Environmental Risk Assessment Summary
Lidocaine

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.

Summary

The local anaesthetic Lidocaine [6] is used together with the antibiotic Roche product Rocephin in intramuscular application.

Lidocaine undergoes enzymatic degradation primarily in the liver. Some degradation may take place in tissues other than liver. The main pathway involves oxidative de-ethylation to monoethylglycinexylidide followed by a subsequent hydrolysis to xylidine [2].

The excretion occurs via the kidney with less than 5% in the unchanged form appearing in the urine [2].

Lidocaine is not readily biodegradable [1]. Degradation was observed in surface water experiments [12].

The PEC/PNEC ratio is 0.03. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [4], a PEC/PNEC ratio of <1 means that Lidocaine and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Predicted Environmental Concentration (PEC)

The PEC is based on the following data:

PEC (mg/L) = (A × 10^9 × (1–R)) ÷ (365 × P × V × D)

A	Total patient consumption of Lidocaine in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [7])
R	Removal rate during sewage treatment (default value) = 0 [4]
P	Number of inhabitants in the country with the highest per capita use in the respective year of the period 2013–2017 [5]; resulting in a consumption of 468 mg/inhabitant
V	Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [4]
D	Dilution factor of wastewater by surface water flow (default value) = 10 [4]

PEC = 0.641 µg/L

Note: Lidocaine is at least partially metabolised in the body. 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 Lidocaine.

Predicted No Effect Concentration (PNEC)

The PNEC is derived from the lowest EC50/LC50 from acute studies with algae, *Daphnia* and fish and fish embryos according to OECD Test Guidelines [11]. The lowest LC50 is 23.0 mg/L of the 48 h FET test with embryos of *Danio rerio* according to OECD 236 [8]. Applying an assessment factor of 1000 according to the REACH Guidance [2] results in a PNEC value of 23.0 µg/L.

PNEC = 23000 mg/L / 1000 = 23.0 µg/L

PEC/PNEC ratio

PEC = 0.641 µg/L
PNEC = 23.0 µg/L

PEC/PNEC = 0.03

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [4], a PEC/PNEC ratio of 0.03 (i.e. <1) means that Lidocaine and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Lidocaine

Study	Guideline	Results	Ref.
Algal growth inhibition test with the green alga *Raphidocelis subcapitata*	OECD 201	72 h EC50 780 mg/L	[1]
Algal growth inhibition test with the green alga *Scenedesmus vacuolatus*	NA	24 h EC50 (growth rate) 135 mg/L (pH 6.5) 24 h EC50 (growth rate) 161 mg/L (pH 7.5) 24 h EC50 (growth rate) 142 mg/L (pH 8.5) 24 h EC50 (growth rate) 128 mg/L (pH 9.0) 24 h EC50 (growth rate) 108 mg/L (pH 10.0)	[10]
Acute immobilisation test with *Daphnia magna*	OECD 202	48 h EC50 104 mg/L	[1]
Acute toxicity to the beavertail fairy shrimp, *Thamnocephalus platyurus*	Rapidtoxkit Thamnotoxkit	1 h EC50 36.0 mg/L 24 h LC50 81.7 mg/L	[9] [9]
Acute toxicity to zebrafish (*Danio rerio*)	OECD 203	96 h LC50 106 mg/L	[1]
Fish embryo test (FET) with zebrafish (*Danio rerio*)	OECD 236	48 h LC50 23.0 mg/L 48 h NOEC (morphological effects) <13.0 mg/L	[8]

EC50 Concentration of the test substance that results in 50% effect
LC50 Concentration of the test substance that results in 50% mortality
NOEC No Observed Effect Concentration

Environmental Fate Data for Lidocaine

Study	Guideline	Results	Ref.
Ready biodegradability	ISO 7827	<5% DOC removal after 30 days	[1]
Degradation in surface water	NA	Half-life 92 days (river water, in the dark) Half-life 110 days (river water, in the dark, field experiment)	[12]
Photodegradation	NA	Half-life 29.5 days (ultrapure water, pH 6.9, Hg lamp) Half-life 65.5 days (ultrapure water, pH 6.9, sunlight) Half-life 10.7 days (river water, pH 7.5, Hg lamp) Half-life 1.3 days (river water, pH 7.5, sunlight)	[12]

DOC Dissolved organic carbon

Physical Chemical Data for Lidocaine

Study	Guideline	Results	Ref.
Water solubility	NA	~50 g/L	[6]
n-Octanol/water distribution coefficient	NA	log D_{OW} = 1.63 (pH 7.4, 25 °C)	[13]
Dissociation constant	NA	pKa 8.19 (25 °C) pKa 7.77 (36 °C)	[13]

References

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