Environmental Risk Assessment Summary
Isotretinoin

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

Isotretinoin is a retinoid compound and a derivative of vitamin A. Isotretinoin is used for the systemic treatment of acne. Isotretinoin is the active pharmaceutical ingredient in the Roche product Roaccutane [11]. Isotretinoin is a stereoisomer of all-trans retinoic acid (tretinoin). It has been established that the improvement observed in the clinical picture of severe acne is associated with suppression of sebaceous gland activity and reduction in the size of the sebaceous glands. Isotretinoin inhibits proliferation of sebocytes and appears to act in acne by re-setting the orderly program of differentiation. Like all retinoids, Isotretinoin is teratogen and is contraindicated during pregnancy to avoid congenital defects [6].

After oral administration of Isotretinoin, three major metabolites have been identified in plasma that are biologically active: 4-oxo-isotretinoin, tretinoin (all-trans retinoic acid) and 4-oxo-tretinoin. Isotretinoin and tretinoin are reversibly metabolised (interconverted). It has been estimated that 20–30% of an Isotretinoin dose is metabolised by isomerisation. After oral administration of Isotretinoin equal fractions of the dose were recovered in urine and faeces [6].

Ready biodegradability of Isotretinoin is not tested. In an inherent biodegradability test according to OECD 302 C a biodegradation based on oxygen consumption of 59% after 28 days was observed [10].

The PEC/PNEC ratio is 0.374. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [7], a PEC/PNEC ratio of <1 means that Isotretinoin 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) = $(A \times 10^9 \times (1\text{-}R)) / (365 \times P \times V \times D)$

A	Total patient consumption of Isotretinoin in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [12])
R	Removal rate during sewage treatment = 0 (default value)
P	Number of inhabitants in the country with the highest per capita use in the respective year of the period 2013–2017 [8]; resulting in a consumption of 8.19 mg/inhabitant
V	Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [7]
D	Dilution factor of wastewater by surface water flow (default value) = 10 [7]

PEC = 0.011 µg/L

Note: Isotretinoin 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 Isotretinoin.

Predicted No Effect Concentration (PNEC)

Acute studies have been performed for species from three trophic levels, based on OECD Test Guidelines. Additionally, results of the Frog Embryo Teratogenesis Assay-Xenopus (FETAX) can be found in the peer-reviewed literature [3]. The 96 h LC50 for mortality in the FETAX is 0.030 mg/L. Applying an assessment factor of 1000 according to the REACH Guidance [4] results in a PNEC value of 0.03 µg/L.

PNEC = 30 µg/L / 1000 = 0.03 µg/L

PEC/PNEC ratio

PEC = 0.011 µg/L
PNEC = 0.03 µg/L

PEC/PNEC = 0.374

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [7], a PEC/PNEC ratio of 0.374 (i.e. <1) means that Isotretinoin and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Isotretinoin

Study	Guideline	Results	Ref.
Algal growth inhibition test with the green alga *Raphidocelis subcapitata*	OECD 201	72 h EC50 (growth rate) 14.4 mg/L MC 72 h EC50 (biomass) 1.39 mg/L MC 72 h NOEC 0.8 mg/L MC	[1]
Acute immobilisation test with *Daphnia magna*	FDA No. 4.08 OECD 202	48 h EC50 2.06 mg/L MC 48 h EC50 5.4 mg/L NC	[14] [2]
Acute toxicity to rainbow trout (*Oncorhynchus mykiss*)	OECD 203	96 h LC50 0.52 mg/L MC 96 h NOEC 0.05 mg/L MC	[13]
Frog embryo teratogenesis assay with *Xenopus laevis* (FETAX)	NA	96 h LC50 (mortality) 0.030 mg/L 96 h EC50 (development) 0.003 mg/L [1)]	[3]
Activated sludge, respiration inhibition test	OECD 209	3 h EC50 >100 mg/L NC	[9]

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

1) According to the Technical Guidance for Deriving Environmental Quality Standards [5], the study endpoints (mortality, development and malformation) are considered rather as acute for the derivation of environmental quality standards, albeit the endpoints development and malformation may indicate the presence of chronic effects. Therefore, the LC50 for mortality is regarded to be more appropriate to be used in an acute assessment.

Environmental Fate Data for Isotretinoin

Study			Ref.
Inherent biodegradability	OECD 302 C	59% after 28 days (BOD/ThOD) [1)]	[10]

BOD Biochemical oxygen demand
ThOD Theoretical oxygen demand

1) After a short adaption period of 3 days, Isotretinoin showed a maximum degradation rate of about 11% per day. After 7 days the rate decreased to about 1.5% per day. The endpoint of degradation was reached after 21 days. After 28 days of testing, Isotretinoin showed a biodegradability of 59%.

Physical Chemical Data for Isotretinoin

Study	Guideline	Results	Ref.
Water solubility	NA	<100 mg/L (25 °C)	[11]
Dissociation constant (pKa)	calculated	4.76 [1)]	
n-Octanol/Water Partition	NA	log P_{OW} 6.3	[11]
Coefficient	calculated	log P_{OW} 7.85	[15]
	calculated	log P_{OW} 5.01 (https://chemicalize.com)	
	calculated	log P_{OW} 7.61 (http://www.archemcalc.com/sparc)	
n-Octanol/Water Distribution	calculated	(https://chemicalize.com) [1)]	
Coefficient		log D_{OW} 4.58 (pH 5)	
		log D_{OW} 2.79 (pH 7)	
		log D_{OW} 1.56 (pH 9)	

1) The calculated data suggest that Isotretinoin is predominantly in the ionic form at neutral pH and above.

References

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