Environmental Risk Assessment Summary
Ceftriaxone

Introduction

The publication of environmental risk assessment summaries is part of Roche's engagement on developing a better understanding of issues regarding pharmaceuticals in the environment (PiE).

New pharmaceutical substances are investigated for biodegradability and initial ecotoxicity during their development. For registration, a full state-of-the-art environmental risk assessment is developed based on chronic environmental effects and advanced environmental fate data, as required by the pertinent regulations. While not a regulatory requirement, Roche also investigates older pharmaceutical substances, normally at a simpler scale, in order to assess their environmental risks.

For active pharmaceutical ingredients, the potential environmental risk is calculated from the ratio between the predicted environmental concentration (PEC) of the substance in the aquatic environment based on a conservative emission scenario and the predicted no effect concentration (PNEC), a concentration below which no adverse effects on the environment have to be expected.

If measured environmental concentrations (MECs) are available, these are also compared with the PNEC.

Summary

Ceftriaxone [9] is an antibiotic used to treat a wide range of bacterial infections including pneumonia (infection of the lungs) and meningitis (infection of the membranes around the brain and spine). Ceftriaxone belongs to the group of third-generation cephalosporins; it works by attaching to proteins on the surface of bacteria. This prevents the bacteria from building their cell walls, and eventually kills them (https://www.drugbank.ca). Cephalosporins belong to the beta-lactam antibiotics that contain a beta-lactam ring in their chemical structure. Ceftriaxone disodium is the active pharmaceutical ingredient used in the Roche product Rocephin [8].

Ceftriaxone is metabolized to a small extent in the intestines after biliary elimination. Eliminated is by renal and nonrenal mechanisms. 33–67% eliminated in urine by glomerular filtration as unchanged drug; remainder eliminated in faeces via bile as unchanged drug and microbiologically inactive metabolites (https://www.drugs.com)

Ceftriaxone is neither readily [1] nor inherently ([9] [11]) biodegradable in standard OECD tests over 28 days. No degradation was also observed in a simulation test in a laboratory scale sewage treatment plant [14]. However, primary degradation of about 30% was observed in degradation tests over 28 days ([1] [15]). However, complete primary degradation was observed in a recent OECD 314B study, a simulation test to assess the biodegradability of chemicals discharged in wastewater [20]. Moreover, substance specific analysis by LC-MS revealed that the beta-lactam ring was cleaved [20] thereby demonstrating complete loss of antibiotic activity by Ceftriaxone and/or its metabolites.

The PEC/$PNEC_{ENV}$ ratio for ecotoxicology is 1.90. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [6], a PEC/$PNEC_{ENV}$ ratio of ≥1 means that Ceftriaxone and/or its metabolites represent a potential risk to the aquatic environment.

Predicted Environmental Concentration (PEC)

The PEC is based on the following data:

$PEC\ (mg/L) = (A \times 10^9 \times (1–R)) \div (365 \times P \times V \times D)$

A Total patient consumption of Ceftriaxone in the European country with the highest yearly per capita use in the period 2016–2020 (data from IQVIA [12])
R Removal rate during sewage treatment = 0.337 (33.7% as calculated by the fate and emission prediction model SimpleTreat 4.0 [21]
P Number of inhabitants in the country with the highest per capita use in the respective year of the period 2016–2020 [7]; resulting in a consumption of 451 mg/inhabitant
V Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [6]
D Dilution factor of wastewater by surface water flow (default value) = 10 [6]

PEC = 0.589 µg/L

Note: Ceftriaxone is metabolised in the body to an extent of up to 90%. Since little is known about the ecotoxicity of these metabolites, it is assumed as a worst case that they have the same ecotoxicological relevance as Ceftriaxone.

Predicted No Effect Concentration for Aquatic Ecosystem Function ($PNEC_{ENV}$)

Chronic data, assessed based on OECD Test Guidelines [18], have been used to calculate the $PNEC_{ENV}$. The lowest chronic effective concentration is 3.31 µg/L, the 72 h EC10 for growth rate inhibition of the cyanobacteria *Anabaena flos-aquae* [19]. Applying an assessment factor of 10 according to the EMA Guideline [6], this results in a $PNEC_{ENV}$ of 0.331 µg/L.

$PNEC_{SW} = 3.31\ µg/L \div 10 = 0.331\ µg/L$

PEC/PNEC ratio

PEC = 0.589 µg/L
$PNEC_{ENV}$ = 0.331 µg/L

PEC/$PNEC_{ENV}$ = 1.78

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [6], a PEC/$PNEC_{ENV}$ ratio of 1.90 (i.e. ≥1) means that Ceftriaxone and/or its metabolites represent a potential risk to the aquatic environment.

Predicted No Effect Concentration for Antimicrobial Resistance Promotion ($PNEC_{MIC}$)

In the discussion about antimicrobial resistance (AMR) promotion, $PNEC_{MIC}$ values are derived. An approach is to use the 1st percentile of the minimal inhibitory concentrations (MIC) for different bacteria genera, corresponding to the value containing the bottom 1% of the MIC values and by applying a safety factor of 10. With this approach a $PNEC_{MIC}$ of 0.03 µg/L was derived ([2] [5] [22]).

