Environmental Risk Assessment Summary
Sulfamethoxazole

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.

If measured environmental concentrations (MECs) are available, these are also compared with the PNEC.

Summary

Sulfamethoxazole is a sulphonamide antimicrobial agent. It is commonly used in combination with Trimethoprim. Sulfamethoxazole competitively inhibits dihydropteroate synthase preventing the formation of dihydropteroic acid, a precursor of folic acid which is required for bacterial growth [22].

Sulfamethoxazole is the active pharmaceutical ingredient used in combination with Trimethoprim in the Roche product Bactrim.

Sulfamethoxazole (SMX) is rapidly absorbed on oral administration; metabolism is mainly hepatic, with the formation of predominantly N4-acetyl-SMX (NAcSMX) and glucuronide conjugates (GluSMX). Excretion is renal, with a half-life of 7 h to 12 h, most of the excreted substance being NAcSMX (30–70% of administered), followed by Sulfamethoxazole (10–40%) and GluSMX [22].

Sulfamethoxazole is neither readily nor inherently biodegradable in standard OECD tests over 28 days. However, based on 190 data of full-scale working sewage treatment plants (STP) the median removal rate amount to 49% [22].

The $PEC/PNEC_{ENV}$ ratio for ecotoxicology is 0.07. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [11], a $PEC/PNEC_{ENV}$ ratio of <1 means that Sulfamethoxazole and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Also when considering a PEC/$PNEC_{MIC}$ ratio of 0.03 (i.e. <1) for antimicrobial resistance (AMR) promotion, Sulfamethoxazole 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 Sulfamethoxazole in the European country with the highest yearly per capita use in the period 2017–2021 (data from IQVIA [18])
R Removal rate during sewage treatment (default value) = 0 [11] as a worst case; the median removal rate in full-scale working STPs would amount to 49% [22]
P Number of inhabitants in the country with the highest per capita use in the respective year of the period 2017–2021 [13]; resulting in a consumption of 340 mg/inhabitant
V Volume of wastewater per inhabitant and day (default value) = 200 L day^{-1} [11]
D Dilution factor of wastewater by surface water flow (default value) = 10 [11]

PEC = 0.465 µg/L (without elimination in STP, default value as a worst case [11])
PEC = 0.237 µg/L (with elimination in STP [22])

Note: Sulfamethoxazole is metabolised in the body to an extent of up to 90%. 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 Sulfamethoxazole.

Measured Environmental Concentration (MEC)

Based on about 5000 MEC data for Europe the calculated 50th and 95th percentiles (MEC_{50} and MEC_{95}, respectively) for Sulfamethoxazole were 0.052 µg/L and 0.286 µg/L, respectively [22].

Taking into account a removal rate of 49% in full-scale working STPs [22] the MEC_{95} of 0.286 µg/L is in good agreement with the calculated PEC for Sulfamethoxazole of 0.237 µg/L.

Predicted No Effect Concentration for Aquatic Ecosystem Function ($PNEC_{ENV}$)

Acute and chronic data for species from three trophic levels, partially assessed according to OECD Test Guidelines [21], but also taken from the literature, have been considered in this report. For the derivation of the $PNEC_{ENV}$ in the course of a tailored environmental risk assessment for antibiotics according to the new draft EMA ERA guidance [12] data assessed in compliance with OECD's Good Laboratory Practice (GLP) for the following endpoints were used: growth inhibition test with two cyanobacteria species and one green algae species and the *Daphnia magna*, reproduction test.

The lowest EC10 is 0.066 mg/L (66 µg/L) of the 72 h growth inhibition test with the cyanobacteria *Synechococcus leopoliensis* according to OECD 201 [4] Applying an assessment factor of 10 according to the EMA Guideline [11] this results in a $PNEC_{ENV}$ of 6.6 µg/L.

$PNEC_{ENV}$ = 6.6 µg/L

Predicted No Effect Concentration for Antimicrobial Resistance Promotion ($PNEC_{MIC}$)

In the discussion about antimicrobial resistance (AMR) promotion, $PNEC_{MIC}$ values are derived. An approach is to use the 1st percentile of the minimal inhibitory concentrations (MIC) for different bacteria genera, corresponding to the value containing the bottom 1% of the MIC values and by applying a safety factor of 10. With this approach a $PNEC_{MIC}$ of 16 µg/L was derived ([7] [8] [23]).

$PNEC_{MIC}$ = 16 µg/L

PEC/PNEC ratios

PEC = 0.465 µg/L
$PNEC_{ENV}$ = 6.6 µg/L
$PNEC_{MIC}$ = 16 µg/L

$PEC/PNEC_{ENV}$ = 0.07
$PEC/PNEC_{MIC}$ = 0.03

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [11], a $PEC/PNEC_{ENV}$ ratio of 0.07 (i.e. <1) means that Sulfamethoxazole and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Also when considering a $PEC/PNEC_{MIC}$ ratio of 0.03 (i.e. <1) for AMR promotion, Sulfamethoxazole and/or its metabolites are unlikely to represent a risk to the aquatic environment.

