Environmental Risk Assessment Summary
Peginterferon alpha-2a

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

Peginterferon alpha-2a is indicated as monotherapy for the treatment of hepatitis B virus (HCB) infections or in combination with or without Ribavirin and other antiviral agent for the treatment of hepatitis C virus (HCV) infections [3].

Peginterferon alpha-2a is the active pharmaceutical ingredient used in the Roche product Pegasys [5].

Peginterferon alpha-2a (Polyethylen glycol–Interferon alfa-2a) is one molecule of Interferon alfa-2a conjugated with a branched polyethylene glycol (PEG) chain [5]. Pegylation of proteins has been specifically developed for medical applications as it strongly extends the human half-life of elimination, delaying both enzymatic metabolisation and urinary excretion [10].

During human metabolism the pharmacologically active interferon moiety is at least partly degraded through proteolytic mechanisms, with mostly only the PEG moiety being excreted whole [3].

Peginterferon alpha-2a is not readily biodegradable in a standard OECD tests over 28 days [3] [9].

The PEC/PNEC ratio is 0.00000003. 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 Peginterferon alpha-2a 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 (µg/L) = (A x 10^9 x (1-R)) / (365 x P x V x D)

A	Total patient consumption of Peginterferon alpha-2a in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [6])
R	Removal rate during sewage treatment (default value) = 0 [2]
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 0.007 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 = 0.00001 µg/L

Note: Peginterferon alpha-2a 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 Peginterferon alpha-2a.

Predicted No Effect Concentration (PNEC)

Acute studies have been performed for daphnids [7] and fish [8] based on OECD Test Guidelines. No effects were observed in both studies at a nominal concentration of 300 mg/L (i.e. 300000 µg/L). Applying an assessment factor of 1000 according to the REACH Guidance [1] results in a PNEC value of 300 µg/L.

PNEC = 300000 µg/L / 1000 = 300 µg/L

PEC/PNEC ratio

PEC = 0.00001 µg/L
PNEC = 300 µg/L

PEC/PNEC = 0.00000003

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 0.00000003 (i.e. <1) means that Peginterferon alpha-2a and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Peginterferon alpha-2a

Study	Guideline	Results	Ref.
Acute immobilisation test with *Daphnia magna*	OECD 202	48 h EC50 >300 mg/L NC HTC [1)] 48 h NOEC 300 mg/L NC HTC [1)]	[7]
Acute Toxicity to carp (*Cyprinus carpio*)	OECD 203	96 h LC50 >300 mg/L NC HTC [1)] 96 h NOEC 300 mg/L NC HTC [1)]	[8]
Toxicity to microorganisms (toxicity control)	OECD 301 D	28 d NOEC 3.36 mg/L NC HTC [2)]	[9]

EC50 concentration of the test substance that results in 50% effect
NOEC No Observed Effect Concentration
HTC Highest tested concentration
NC Nominal concentration
1) Equivalent to 100 mg Interferon alfa-2a moiety/L
2) Equivalent to 1.12 mg Interferon alfa-2a moiety/L

Environmental Fate Data for Peginterferon alpha-2a

Study	Guideline	Results	Ref.
Ready biodegradability	OECD 301 D	BOD/ThOD (mineralisation) 22% after 28 days Not readily biodegradable	[9]

BOD Biochemical oxygen demand
ThOD Theoretical oxygen demand

Physical Chemical Data for Peginterferon alpha-2a

Study	Guideline	Results	Ref.
Water solubility	NA	Moderately soluble (1–10%)	[5]
n-Octanol/Water Partition Coefficient	QSAR	log P_{OW} = –0.34	

References

[1] European Chemicals Agency (ECHA)(2008): Guidance on information requirements and chemical safety assessment Chapter R.10: Characterisation of dose [concentration]-response for environment

[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

[3] European Medicines Agency (EMA) (2013): Assessment report for Pegasys. EMA/CHMP/83314/2013

[4] Eurostat. Population data. https://ec.europa.eu/eurostat/web/population-demography-migration-projections/data

[5] F. Hoffmann-La Roche Ltd (2021): Safety data sheet for Pegasys, 20 April 2021. https://www.roche.com/sustainability/environment/global_product_strategy_and_safety_data_sheets.htm

[6] IQVIA MIDAS Quantum, Q1 2018

[7] NOTOX B.V., on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2000): Acute toxicity study in *Daphnia magna* with Pegasys (semi-static). NOTOX study no. 281745

[8] NOTOX B.V., on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2000): 96-Hour acute toxicity study in carp with Pegasys. NOTOX study no. 281734

[9] NOTOX B.V., on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2000): Ready biodegradability: Closed bottle test with Pegasys. NOTOX study no. 281723

[10] Webster R, Didier E, Harris P, Siegel N, Stadler J, Tilbury L, Smith D (2007): PEGylated proteins: evaluation of their safety in the absence of definitive metabolism studies. Drug Metab Dispos;35: 9–16. https://doi.org/10.1124/dmd.106.012419