

Rocephalin[®] med lidokain

M R F

Roche

Pulver och vätska till injektionsvätska, lösning 1 g

(Pulver: vitt till gulorange kristallint pulver. Lösning: klar färglös lösning.)

Antibiotikum av cefalosporintyp, betalaktamasstabil

Aktiva substanser (i bokstavsordning):

Ceftriaxon

Lidokain

ATC-kod:

J01DD54

Läkemedel från Roche omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Ceftriaxon

Miljörisk: Användning av ceftriaxon har bedömts medföra försumbar risk för miljöpåverkan.

Nedbrytning: Ceftriaxon bryts ned i miljön.

Bioackumulering: Ceftriaxon har låg potential att bioackumuleras.

Detaljerad miljöinformation

Identification and characterisation

Chemical name: Ceftriaxone disodium salt hemi(heptahydrate)

CAS number: 104376-79-6 [1]

Molecular weight: 661.6 [1]

Remark: -

Brand name: Rocephalin® med lidokain [1]

Chemical name: Ceftriaxone (active substance)

CAS number: 73384-59-5

Molecular weight: 554.5872

Physico-chemical properties

Aqueous solubility: 470 g/l (22 °C) [1]

Dissociation constant, pKa: 3, approximate value [3]

Melting point: >155 °C (with decomposition) [1]

Vapour pressure: ND

Boiling point: ND

K_H : <1*E-30 atm*m3/mol QSAR

QSAR = QSAR-modelled (EPISuite, SPARC, ACD Solaris)

Predicted Environmental Concentration (PEC)

PEC is calculated according to the formula:

$$\begin{aligned} \text{PEC } (\mu\text{g/L}) &= (A \times 1'000'000'000 \times (100-R)) / (365 \times P \times V \times D \times 100) \\ &= 1.37 \times 10^{-6} \times A \times (100 - R) = 0.008 \mu\text{g/l} \end{aligned}$$

(PEC is given for the active substance Ceftriaxone)

Where: Ceftriaxone disodium salt hemi(heptahydrate) 102,0281 sales data from IQVIA / LIF - kg consumption 2021

A Sold quantity = 85,5252 kg/y calculated data for the active ingredient Ceftriaxone

R Removal rate = 33.7 % calculated with Simple Treat 4.0 [16]

P Population of Sweden = 10 000 000

V Volume of Wastewater = 200 l/day Default value [2]

D Factor for Dilution = 10 Default value [2]

Predicted No Effect Concentration (PNEC)

Ecotoxicological Studies

Green alga (*Raphidocelis subcapitata*): [5]

ErC50 72 h (growth rate) >100 mg/l (OECD 201)

EbC50 72 h (biomass) >100 mg/l (OECD 201)

NOEC 72 h (growth rate + biomass) = 100 mg/l (OECD 201)

Cyanobacteria (*Synechococcus leopoliensis*): [11]

ErC50 72 h (growth rate) = 0.586 mg/l active substance (OECD 201)

ErC10 72 h (growth rate) = 0.294 mg/l active substance (OECD 201)

EyC50 72 h (yield) = 0.324 mg/l active substance (OECD 201)

EyC10 72 h (yield) = 0.173 mg/l active substance (OECD 201)

NOEC 72 h (growth rate + yield) = 0.1 mg/l active substance (OECD 201)

Cyanobacteria (*Anabaena flos-aquae*): [13]

ErC50 72 h (growth rate) = 0.0061 mg/l active substance (OECD 201)

ErC10 72 h (growth rate) = 0.00331 mg/l active substance (OECD 201)

EyC50 72 h (yield) = 0.00385 mg/l active substance (OECD 201)
EyC10 72 h (yield) = 0.00186 mg/l active substance (OECD 201)
NOEC 72 h (growth rate + yield) = 0.0016 mg/l active substance (OECD 201)

Water-flea (*Daphnia magna*): [6]

EC50 48 h (immobilization) > 100 mg/l (OECD 202)

NOEC 48 h (immobilization) = 100 mg/l (OECD 202)

Daphnia magna Reproduction: [12]

NOEC 21 d (reproductive output) = 92.0 mg/l active substance (OECD 211)

NOEC 21 d (intrinsic rate of population increase) = 28.5 mg/l active substance (OECD 211)

NOEC 21 d (overall) = 28.5 mg/l active substance (OECD 211)

Respiration inhibition test: [7]

NOEC 3 h (respiration inhibition) = 10 mg/l (OECD 209) [7]

