PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR CEFTRIAXONE FOR INJECTION USP 1 mg

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1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted Daily Exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects. In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of **Ceftriaxone** have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

2. INTRODUCTION:

Ceftriaxone is a third-generation cephalosporin antibiotic used for the treatment of a number of bacterial infections. These include middle ear infections, endocarditis, meningitis, pneumonia, bone and joint infections, intra-abdominal infections, skin infections, urinary tract infections, gonorrhea, and pelvic inflammatory disease. It is also sometimes used before surgery and following a bite wound to try to prevent infection. Ceftriaxone can be given by injection into a vein or into a muscle.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Ceftriaxone in the form of the disodium salt. Ceftriaxone Sodium for Injection contains approximately 83 mg (3.6 mEq) of sodium per gram of Ceftriaxone. Vials are colorless and contain dry substance which is a white or yellowish crystalline powder equivalent to 1g or 2g Ceftriaxone.

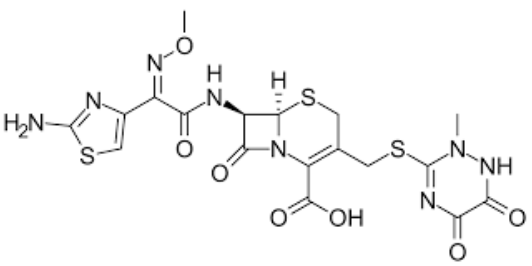
IUPAC NAME: (6R,7R)-7-{[(2Z)-2-(2-amino-1, 3-thiazol-4-yl)->2-(methoxyimino)acetyl]amino}-3-{[(2-methyl-5, 6-dioxo-1,2,5,6-tetrahydro-1, 2,4-triazin-3-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-Carboxylic acid

Chemical Abstract Services (CAS) Registry Number: 73384-59-5

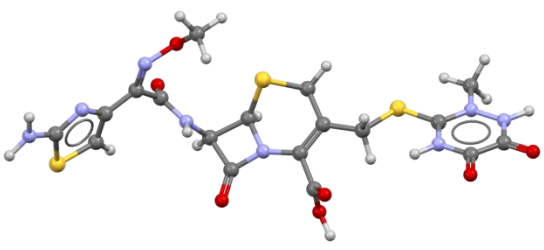
Molecular Weight: 554.57 g·mol−1

Chemical Formula: $C_{18}H_{18}N_8O_7S_3$

Molecular Structure:



2D



3D

4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
Toxicity	**Yes**	**No**	**Unknown**
Genotoxicant		√	
Carcinogen		√	
Reproductive/Developmentaltoxicity		√	
Highly sensitizingpotential		√	

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5. SUMMARY OF ASSESSMENT PROCESS:

HAZARD IDENTIFICATION	
Pharmacodynamics data	Ceftriaxone is a cephalosporin/cephamycin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms. Ceftriaxone has *in vitro* activity against gram-positive aerobic, gram-negative aerobic, and anaerobic bacteria. The bactericidal activity of ceftriaxone results from the inhibition of cell wall synthesis and is mediated through ceftriaxone binding to penicillin-binding proteins (PBPs). Ceftriaxone is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended-spectrum beta-lactamases. However, resistance to ceftriaxone usually occurs through beta-lactamase hydrolysis, altered PBPs, or reduced bacterial cell permeability. Ceftriaxone should not be mixed with or giving in the same IV line as diluents/products containing calcium as they may cause ceftriaxone to precipitate. Ceftriaxone use may also cause biliary sludge or gallbladder pseudolithiasis.
Pharmacokinetic data	Ceftriaxone works by inhibiting the mucopeptide synthesis in the bacterial cell wall. The beta-lactam moiety of ceftriaxone binds to carboxypeptidases, endopeptidases, and transpeptidases in the bacterial cytoplasmic membrane. These enzymes are involved in cell-wall synthesis and cell division. Binding of ceftriaxone to these enzymes causes the enzyme to lose activity; therefore, the bacteria produce defective cell walls, causing cell death. **Absorption:** Ceftriaxone is only given as an injection, either intramuscularly or intravenously. Ceftriaxone is less than 1% bioavailable if given orally. **Volume of distribution:** The apparent volume of distribution of an intravenous or intramuscular dose in healthy patients is 5.78 to 13.5 L.11 The volume of distribution of an intravenous or intramuscular dose in septic patients is 6.48 to 35.2 L.4 Ceftriaxone has good enough CSF penetration to be used as an effective treatment of bacterial meningitis. **Protein binding:** Ceftriaxone is 95% protein bound. **Metabolism:** Metabolism of ceftriaxone is negligible. **Route of elimination:** Ceftriaxone is primarily eliminated in the urine (33-67%). The remainder is eliminated through secretion in the bile and removed from the body via the feces.
Acute toxicity	**Species** **Route** **End Point** **Dose** Rat Oral LD_{50} > 10 g/kg Rat Subcutaneous LD_{50} > 5g/kg

