Environmental Risk Assessment Summary
Capecitabine / 5-Fluorouracil

Introduction

The publication of environmental risk assessment (ERA) 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 cytostatic drug Capecitabine (CAP) is used to treat patients with colorectal, breast, or colon cancer. CAP [16] is the active pharmaceutical ingredient in the Roche product Xeloda [17].

CAP is a prodrug of and is rapidly metabolized to the active substance 5-Fluorouracil (5-FU [15]). 5-FU is an antimetabolite that hinders cell growth through inhibition of thymidilate synthetase, driving the biosynthesis of desoxythymidine monophosphate, thereby obstructing thymidine synthesis and ultimately blocking normal DNA replication. Moreover, it also causes the synthesis of faulty DNA through incorporation of 5-FU in lieu of pyrimidine bases [22].

CAP is administered orally, readily absorbed from the gastrointestinal tract, and converted to the active 5-FU, which is further metabolized to inactive compounds. Metabolism of CAP to 5-FU proceeds rapidly ($t_{1/2}$ ~45 min). The biological half-life of 5-FU is about 46 min. All metabolites beyond 5-FU are stated to be pharmacologically inactive. Excretion of CAP, 5-FU, and their metabolites is mainly pulmonary and renal; 2.9% is excreted as CAP and only 0.5% as 5-FU [22].

The ERA is performed for the active substance 5-FU.

Results from standard tests suggest that 5-FU is neither readily nor inherently biodegradable. However, in surface water degradation tests a significant mineralisation with a $t_{1/2}$ of 9–10 d was observed. In batch tests using an activated sludge concentration of 4 g/L complete mineralisation within about 4 days was observed [22], indicating that 5-FU is not a persistent compound.

The PEC/PNEC ratio is 0.45. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [12], a PEC/PNEC ratio of <1 means that CAP, 5-FU and/or their metabolites are unlikely to represent a risk to the aquatic environment.

Predicted Environmental Concentration (PEC)

The PEC is based on the following data:

$PEC\ (\mu g/L) = (A \times 10^9 \times (1–R)) \div (365 \times P \times V \times D)$

- A Total patient consumption of 5-FU (as the sum of CAP and 5-FU) in the European country with the highest yearly per capita use in the period 2019–2023 (data from IQVIA [18])
- R Removal rate during sewage treatment = 0.15; i.e. 15% [23]
- P Number of inhabitants in the country with the highest per capita use in the respective year of the period 2019–2023 [13]; resulting in a consumption of 76.5 mg/y per inhabitant
- V Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [12]
- D Dilution factor of wastewater by surface water flow (default value) = 10 [12]

PEC = 0.089 µg/L

Note: CAP and 5-FU are 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 CAP and 5-FU.

Predicted No Effect Concentration (PNEC)

Chronic studies have been performed with 5-FU based on OECD Test Guidelines [21] for species from three trophic levels (green algae, invertebrates, fish) and by including a cyanobacteria species. The lowest no observed effect concentration (NOEC) is 0.002 mg/L (2 µg/L) for 5-FU, assessed in a cyanobacteria test with *Anabaena flos-aquae* [9]. Applying an assessment factor of 10 according to the EMA Guideline [12], this results in a PNEC value of 0.2 µg/L.

PNEC = 2 µg/L ÷ 10 = 0.2 µg/L

PEC/PNEC Ratio

PEC = 0.089 µg/L
PNEC = 0.2 µg/L

PEC/PNEC = 0.45

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [12], a PEC/PNEC ratio of 0.45 (i.e. <1) means that CAP, 5-FU and/or their metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Capecitabine (CAP) and 5-Fluorouracil (5-FU)

