) prior to and during mating, during gestation, and through weaning of two successive litters.[12]

F. Genotoxicity/Mutagenicity:

Erythromycin stearate was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without activation, equivocally mutagenic in the mouse L5178Y lymphoma assay without activation, and not mutagenic in the mouse L5178Y lymphoma assay with activation. Erythromycin stearate did not cause sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells with or without activation.[11]

V. HUMAN USE AND EXPERIENCE

Erythromycin is a macrolide antibiotic and is used therapeutically for treatment of gram-positive bacterial infections. Erythromycin inhibits protein synthesis by a bacteria-specific mechanism.

A. Metabolism and Pharmacokinetics

Erythromycin is rapidly inactivated by acidic gastric juice. It is, therefore, administered orally as an enteric-coated tablet; it is absorbed from the upper part of the small intestine. Peak plasma concentrations range from 0.3 to 1.9 µg/mL after an oral dose of 500 mg. Ester derivatives of erythromycin have been prepared which attempt to enhance the absorption and acid stability of the drug. Antibacterial activity is associated only with the free base. Erythromycin is primarily excreted by the liver via bile with a relatively short plasma half-life of 1.6 hours. Erythromycin crosses the placental barrier, producing fetal plasma concentrations 5–20% of that in the maternal circulation.[3]

B. Clinical — Oral

The usual oral dose is 1–4 g per day for adults in divided doses.[3] Reported adverse effects from therapeutic use include gastrointestinal discomfort and rare allergic reactions in susceptible individuals.[3] Temporary hearing impairment has occurred in patients taking high doses (4 g/day, 57 mg/kg). When the dose was reduced or discontinued, hearing returned to normal.[13–15]

Hepatotoxicity is associated with erythromycin derivatives, but this effect has been attributed to the salt formulations and not been associated with the free erythromycin base.[3,16]

An increased incidence of pyloric stenosis (hypertrophy of the pyloric muscle that results in projectile vomiting) in infants receiving erythromycin was reported.[17] However, pyloric stenosis was not found in a subsequent study when pregnant mothers were treated with erythromycin.[18,19] Czeizel[20] reported no increase in congenital abnormalities in newborns following the treatment of pregnant women with erythromycin.

C. Clinical — Topical (dermal)

Several topical preparations for erythromycin are available for treatment of acne vulgaris. Products

range from 1.5 to 2% erythromycin in alcoholic solution or ointment.[21]

D. Clinical — Topical (ocular)

Erythromycin is applied as a sterile ophthalmic 0.5% ointment for treatment of superficial eye infections.[21]

E. Industrial

Erythromycin has been manufactured since the 1950s, however, no documented exposure data were found. Elevated liver enzymes were reported in pharmaceutical workers exposed to numerous chemicals, including erythromycin.[22] Exposure levels were described as low, but were not quantified. The extent to which the results can be attributed to erythromycin is questionable given the lack of liver enzyme effects in patients. A review of the published literature found no reports of emergence of clinical resistance as a result of workplace exposure.

VI. RATIONALE

The recommended OEL is based on the extensive clinical use and industrial experience. Therapeutic doses of 1-4 gm extrapolate to inhalation exposures of approximately 100-400 mg/m^3. Exposure to 3 mg/m^3, which is well below the daily therapeutic dose, is expected to be protective for therapeutic and adverse effects.

VII. RECOMMENDED OEL

8-hr TWA: 3 mg/m^3

VIII. REFERENCES

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