Aquatic Toxicity Data for Sulfamethoxazole

Study	Guideline	Results	Ref.
Growth inhibition test with the green alga *Raphidocelis subcapitata*	OECD 201	72 h EC50 (growth rate) 3.4 mg/L NC 72 h EC50 (biomass) 0.81 mg/L NC 72 h EC10 (growth rate) 0.4 mg/L NC 72 h EC10 (biomass) 0.17 mg/L NC	[19]
	not specified	96 h EC50 0.146 mg/L 96 h NOEC 0.090 mg/L	[15]
Growth inhibition test with the green alga *Chlorella vulgaris*	OECD 201	72 h EC50 1.51 mg/L	[9]
Growth inhibition test with the cyanobacteria *Anabaena flos-aquae*	OECD 201	72 h EC50 (growth rate) 190 mg/L NC 72 h EC50 (yield) 0.155 mg/L NC 72 h EC10 (growth rate) 0.104 mg/L NC 72 h EC10 (yield) 0.014 mg/L NC	[3]
Growth inhibition test with the cyanobacteria *Synechococcus leopoliensis*	OECD 201	72 h EC50 (growth rate) 7.44 mg/L NC 72 h EC50 (yield) 0.176 mg/L NC 72 h EC10 (growth rate) 0.066 mg/L NC 72 h EC10 (yield) 0.020 mg/L NC	[4]
	not specified	96 h EC50 0.0268 mg/L 96 h NOEC 0.0059 mg/L	[15]
Growth inhibition test with the duckweed *Lemna gibba*	ASTM	7 d EC50 (frond no.) 0.249 mg/L 7 d EC50 (wet weight) 0.081 mg/L 7 d EC10 (frond no.) 0.011 mg/L 7 d EC10 (wet weight) 0.017 mg/L	[10]
Acute immobilisation test with *Daphnia magna*	OECD 202	48 h EC50 75 mg/L 48 h NOEC 36 mg/L	[20]
Daphnia magna, reproduction test	OECD 211	21 d LOEC (overall) 0.625 mg/L NC 21 d NOEC (overall) <0.625 mg/L NC	[5]
Ceriodaphnia dubia, reproduction and survival test	AFNOR T90-376	7 d NOEC 0.25 mg/L	[15]
Fish embryo toxicity test with zebrafish (*Danio rerio*)	ISO 12890	10 d NOEC 8 mg/L	[15]
Zebrafish (*Danio rerio*) partial life-cycle test	not specified	150 d NOEC (overall) 0.02 mg/L 96 h NOEC (next generation) 0.02 mg/L	[24]
Activated sludge respiration inhibition test	OECD 209 (2010)	<u>Total respiration rate</u> EC50 4280 mg/L EC10 444 mg/L NOEC 100 mg/L <u>Heterotrophic respiration rate</u> EC50 3070 mg/L EC10 473 mg/L NOEC 100 mg/L <u>Nitrification respiration rate</u> EC50 7950 mg/L EC10 429 mg/L NOEC 100 mg/L	[6] [6] [6]
Anaerobic inhibition	OECD 224	NOEC 100 mg/L	[16]

EC50 concentration of the test substance that results in 50% effect
EC10 concentration of the test substance that results in 10% effect
LOEC Lowest observed effect concentration
NOEC No observed effect concentration
NC Nominal concentration

Shaded test data were assessed according to the new EMA ERA guidance [12] and in compliance with GLP and were consequently used for the derivation of the $PNEC_{ENV}$.

Environmental Fate Data for Sulfamethoxazole

Study	Guideline	Results	Ref.
Ready Biodegradability Test	OECD 301 D	2% after 14 days with respect to BOD 4% after 28 days with respect to BOD	[2]
		0% after 28 days with respect to BOD 0% after 40 days with respect to BOD not readily biodegradable	[1]
Inherent Biodegradability Test	OECD 302 B	0% after 28 days with respect to TOC (mineralization) 13% after 28 days with respect to TOC (DOC elimination) not inherently biodegradable	[17]
Anaerobic Biodegradability test	ISO 11734	0% after 60 days with respect to TOC (biogas production) 0% after 60 days with respect to TOC (DOC elimination) not anaerobically biodegradable	[16]

BOD Biochemical oxygen demand
TOC Total organic carbon

Physical Chemical Data for Sulfamethoxazole

Study	Guideline	Results	Ref.
Water solubility		136 mg/L (37 °C)	[14]
n-Octanol-water partition coefficient		log P_{OW} = 0.89	[14]

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