Study	Guideline	Results	Test item	Ref.
Growth inhibition test with green algae (*Raphidocelis subcapitata*)	OECD 201	72 h EC50 (growth rate) 200 mg/L MMC 72 h EC50 (yield) 58 mg/L MMC 72 h NOEC 14 mg/L MMC	CAP	[1]
		72 h EC50 0.11 mg/L	5-FU	[24]
Growth inhibition test with green algae (*Desmodesmus subspicatus*)	OECD 201	72 h EC50 21 mg/L 72 h EC10 11 mg/L	5-FU	[8]
Growth inhibition test with cyanobacteria (*Anabaena flos-aquae*)	OECD 201	72 h EC50 (growth rate) 24.0 mg/L GMC 72 h EC50 (yield) 7.4 mg/L GMC 72 h EC10 (growth rate) 11.2 mg/L GMC 72 h EC10 (yield) 2.0 mg/L GMC 72 h NOEC 2.0 mg/L GMC	5-FU	[9]
Acute immobilisation test with *Daphnia magna*	OECD 202	48 h EC50 >850 mg/L MMC 48 h NOEC 500 mg/L MMC	CAP	[2]
		48 h EC50 25 mg/L 48 h EC10 1.3 mg/L	5-FU	[8]
Daphnia magna, Reproduction Test	OECD 211	21 d EC50 >112 mg/L MMC 21 d NOEC 112 mg/L MMC	CAP	[7]
		21 d NOEC 3 mg/L TWM	5-FU	[10]
Acute toxicity to rainbow trout (*Oncorhynchus mykiss*)	OECD 203	96 h LC50 >867 mg/L MMC 96 h NOEC 867 mg/L MMC	CAP	[3]
	NA	48 h NOEC ≥1000 mg/L	5-FU	[14]
Fish, early-life stage toxicity test with zebrafish (*Danio rerio*)	OECD 210	36 d EC10 (mortality) 20.9 mg/L MMC 36 d NOEC 32 mg/L MMC	5-FU	[11]
Activated sludge respiration inhibition test	OECD 209	3 h EC50 >1000 mg/L NC	CAP	[4]
	NA	21 d NOEC/LOEC 100 mg/L	5-FU	[14]

EC10 concentration of the test substance that results in 10% effect
EC50 concentration of the test substance that results in 50% effect
NOEC No observed effect concentration
GMC Geometric mean measured concentration
MMC Mean measured concentration
TWM Time-weighted mean measured concentration

Environmental Fate Data for Capecitabine (CAP) and 5-Fluorouracil (5-FU)

Study	Guideline	Results	Test item	Ref.
Ready biodegradability	OECD 301 B	CO2 ÷ TOC (mineralisation) 86% after 28 d 40% at the end of the 10-d window inherently biodegradable	CAP	[5]
	OECD 301 C	BOD ÷ ThOD (mineralisation) 0% after 21 d	5-FU	[14]
	OECD 301 D	BOD ÷ ThOD (mineralisation) 0% after 28 d 0% after 40 d	5-FU	[19]
Inherent biodegradability	OECD 302 C	BOD ÷ ThOD (mineralisation) 29% after 28 d 44% after 56 d 55% after 84 d DOC elimination 68% after 28 d kd 272 L/kg (based on 3 h data) Primary degradation ~100% after 28–41 d (an unkown metabolite was formed)	CAP	[6]
	OECD 302 B	DOC elimination 0% after 21 d	5-FU	[14]
		DOC elimination 2% after 28 d	5-FU	[19]
Inherent biodegradability in tap water, activated sludge 4 g/L	NA	[14C]CO2 (mineralisation) >25% after 1 d 65–100% in 4 d 81– >100% in 7 d 97.5– >100% in 15 d	5-FU	[20]
Surface water biodegradation	OECD 309	DT50 9–10 d	5-FU	[20]
Aerobic transformation in aquatic sediment systems	OECD 308	DT50 (total system) 2 d ~80% [14C]CO2 in 24 d	5-FU	[20]

BOD Biochemical oxygen demand
CO2 Carbon dioxide produced
DOC Dissolved organic carbon
DT50 Half life
kd Partition coefficient in activated sludge (estimate)
ThOD Theoretical oxygen demand
TOC Total organic carbon

Physical Chemical Data for Capecitabine (CAP) and 5-Fluorouracil (5-FU)

Study	Guideline	Results	Test item	Ref.
Water solubility	NA	26 g/L (20 °C)	CAP	[16]
	NA	10 g/L (20 °C)	5-FU	[15]
Dissociation constant pKa	NA	8.8	CAP	[16]
n-Octanol-water	NA	logDow ~4.5 (pH 7.4)	CAP	[16]
distribution coefficient	NA	logDow -0.69 (literature value)	5-FU	[15]

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