Environmental Risk Assessment Summary
Levodopa

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 Roche product Madopar is a combination of two active pharmaceutical ingredients, Levodopa and Benserazide hydrochloride, in the ratio 4:1. Madopar is used to treat Parkinson's disease [9].

Levodopa is the metabolic precursor of dopamine, whereas Benserazide hydrochloride is a peripheral decarboxylase inhibitor [2].

The 2 major routes of metabolism of levodopa are decarboxylation to form dopamine, which in turn is converted to a minor degree to norepinephrine and to a greater extent, to inactive metabolites, and O-methylation, forming 3-O-methyldopa, which has an elimination half-life of approximately 15 hours and accumulates in patients receiving therapeutic doses of Madopar. In the presence of the peripheral decarboxylase inhibitor, Benserazide hydrochloride, the elimination half-life of levodopa is approximately 1.5 hours. [2].

Levodopa is readily biodegradable [1][7].

The PEC/PNEC ratio is 0.049. 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 Levodopa 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 Levodopa in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [10])
R Removal rate during sewage treatment = 0.92 (92% as calculated by the fate and emission prediction model SimpleTreat 4.0 [14])
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 673 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 = 0.074 µg/L

Note: Levodopa 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 Levodopa.

Predicted No Effect Concentration (PNEC)

Acute studies have been performed for species from three trophic levels, based on OECD Test Guidelines. The lowest EC50/LC50 is 1.5 mg/L of the 72 h growth inhibition test with the green alga *Raphidocelis subcapitata* according to OECD 201 [11]. Applying an assessment factor of 1000 according to the REACH Guidance [3] results in a PNEC value of 1.5 µg/L.

PNEC = 1500 µg/L / 1000 = 1.5 µg/L

PEC/PNEC ratio

PEC = 0.074 µg/L
PNEC = 1.5 µg/L

PEC/PNEC = 0.049

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 0.049 (i.e. <1) means that Levodopa and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Levodopa

Study	Guideline	Results	Ref.
Algal growth inhibition test with the green alga *Raphidocelis subcapitata*	OECD 201	72 h EC50 (growth rate) = 3.2–5.6 mg/L NC 72 h EC50 (biomass) = 1.5 mg/L NC 72 h NOEC = 0.32 mg/L NC	[11]
Acute Immobilisation Test with *Daphnia magna*	OECD 202	48 h EC50 >100 mg/L NC 48 h NOEC = 100 mg/L NC	[12]
Acute toxicity to rainbow trout (*Oncorhynchus mykiss*)	OECD 203	96 h LC50 >100 mg/L NC 96 h NOEC = 100 mg/L NC	[6]
Bacteria toxicity (toxicity control in ready biodegradability test)	OECD 301 F	14 d NOEC = 100 mg/L	[7]

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

Environmental Fate Data for Levodopa

Study	Guideline	Results	Ref.
Ready Biodegradability Test	OECD 301 F	BOD/ThOD (mineralisation) 72% after 28 days 67% at the end of the 10-d window Readily biodegradable DOC elimination 100% after 28 day	[1] a)
Ready Biodegradability Test	OECD 301 F	BOD/ThOD (mineralisation) 72% after 28 days 69% at the end of the 10-d window Readily biodegradable	[7] b)
Ready Biodegradability Test	OECD 301 B	CO2 evolution (mineralization) 28% after 28 days Not readily biodegradable	[13] c)

BOD Biochemical oxygen demand
DOC Dissolved organic carbon
ThOD Theoretical oxygen demand
a) Test series with inhibition of nitrification (addition of allylthiourea); inoculum: activated sludge with 30 mg/L with respect to dry weight
b) Inoculum: activated sludge with 30 mg/L with respect to dry weight
c) Inoculum: secondary effluent (10 ml/L supernatant of a 2.8 g/l activated sludge suspension)

Physical Chemical Data for Levodopa

Study	Guideline	Results	Ref.
Water solubility		2700 mg/L	[8]
n-Octanol/Water Partition Coefficient		log P_{OW} -2.39	[8]

References

[1] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2010): Levodopa: Ready Biodegradability - Evaluation of the aerobic biodegradability in an aqueous medium: Manometric Respirometry Test. BMG study no. A09-02230

[2] electronic Medicines Compendium (eMC). https://www.medicines.org.uk/emc/

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

[4] 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

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

[6] F. Hoffmann-La Roche Ltd (1996): 96-Hour acute toxicity test with Levodopa in rainbow trout in a semi-static test. PSU study no. 96/3-FT

[7] F. Hoffmann-La Roche Ltd (1996): Ready Biodegradability: Manometric Respirometry Test for Levodopa. PSU study no. 96/3-BOD

[8] F. Hoffmann-La Roche Ltd (2020): Safety data sheet for Levodopa, 12 March 2020. https://www.roche.com/sustainability/environment/global_product_strategy_and_safety_data_sheets.htm

[9] F. Hoffmann-La Roche Ltd (2020): Safety data sheet for Madopar, 8 April 2020. https://www.roche.com/sustainability/environment/global_product_strategy_and_safety_data_sheets.htm

[10] IQVIA MIDAS Quantum, Q1 2018

[11] NOTOX B.V., on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (1996): Fresh water growth inhibition test with Levodopa. NOTOX study no. 180102

[12] NOTOX B.V., on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (1996): Acute toxicity study in *Daphnia magna*. NOTOX study no. 180023

[13] NOTOX B.V., on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (1998): Determination of ready biodegradability: carbon dioxide (CO2) evolution test (Modified Sturm Test) with Levodopa. NOTOX study no. 215415

[14] 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