Micro-organisms: [8]

28 d LOEC (toxicity control, CFU) = 0.005 mg/l (OECD 301 D)

PNEC Derivation

The PNEC is based on the following data:

PNEC ($\mu\text{g/l}$) = lowest ErC10/10, where 10 is the assessment factor used. An ErC10 of 0.00331 mg/l (3.31 $\mu\text{g/l}$) for the cyanobacteria *Anabaena flos-aquae* has been used for this calculation. Fish has been considered not to be the relevant species, due to the low acute toxicity. This is a joint assessment performed by the AMR Industry Alliance. [1]

PNEC = $3.31 \mu\text{g/l} / 10 = 0.331 \mu\text{g/l}$ active substance

Environmental Risk Classification (PEC/PNEC Ratio)

PEC Predicted Environmental Concentration = 0.008 µg/l

PNEC Predicted No Effect Concentration = 0.331 µg/l

Ratio PEC/PNEC = 0.023

PEC/PNEC 0.008/0.331 = 0.023 = for Ceftriaxone active substance, which justifies the phrase 'Use of Ceftriaxone disodium has been considered to result in insignificant environmental risk.'

Degradation

Biotic Degradation

Ready biodegradability: [8]

3% after 28 days of incubation BOD/ThOD (OECD 301 D)

Inherent biodegradability: [7]

0% after 28 days of incubation BOD/ThOD (OECD 302 C)

Biodegradation in Activated Sludge (OECD 314 B) [15]

Total system DT50 primary: 0.000445 days

Total system DegT50 primary: 0.43 days

Degradation rate k based on DegT50 primary: 0.0672 h⁻¹, used for calculation of elimination in SimpleTreat 4.0

Mineralisation DT50 ultimate: 188 days

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 in SimpleTreat

DT50 ultimate = DegT50 ultimate

Using the primary degradation rate of 0.0672 h⁻¹ in SimpleTreat 4.0, this results in a biodegradation of 33.7% in sewage treatment. [16]

Substance specific analysis by LC-MS showed cleavage of the beta-lactam ring; demonstrating complete loss of antibiotic activity by Ceftriaxone and/or its metabolites.

Abiotic Degradation

Photodegradation:

$t^{1/2} = 4$ d (20 °C, light) [3]

Hydrolysis:

$t^{1/2} = 61$ d (4 °C, in the dark) [3]

$t^{1/2} = 11$ d (15 °C, in the dark) [3]

$t^{1/2} = 5$ d (20 °C, in the dark) [3]

$t^{1/2}$ (20°C, buffer of ionic strength 0.6) = 8.9 h at pH 5.0, 7 d at pH 5.6, 18 d at pH 6.2, 36 d at pH 6.8, 32 d at pH 7.4, 16 d at pH 8.0; hydrolysis even faster at higher ionic strength, i.e., faster in seawater or sewage than in 'clean' water. [9]

Ceftriaxone disodium salt hemi(heptahydrate) is neither readily, nor inherently biodegradable. However, biodegradation in sewage sludge according to OECD 314 B showed a fast primary degradation of Ceftriaxone with cleavage of the beta-lactam ring, thereby demonstrating that the antibiotic activity is completely lost during sewage treatment. With a primary degradation DegT50 of 0.43 days, this justifies the phrase 'Ceftriaxone disodium salt hemi(heptahydrate) is degraded in the environment.'

Bioaccumulation/Adsorption

$\log P_{ow}$ 0.025 pH 2.0 experimental, method unknown [1]

$\log D$ -1.2 pH 7.4 experimental, method unknown [10]

$K_{OC} \leq 2713$ pH-sensitive, QSAR; low adsorption based on $\log P_{ow}$

BCF <10 QSAR

Ceftriaxone disodium has low potential for bioaccumulation.

Excretion/metabolism

Ceftriaxone is metabolised in part (unquantified) to inactive compounds. [4]

References

1. F. Hoffmann-La Roche Ltd (2022): Environmental Risk Assessment Summary for Ceftriaxone.
<https://www.roche.com/sustainability/environment/environmental-risk>.
2. European Medicines Agency (EMA) (2006/2015): Guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), 01 June 2006, EMA/CHMP/SWP/447/00 corr 2.
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6. Study Report: NOTOX Project no. 180012: Acute toxicity study in *Daphnia magna* with Rocephin, January 2008.