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HAZARD IDENTIFICATION	
Repeated dose toxicity	A 6-month rodent toxicology and pharmacokinetic (PK) study was performed to provide supportive safety data for long-term use of intravenous ceftriaxone in a clinical trial in patients with amyotrophic lateral sclerosis (ALS). Ceftriaxone was administered by subcutaneous injection at up to 2 g/kg/day to Sprague-Dawley Crl: CD (SD) rats. Ceftriaxone was found to be safe and well tolerated. Specifically, no significant differences in body weight and food consumption were observed between the treatment and control groups. With the exception of in red cell parameters decrease, there were no ceftriaxone-related changes in hematology, coagulation, clinical chemistry and urinalysis parameters. Injection site trauma and associated reversible anemia, likely due to chronic blood loss at the injection site, were all attributable to subcutaneous route of administration. Cecum dilatation and some skin changes were reversible after recovery period, while bile duct dilatation, observed only in a few animals, persisted. Changes in the non-glandular stomach do not have a human correlate. **The no-observed-adverse-effect dose level (NOAEL) was 0.5 g/kg/day ceftriaxone in both sexes.** Ceftriaxone showed rapid absorption with half-life values ranging between 1 and 1.5 hours. Additionally, there was no evidence of accumulation and a virtually complete elimination by 16 hours after the last dose. Overall there were no toxicologically meaningful drug-related animal findings associated with the long-term administration (6 months) of ceftriaxone. These results support safety of long-term use of ceftriaxone in human clinical trials.
Carcinogenicity	Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was 6 months.
Genotoxicity studies	Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured in vitro with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.
Reproductive/Developmentaltoxicity	**Impairment of Fertility:** Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 g/day. **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately 3 times the human dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nonteratogenic Effects:** In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive

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HAZARD IDENTIFICATION	
	parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.
Highly sensitizing potential	Ceftriaxone is contraindicated in patients with known hypersensitivity to ceftriaxone, any of its excipient or to any other cephalosporin. Patients with previous hypersensitivity reactions to penicillin and other beta lactam antibacterial agents may be at greater risk of hypersensitivity to ceftriaxone.
Hazard Identification	 GHS07 (Irritant)  GHS08 (Health Hazard)

IDENTIFICATION OF CRITICAL EFFECTS	
Clinical therapeutic and adverse effects	**Therapeutic Effect:** Ceftriaxone is used to treat bacterial infections in many different parts of the body. **Adverse Effect:** Black, tarry stools, Chest pain, Chills, Fever, Shortness of breath, Sores, ulcers, or white spots on the lips or in the mouth. Unusual tiredness or weakness.

NOAEL	The no-observed-adverse-effect dose level (NOAEL) was 0.5 g/kg/day ceftriaxone in both sexes. **Time period:** 06 months

APPLICATION OF ADJUSTMENT FACTORS- PDE calculation		
F1: Extrapolation between species	5	Based on the selection of toxicity study of rats.
F2: Inter-individual variability	10	Conventionally used to allow for differences betweenindividuals in the human population
F3: Duration of toxicity	2	Short term (6-Month) toxicity study in rats
F4: Severe toxicity (1-10)	1	No any toxicity
F5: NOAEL Vs LOAEL (10if LOAEL)	1	Selection of NOAEL dose.
PK correction		For PDE calculation, no factor is applied.

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PDE CALCULATION:

$$\text{PDE (mg/day)} = \frac{\text{NOAEL (mg/day) x Body weight (kg)}}{\text{F1x F2 x F3 x F4 x F5}}$$

$$= \frac{500 \times 50}{5 \times 10 \times 2 \times 1 \times 1}$$

= **250 mg/day**

6. REFERENCES:

- https://go.drugbank.com/drugs/DB01212
- https://pubmed.ncbi.nlm.nih.gov/26705515/
- https://www.drugs.com/pro/ceftriaxone.html
- https://pfe-pfizercom prod.s3.amazonaws.com/products/material_safety_data/Ceftriaxone_for_injection%28Hospira%29_28-Oct-2016.pdf

7. GLOSSARY:

PDE: Permitted daily exposure
AUC: Area under the curve **GRAS:**
Generally regarded as safe**GLP:** Good
laboratory practice
GMP: Good manufacturing practice
LD: Lethal dose
LED: Lowest-effective dose
TDLo (Toxic Dose Low): Lowest published toxic dose
LOAEL: Lowest-observed-adverse-effect level **LOEL:**
Lowest-observed-effect level
MSDS: Material safety data sheet
MTD: Maximum tolerable dose
MPDD: Maximum permissible daily dose
MTEL: Maximum tolerable exposure level**NEL:**
No-effect level
NOAEL: No-observed-adverse-effect level
NOEL: No-observed-effect level
OEL: Occupational exposure limit
QSAR: Quantitative structure–activity relationship
SDS: Safety data sheet
ADI: Acceptable daily intake. Estimate by JECFA; the amount of a food additive, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk.

Area under the curve (AUC): Area between a curve and the abscissa (horizontal axis), i.e., the area underneath the graph of a function; often, the area under the tissue (plasma) concentration curve of a substance expressed as a function of time.

Bioaccumulation: progressive increase in the amount of a substance in an organism or partof an organism that occurs because the rate of intake exceeds the organism's ability to remove the substance from the body.

Bioavailability: biological and physiological availability. Extent of absorption of a substanceby a living organism compared to a standard system.

Biological half-life: for a substance, the time required for the amount of that substance in a biological system to be reduced to one-half of its value by biological processes, when the rate of removal is approximately exponential.

Carcinogen: agent (chemical, physical, or biological) that is capable of increasing the incidence of malignant neoplasms, thus causing cancer.

Clastogen: agent causing chromosome breakage and (or) consequent gain, loss, or rearrangement of pieces of chromosomes.

Clearance: volume of blood or plasma or mass of an organ effectively cleared of a substance by elimination (metabolism and excretion) divided by time of elimination.

Cmax: used in pharmacokinetics referring to the maximum (or peak) serum concentrationthat a drug achieves in a specified compartment or test area after the drug has been administrated and before the administration of a second dose.

Critical dose: dose of a substance at and above which adverse functional changes, reversible or irreversible, occur in a cell or an organ.

Critical effect: for deterministic effects, the first adverse effect that appears when the threshold (critical) concentration or dose is reached in the critical organ:

Adverse effects with no defined threshold concentration are regarded as critical. Dose (of a substance): total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue.

Draize test: evaluation of materials for their potential to cause dermal or ocular irritation and corrosion following local exposure; generally using the rabbit model (almost exclusively the New Zealand White) although other animal species have been used.

Elimination (in toxicology): disappearance of a substance from an organism or a partthereof, by processes of metabolism, secretion, or excretion.

Embryotoxicity: production by a substance of toxic effects in progeny in the first period of pregnancy between conception and the fetal stage.

Fetotoxicity: production by a substance of toxic effects in progeny in the second period of pregnancy between fetal stage and delivery.

First-pass effect: biotransformation and, in some cases, elimination of a substance in theliver after absorption from the intestine and before it reaches the systemic circulation.

Gavage: administration of materials directly into the stomach by esophageal intubation.

Generally regarded as safe (GRAS): phrase used to describe the USFDA philosophy that justifies approval of food additives that may not meet the usual test criteria for safety but have been used extensively and have not demonstrated that they cause any harm to consumers.

Genotoxic: capable of causing a change to the structure of the genome.

Good laboratory practice (GLP) principles: fundamental rules incorporated in OECDguidelines and national regulations concerned with the process of effective organization and the conditions under which laboratory studies are properly planned, performed, monitored, recorded, and reported.

Hazard identification: determination of substances of concern, their adverse effects, target

populations, and conditions of exposure, taking into account toxicity data and knowledge of effects on human health, other organisms, and their environment.

Hypersensitivity: state in which an individual reacts with allergic effects following exposure to a certain substance (allergen) after having been exposed previously to the same substance.

In silico: phrase applied to data generated and analyzed using computer modeling and information technology.

In vitro: in glass, referring to a study in the laboratory usually involving isolated organ, tissue, cell, or biochemical systems.

In vivo: In the living body, referring to a study performed on a living organism.

Lethal dose (LD): amount of a substance or physical agent (e.g., radiation) that causes death when taken into the body.

Lowest-effective dose (LED): lowest dose of a chemical inducing a specified effect in a specified fraction of exposed individuals.

Lowest published toxic dose (Toxic Dose Low, TDLo): the lowest dosage per unit of bodyweight (typically stated in milligrams per kilogram) of a substance known to have produced signs of toxicity in a particular animal species.

Lowest-observed-adverse-effect level (LOAEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure.

Lowest-observed-effect level (LOEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes any alteration in morphology, functional capacity, growth, development, or life span of target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Material safety data sheet (MSDS): compilation of information required under the U.S. OSHA Hazard Communication Standard on the identity of hazardous substances, health and physical hazards, exposure limits, and precautions.

Maximum permissible daily dose (MPDD): maximum daily dose of substance whose penetration into a human body during a lifetime will not cause diseases or health hazards that can be detected by current investigation methods and will not adversely affect future generations.

Maximum tolerable dose (MTD): highest amount of a substance that, when introduced into the body, does not kill test animals (denoted by LD0).

Maximum tolerable exposure level (MTEL): maximum amount (dose) or concentration of a substance to which an organism can be exposed without leading to an adverse effect after prolonged exposure time. Maximum tolerated dose (MTD): high dose used in chronic toxicity testing that is expected on the basis of an adequate sub-chronic study to produce limited toxicity when

administered for the duration of the test period.

Median lethal dose (LD50): statistically derived median dose of a chemical or physical agent (radiation) expected to kill 50 % of organisms in a given population under a defined set of conditions.

Mutagenicity: ability of a physical, chemical, or biological agent to induce (or generate) heritable changes (mutations) in the genotype in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof).

No-effect level (NEL): maximum dose (of a substance) that produces no detectable changes under defined conditions of exposure.

No-observed-adverse-effect level (NOAEL): greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

No-observed-effect level (NOEL): greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Quantitative structure–activity relationship (QSAR): quantitative structure–biological activity model derived using regression analysis and containing as parameters physicochemical constants, indicator variables, or theoretically calculated values.

Safety data sheet (SDS): single page giving toxicological and other safety advice, usually associated with a particular preparation, substance, or process.

Target (in biology): any organism, organ, tissue, cell or cell constituent that is subject to the action of an agent.