Environmental Risk Assessment Summary
Erlotinib

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

Erlotinib is a once-daily, oral, non-chemotherapy treatment for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC). It has been shown to potently inhibit the epidermal growth factor receptor (EGFR), a protein involved in the growth and development of cancers [3].

Erlotinib is the active pharmaceutical ingredient used in the Roche product Tarceva.

Erlotinib is mainly Phase-I-metabolised by hepatic cytochrome -P450 enzymes CYP3A4 and, to a lesser extent, CYP1A2 as well as by pulmonary CYP1A1. Excretion of Erlotinib and its metabolites in man is mainly (≥90%) by faecal and secondarily by urinary pathway. The median half-life of elimination on repeated once-daily administration in patients is approximately 36 hours [3].

Erlotinib is neither readily nor inherently biodegradable in standard OECD tests over 28 days. In water/sediment systems over 102 days, Erlotinib was partially transformed. However, no significant mineralisation (formation of CO_2) was observed.

The PEC/PNEC ratio is 0.00005. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [2], a PEC/PNEC ratio of ≤1 means that Erlotinib 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) = $(A \times 10^9 \times (1–R)) \div (365 \times P \times V \times D)$

A Total patient consumption of Erlotinib in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [8])
R Removal rate during sewage treatment = 0.05 (5% as calculated by the fate and emission prediction model SimpleTreat 4.0 [18]
P Number of inhabitants in the country with the highest per capita use in the respective year of the period 2013–2017[4]; resulting in a consumption of 2.3 mg/inhabitant
V Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [2]
D Dilution factor of wastewater by surface water flow (default value) = 10 [2]

PEC = 0.003 µg/L

Note: Erlotinib is metabolised in the body to an extent of more than 80%. 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 Erlotinib.

Predicted No Effect Concentration (PNEC)

Chronic studies have been performed for species from three trophic levels, based on OECD Test Guidelines [9]. The lowest No Observed Effect Concentration (NOEC) is 0.56 mg/L (560 µg/L) of the 30 d early life stage test with zebrafish (*Danio rerio*) according to OECD 210 [6]. Applying an assessment factor of 10 according to the EMA Guideline [2], this results in a PNEC value of 56 µg/L.

PNEC = 560 µg/L / 10 = 56 µg/L

PEC/PNEC ratio

PEC = 0.003 µg/L
PNEC = 56 µg/L

PEC/PNEC = 0.00005

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [2], a PEC/PNEC ratio of 0.00005 (i.e. ≤1) means that Erlotinib and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Erlotinib

Study	Guideline	Results	Ref.
Algal Growth Inhibition Test with *Raphidocelis subcapitata*	OECD 201	72 h EC50 (growth rate) >100 mg/L NC 72 h EC50 (biomass) >100 mg/L NC 72 h NOEC = 1.39 mg/L	[15]
Acute Immobilisation Test with *Daphnia magna*	OECD 202	48 h EC50 >100 mg/L NC 48 h NOEC = 0.70 mg/L	[16]
Acute Toxicity to Zebrafish (*Danio rerio*)	OECD 203	96 h LC50 >100 mg/L NC 96 h NOEC = 1.80 mg/L NC	[17]
Daphnia magna, Reproduction Test	OECD 211	21 d NOEC (overall) = 0.6 mg/L	[7]
Fish, Early-life Stage Toxicity Test with Zebrafish (*Danio rerio*)	OECD 210	30 d NOEC (overall) = 0.56 mg/L	[6]
Activated Sludge Respiration Inhibition Test	OECD 209	3 h NOEC = 1000 mg/L	[10]

EC50 concentration of the test substance that results in 50% effect
NOEC No Observed Effect Concentration
NC Nominal concentration

Environmental Fate Data for Erlotinib

Study	Guideline	Results	Ref.
Ready Biodegradability Test	OECD 301 C	0% after 28 days with respect to BOD not readily biodegradable	[13]
Inherent Biodegradability Test	OECD 302 C	0% after 28 days with respect to BOD not readily biodegradable	[5]
Aerobic Transformation in Aquatic Sediment Systems	OECD 308	Half-life (water) <2 d Half-life (total system) = 26–86 d $^{14}CO_2$ evolution <1%	[11] a)
Adsorption Coefficient (artificial water sediment system)	OECD 308 OECD 301 C	Kd = 131 L/kg Koc = 5693 L/kg	[1] b)
Bioaccumulation in rainbow trout (*Oncorhynchus mykiss*)	OECD 305	BCF = 7.8–10.1 L/kg BCFl = 136–176 L/kg	[12] c)

BOD Biochemical oxygen demand
Koc Organic carbon normalised adsorption coefficient
Kd Distribution coefficient for adsorption
a) *Interpretation*: Erlotinib was shown to form non-extractable bound residues through covalent bonding with sediment organic substance. Erlotinib is not biologically mineralised in Sediment/Water Systems.
b) *Interpretation*: The Koc is below the regulatory threshold of 10,000 L/kg
c) *Interpretation*: The whole fish bioconcentration factor (BCF) is low

Physical Chemical Data for Erlotinib

Study	Guideline	Results	Ref.
Water solubility	OECD 105	810 mg/L	[5]
Dissociation constant		pKa = 5.7	[5]
n-Octanol/Water Partition Coefficient	OECD 107	log P_{OW} = 3.57 (pH 4.9–6.5, average ion corrected)	[14]

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