

Environmental Risk Assessment Data Summary

<u>Active Pharmaceutical Ingredient</u>	<u>Medical Product</u>
Pyrimethamine	Daraprim

Executive Summary

GSK is committed to ensuring that our compounds do not adversely affect the environment. We carry out state-of-the-art environmental testing on all our pharmaceuticals and use these data in risk assessments to evaluate potential for harm to the environment. The results of these assessments suggest that no adverse environmental impact is likely to result from post-patient release of GSK pharmaceuticals into the environment.

This Environmental Risk Assessment (ERA) has been conducted for pyrimethamine and demonstrates that the use of this drug substance is considered to result in insignificant environmental risk. This evaluation is based on the Predicted Environmental Concentration (PEC) to Predicted No Effects Concentration (PNEC) ratio of less than 0.1.

GlaxoSmithKline's public position statement on pharmaceuticals in the environment may be accessed via this link - [GlaxoSmithKline's Position: Pharmaceuticals in the Environment](#).

The following pages contain the technical background information.

Technical Background Information

Environmental Fate

Pyrimethamine is not readily biodegradable nor inherently biodegradable and is expected to persist in the environment. This substance is water soluble and a low partition coefficient suggests it is unlikely to bioconcentrate in exposed aquatic organisms. It is not likely to adsorb to sludge or biomass and is not expected to reach the terrestrial compartment to a significant extent.

PEC/PNEC Risk Quotient Calculation

European Union

The PEC/PNEC risk quotient calculation is the standard quantitative method of risk assessment and is approved by major national and international regulatory agencies [2, 3, 4].

Predicted Environmental Concentration

The PEC has been calculated based on the following data:

$$\text{PEC } (\mu\text{g/L}) = \frac{A \times 1\text{E} + 09 \times (100 - R)}{365 \times P \times V \times D \times 100}$$

where:

A (kg/year) = total use of pyrimethamine active based on sales in the European Union in 2012 (IMS Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For pyrimethamine it has been assumed that R = 0% as a worst case scenario [3].

P = number of inhabitants in the European Union (EU 27) = 502.48×10^6 (IMS Data).

V (L/day) = volume of wastewater per capita and day = 200, EMA default [2].

D = factor for dilution of waste water by surface water flow = 10, EMA default [2].

NB: PEC, conservatively, is based on no metabolism and no removal of drug substance to sludge solids. It is assumed that 100% of drug substance enters the aquatic environment.

PEC = 0.0001 $\mu\text{g/L}$

Predicted No Effects Concentration (PNEC)

PNEC ($\mu\text{g/L}$) = lowest EC50/1000, where 1000 is the assessment factor applied for three short-term EC50s. EC50 for water flea (= 4,800 $\mu\text{g/L}$) has been used for this calculation since it is the most sensitive of the three tested species.

$$\text{PNEC} = 4,800/1,000 = 4.80 \mu\text{g/L}$$

PEC/PNEC Risk Characterisation

$$\text{PEC/PNEC} = 0.000046/4.80$$

$$\text{PEC/PNEC}_{(\text{European Union})} = 0.0000096$$

The PEC/PNEC is ≤ 0.1 which means the use of pyrimethamine in the European Union is considered to result in insignificant environmental risk, in accordance with the faas environmental classification scheme [4].

PEC/PNEC Risk Quotient Calculation

United States of America (Not applicable)

The PEC/PNEC risk quotient calculation is the standard quantitative method of risk assessment and is approved by major national and international regulatory agencies [2, 3, 4].

Predicted Environmental Concentration

The PEC has been calculated based on the following data:

$$\text{PEC } (\mu\text{g/L}) = \frac{A \times 1\text{E} + 09 \times (100 - R)}{365 \times P \times V \times D \times 100}$$

where:

A (kg/year) = total use of pyrimethamine active based on sales in the United States of America in 2012 (IMS Data).

R (%) = removal rate due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation. For pyrimethamine it has been assumed that R = 0% as a worst case scenario [3].

P = number of inhabitants in the United States of America = 311.591×10^6 (IMS Data).

V (L/day) = volume of wastewater per capita and day = 370, USGS.

D = factor for dilution of waste water by surface water flow = 10, FDA default [5].

NB: PEC, conservatively, is based on no metabolism and no removal of drug substance to sludge solids. It is assumed that 100% of drug substance enters the aquatic environment.

PEC = 0.00 $\mu\text{g/L}$

Predicted No Effects Concentration (PNEC)

PNEC ($\mu\text{g/L}$) = lowest EC50/1000, where 1000 is the assessment factor applied for three short-term EC50s. EC50 for water flea (= 4,800 $\mu\text{g/L}$) has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 4,800/1,000 = 4.80 $\mu\text{g/L}$

PEC/PNEC Risk Characterisation

PEC/PNEC = Not applicable

All relevant environmental fate and ecotoxicity data are published in Section 12 of the Material Safety Data Sheet (MSDS) for the medical product. The MSDS is publicly available at <http://www.msds-gsk.com/ExtMSDSlist.asp>.

Metabolism and Excretion

Pyrimethamine is predominantly eliminated by metabolism, with up to 30% recovered in the urine as parent compound over a period of several weeks. The mean elimination half-life is 85 hours (ranging from 35 to 175 hours). In AIDS patients, the total clearance is 1.28+/-0.41L/h resulting in an elimination half life of 139+/-34h. Data are lacking on the nature of the metabolites of pyrimethamine, their route/rate of formation and elimination in man and any pharmacological activity, particularly after prolonged daily dosing [1].

References

1. Summary of Product Characteristics Daraprim (Pyrimethamine) tablets. GlaxoSmithKline, July 2013. <http://www.medicines.org.uk/EMC/>
2. Committee for Medicinal Products for Human Use (CHMP); Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. 1 June 2006, Ref EMEA/CPMP/SWP/4447/00. http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf
3. European Chemicals Agency (ECHA). 2008 Guidance on information requirements and chemical safety assessment. http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm
4. Fass Environmental Classification of Pharmaceuticals. 2012 Guidance for Pharmaceutical Companies. www.fass.se
5. Food and Drug Administration (FDA). 1998 Guidance for Industry on Environmental Assessment of Human Drug and Biologics Applications. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf>