FASS

Rocephalin® med lidokain

Roche

Pulver och vätska till injektionsvätska, lösning 1 g
(Pulver: vitt till gulorange kristallint pulver. Lösning: klar färglös lösning.)

Antibiotikum av cefalosporintyp, betalaktamasstabilt

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:

PEC (µg/L) = (A x 1'000'000'000 x (100-R)) / (365 x P x V x D x 100) = 1.37 x 10^{-6} x A x (100 - R) = 0.008 µg/l
(PEC is given for the activ 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 substanc(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 (µg/l) = lowest ErC10/10, where 10 is the assessment factor used. An ErC10 of 0.00331 mg/l (3.31 µg/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 µg/l / 10 =0.331 µg/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:
t½ = 4 d (20 °C, light) [3]

Hydrolysis:
t½ = 61 d (4 °C, in the dark) [3]
t½ = 11 d (15 °C, in the dark) [3]
t½ = 5 d (20 °C, in the dark) [3]
t½ (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} ≤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-assessment-downloads.htm.
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7. Study Report: Roche Project: Oekotoxikologische Beurteilung BWL, August 1983.
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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
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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 fromsales 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:
PEC (µg/L) = (A x 1'000'000'000 x (100-R)) / (365 x P x V x D x 100) = 1.37 x 10^{-6} x A x (100 - R) = 0.267 µg/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 ± 20µEm−2 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 (µg/l) = lowest LC50/1000, where 1000 is the assessment factor used. An LC50 of 23000 µg/l in the Zebra fish (*Danio rerio*) Embryo Test has been used for this calculation.
PNEC = 23000 / 1000 = 23 µg/l

Environmental Risk Classification (PEC/PNEC Ratio)
PEC Predicted Environmental Concentration = 0.267 µg/L
PNEC Predicted No Effect Concentration = 23 µg/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 t½ = 92 d (laboratory, 23 °C, in the dark), t½ = 110 d (field, 2-28 °C, in the dark)

Abiotic Degradation
Photodegradation: t½ = 0.4 d (laboratory, light), t½ = 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} ≤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

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