7. Study Report: Roche Project: Oekotoxikologische Beurteilung BWL, August 1983.
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9. Martinez-Pacheco R, Vila-Jato JL, Gómez-Amoza JL (1987): Effect of different factors on stability of ceftriaxone in solution. *Il Farmaco* 42(5): 131–137.
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11. Study Report: Arcadis Project no. A18-00168: Ceftriaxone disodium salt hemi(heptahydrate). Cyanobacteria growth inhibition test with *Synechococcus leopoliensis*, September 2018.
12. Study Report: Arcadis Project no. A18-00169: Ceftriaxone disodium salt hemi(heptahydrate). *Daphnia magna* Reproduction Test, September 2018.
13. Study Report: Scymaris Project no. 1046.00305: Ceftriaxone disodium salt hemi(heptahydrate). Determination of toxicity to the blue-green alga *Anabaena flos-aquae*, August 2020
14. AMR Industry Alliance (2021): AMR Alliance Science-Based PNEC Targets for Risk Assessments.
<https://www.amrindustryalliance.org/shared-goals/common-antibiotic->
15. Study Report: Scymaris Project no. 1046.00306: [14C]Ceftriaxone disodium salt hemi(heptahydrate): Biodegradation in Activated Sludge, May 2022
16. Struijs (2014). SimpleTreat 4.0: a model to predict fate and emission of chemicals in wastewater treatment plants. RIVM report 601353005/2014. Model downloaded from RIVM.

Lidokain

Miljörisk: Användning av lidokain har bedömts medföra försumbar risk för miljöpåverkan.

Nedbrytning: Lidokain är potentiellt persistent.

Bioackumulering: Lidokain har låg potential att bioackumuleras.

Detaljerad miljöinformation

The assessment for Lidocaine is based on the following entries of sales data from sales data from IQVIA / LIF - kg consumption 2021:

| Substance | CAS no. | M | kg (2021) |
|--------------------------------------|-----------|----------|-----------|
| Lidocaine | 137-58-6 | 234.3408 | 1237.9284 |
| Lidocaine hydrochloride (monohydrat) | 6108-05-0 | 288.8165 | 863.4509 |
| Lidocaine hydrochloride (water free) | 73-78-9 | 270.8017 | 11.2757 |
| Lidocaine (total) | | | 1948.2753 |

Identification and characterisation

Chemical name: Lidocaine

CAS number: 137-58-6

Molecular weight: 234.3408 [1]

Remark: -

Brand name: Rocephalin® med lidokain [1]

Physico-chemical properties

Water solubility:

4000 mg/l as Lidocaine base [10]

680000 mg/l as Lidocaine hydrochloride monohydrate [10]

Dissociation constant, pKa:

8.05 (in 170 mM NaCl at 25 °C, with no added buffers) [9]

7.84 (25 °C) [10]

Melting point:

68-69 °C as Lidocaine base [10]

76-79 °C as Lidocaine hydrochloride monohydrate [10]

Vapour pressure: ND

Boiling point: ND

K_H : 8.77*E-09 atm*m3/mol QSAR

QSAR = QSAR-modelled (EPISuite, SPARC, ACD Solaris)

Predicted Environmental Concentration (PEC)

PEC is calculated according to the formula:

$$\text{PEC } (\mu\text{g/L}) = (A \times 1'000'000'000 \times (100-R)) / (365 \times P \times V \times D \times 100)$$

$$= 1.37 \times 10^{-6} \times A \times (100 - R) = 0.267 \mu\text{g/l}$$

Where:

A Sold quantity = 1948.2753 kg/y sales data from IQVIA / LIF - kg consumption 2020

R Removal rate = 0 % Default value [2]

P Population of Sweden = 10 000 000

V Volume of Wastewater = 200 l/day Default value [2]

D Factor for Dilution = 10 Default value [2]

Predicted No Effect Concentration (PNEC)

Ecotoxicological Studies

Green alga (*Scenedesmus vacuolatus*): [4]

ErC50 24 h (growth rate) at pH 6.5 = 135 mg/l (no standard method)

ErC50 24 h (growth rate) at pH 7.5 = 161 mg/l (no standard method)

ErC50 24 h (growth rate) at pH 8.5 = 142 mg/l (no standard method)

ErC50 24 h (growth rate) at pH 9.0 = 128 mg/l (no standard method)

ErC50 24 h (growth rate) at pH 10.0 = 108 mg/l (no standard method)