$PNEC_{MIC}$ = 0.03 µg/L

However, substance specific analysis by LC-MS in the course of an OECD 314B fate study revealed that the beta-lactam ring was cleaved [20] thereby demonstrating complete loss of antibiotic activity by Ceftriaxone and/or its metabolites.

Aquatic Toxicity Data for Ceftriaxone

Study	Guideline	Results	Ref.
Growth inhibition test with the green alga *Raphidocelis subcapitata*	OECD 201	72 h EC50 (growth rate) >100 mg/L NC 72 h EC50 (biomass) >100 mg/L NC 72 h NOEC 100 mg/L NC	[16]
Growth inhibition test with the cyanobacteria *Synechococcus leopoliensis*	OECD 201	72 h EC50 (growth rate) 0.586 mg/L GMC 72 h EC50 (yield) 0.324 mg/L GMC 72 h EC10 (growth rate) 0.294 mg/L GMC 72 h EC10 (yield) 0.173 mg/L GMC 72 h NOEC 0.100 mg/L GMC	[3]
Growth inhibition test with the cyanobacteria *Anabaena flos-aquae*	OECD 201	72 h EC50 (growth rate) 6.10 mg/L NC 72 h EC50 (yield) 3.85 mg/L NC 72 h EC10 (growth rate) 3.31 mg/L NC 72 h EC10 (yield) 1.86 mg/L NC 72 h NOEC 1.60 mg/L NC	[19]
Acute immobilisation test with *Daphnia magna*	OECD 202	48 h EC50 >100 mg/L NC HTC 48 h NOEC 100 mg/L NC HTC 48 h NOEC 86 mg/L MMC HTC 48 h EC50 98.01 mg/L	[17]
Daphnia magna, reproduction test	OECD 211	21d EC10 (reproduction and intrinsic rate of population increase) >92.0 mg/L MMC 21d NOEC (reproduction) 92.0 mg/L MMC 21d NOEC (intrinsic rate of population increase) 28.5 mg/L MMC	[4]
Acute toxicity to rainbow trout (*Oncorhynchus mykiss*)	OECD 203	96 h NOEC 1000 mg/L NC	[9]
Bacteria toxicity	OECD 209	3 h NOEC 10 mg/L NC	[9]
Microbial inhibition	OECD 301 D	28 d NOEC 5.32 mg/L NC (toxicity control) 28 d LOEC 0.005 mg/L NC (analysis of colony forming units, CFU)	[1]
Anaerobic inhibition	OECD 224	7 d EC50 307 mg/L 7 d EC10 5.5 mg/L	[10]

EC10 concentration of the test substance that results in 10% effect
EC50 concentration of the test substance that results in 50% effect
NOEC No observed effect concentration
GMC Geometric mean measured concentration
HTC Highest tested concentration
MMC Mean measured concentration
NC Nominal concentration

Environmental Fate Data for Ceftriaxone

Study	Guideline	Results	Ref.
Ready biodegradability	OECD 301 D	BOD ÷ ThOD (mineralisation) 1% after 14 days 13% after 28 days not readily biodegradable Primary degradation (LC-UV) 30% after 28 days	[1] [15]
Inherent biodegradability	OECD 302 B	<5% after 28 days with respect to TOC (mineralization) <10% after 28 days with respect to TOC (DOC elimination) not inherently biodegradable	[11]
	OECD 302 C	BOD ÷ ThOD (mineralisation) 0% after 28 days	[9]
Simulation test	OECD 303 A (modified)	Mineralisation ($^{14}CO_2$) <1% $^{14}CO_2$ recovered in laboratory scale sewage treatment plant: 7% (elimination) DOC elimination: 91% within 6 weeks test duration	[14]
Biodegradation in activated sludge	OECD 314 B	Total system DT50 primary: 0.000445 days Total system DegT50 primary: 0.43 days Mineralisation DT50 ultimate: 188 days Cleavage of beta-lactam ring [1)]	[20]
Fate in sediment/water systems	NA	Half-live (surface water, in the dark): 18.7 d Half-live (surface water, in sunlight): 4.1 d Half-live (sediment, oxic): 2.6–3.1 d Half-live (sediment, anoxic): 3.5–4.1 d	[13] [2)]

BOD	Biochemical oxygen demand
DOC	Dissolved organic carbon
ThOD	Theoretical oxygen demand
TOC	Total organic carbon
DT50 primary	Time taken for 50% of parent to disappear by dissipation, including irreversible binding, and/or degradation processes
DegT50 primary	Time taken for 50% of parent to disappear by degradation processes alone; used for calculation

DT50 ultimate = DegT50 ultimate

1) Substance specific analysis by LC-MS; demonstrating complete loss of antibiotic activity by Ceftriaxone and/or its metabolites

2) The data indicate that direct photolysis was the primary process for elimination of ceftriaxone in the surface water of the lake, whereas biodegradation was responsible for the elimination in the sediment.

Physical Chemical Data for Ceftriaxone

Study	Guideline	Results	Ref.
Water solubility	NA	470 g/L (22 °C)	[9]
n-Octanol-water partition coefficient	QSAR	log K_{OW} ≤-1	
n-Octanol-water distribution coefficient	NA	log D_{OW} 0.025 (pH 2.0)	[9]

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