(Algae were maintained as batch cultures in Talaquil medium at 25 °C under photosynthetically active radiation (PAR) of $170 \pm 20 \mu\text{Em}^{-2} \text{ s}^{-1}$. The buffer constitution of the medium was increased to 20 mM to reach pH-stability over the test period. The buffer constitution was varied with pH as follows: 20mM MES (2-(N morpholino)ethanesulfonic acid, CAS 4432-31-9) was used for pH 6.5, 20 mM MOPS (3-(Nmorpholino) propanesulfonic acid, CAS 1132-61-2) for pH 7.5, 20 mM HEPPS (4 (2-hydroxyethyl)-1-piperazinepropanesulfonic acid, CAS 16052-06-5) for pH 8.5, 20 mM CHES (2-(cyclohexylamino)ethanesulfonic acid, CAS 103-47-9) for pH 9.0, and 20 mM CAPS (3- (cyclohexylamino)-1-propanesulfonic acid, CAS 1135-40-6) for pH 10.0. Algae were grown in medium at the different pH values for at least 3 days before the experiment to allow for adaptation. The test was conducted using OD-readings for the determination of the growth rate μ during 24 h.) [4]

Water-flea (*Daphnia magna*): cited in: [5]

EC50 48 h (immobilization) = 112 mg/l (OECD 202)

Thamnocephalus platyurus (anostracan crustacean) [8]

LC50 24 h (mortality) = 81.7 mg/l (Thamnotoxkit microbiotest)

Zebra fish (*Danio rerio*): cited in: [5]

LC50 96 h (mortality) = 106 mg/l (OECD 203)

Zebra fish (*Danio rerio*) Embryo Test: [11]

LC50 24 h (mortality) = 23 mg/l (OECD 236, adapted)

Micro-organisms:

ND

PNEC Derivation

The PNEC is based on the following data:

PNEC ($\mu\text{g/l}$) = lowest LC50/1000, where 1000 is the assessment factor used. An LC50 of 23000 $\mu\text{g/l}$ in the Zebra fish (*Danio rerio*) Embryo Test has been used for this calculation.

$\text{PNEC} = 23000 / 1000 = 23 \mu\text{g/l}$

Environmental Risk Classification (PEC/PNEC Ratio)

PEC Predicted Environmental Concentration = 0.267 $\mu\text{g/L}$

PNEC Predicted No Effect Concentration = 23 $\mu\text{g/L}$

Ratio PEC/PNEC = 0.012

PEC/PNEC = 0.267/23 = 0.012 for Lidocaine which justifies the phrase 'Use of Lidocaine has been considered to result in insignificant environmental risk.'

Degradation

Biotic Degradation

Ready biodegradability: ND

Inherent biodegradability: ND

Other degradation information: [6]

Degradation in surface water $t_{1/2} = 92$ d (laboratory, 23 °C, in the dark), $t_{1/2} = 110$ d (field, 2-28 °C, in the dark)

Abiotic Degradation

Photodegradation: $t_{1/2} = 0.4$ d (laboratory, light), $t_{1/2} = 1.3$ d (field, light) [6]

Hydrolysis: ND

Lidocaine is neither readily, nor inherently biodegradable. This justifies the phrase 'Lidocaine is potentially persistent.'

Bioaccumulation/Adsorption

$\log P_{OW}$ 1.66 QSAR [3]

$\log P_{OW}$ 2.44 method unknown, cited in: [3]

$\log D_{OW}$ 1.63 (pH 7.4, 25 °C) [9]

$\log D_{OW}$ 1.66 (phosphate buffer, pH 7.4, 25 °C) [10]

$K_{OC} \leq 420$ QSAR [3]

BCF <20 QSAR [3]

Lidocaine has low potential for bioaccumulation ($\log D_{OW} < 4$ at pH 7.4).

Excretion/metabolism

Lidocaine is metabolized chiefly by the liver. Its major degradative pathway is conversion to monoethylglycinexylidide by oxidative N-deethylation followed by hydrolysis to 2,6-xylidine. Further conversion of 2,6-xylidine to 4-hydroxy-2,6-xylidine appears to occur in man, since the latter compound excreted in urine over a 24-hour period has accounted for over 70% of an orally administered dose of lidocaine. No more than 10% of the dose is excreted as parent lidocaine. [7]

References

1. F. Hoffmann-La Roche Ltd (2021): Environmental Risk Assessment Summary for Lidocaine.
<https://www.roche.com/sustainability/environment/environmental-risk>.
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