

# Environmental Risk Assessment Data Summary

<u>Active Pharmaceutical Ingredient</u>	<u>Medical Product</u>
Paroxetine	Seroxat Paxil

## 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 paroxetine 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. Paroxetine is an active ingredient in GSK pharmaceutical products and pharmaceutical products sold by other companies. This assessment takes account of the total quantity of active ingredient marketed by GSK and all other companies.**

*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

This substance has solubility in water and is not likely to partition to air from water very readily. Paroxetine is not readily nor inherently biodegradable and is expected to persist in the environment. This material has been shown to be chemically unstable in water when exposed to light. Aqueous photolysis may be a significant depletion mechanism. Paroxetine is not lipophilic and has a low potential to bioconcentrate in exposed aquatic organisms. Significant removal from the aquatic environment in wastewater treatment plants is not expected. This material 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 paroxetine active based on total sales (GSK + all other companies) in the European Union in 2013 (IMS Data). GSK accounted for 20% of this market in 2013.

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

P = number of inhabitants in the European Union (EU 27) =  $500.151 \times 10^6$  (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 = 0.052  $\mu\text{g/L}$**

## Predicted No Effects Concentration (PNEC)

PNEC ( $\mu\text{g/L}$ ) = lowest NOEC/100, where 100 is the assessment factor applied for one long-term NOEC. NOEC for water flea (= 250  $\mu\text{g/L}$ ) has been used for this calculation since it is the most sensitive of the tested species.

$$\text{PNEC} = 250/100 = 2.50 \mu\text{g/L}$$

## PEC/PNEC Risk Characterisation

$$\text{PEC/PNEC} = 0.052/2.50$$

$$\text{PEC/PNEC}_{(\text{European Union})} = 0.021$$

## 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**

GSK does not market paroxetine in the United States. Therefore, the PEC has not been calculated:

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

where:

A (kg/year) = total use of paroxetine active based on total sales (GSK + all other companies) in the United States of America in 2013 (IMS Data). GSK accounted for 0% of this market in 2013.

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

P = number of inhabitants in the United States of America =  $321.489 \times 10^6$  (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 NOEC/100, where 100 is the assessment factor applied for one long-term NOEC. NOEC for water flea (= 250  $\mu\text{g/L}$ ) has been used for this calculation since it is the most sensitive of the tested species.

**PNEC = 250/100 = 2.50  $\mu\text{g/L}$**

## PEC/PNEC Risk Characterisation

PEC/PNEC = 0.00/2.50

**PEC/PNEC (United States of America) = 0.00**

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

The principal metabolites of paroxetine are polar and conjugated products of oxidation and methylation which are readily cleared. In view of their relative lack of pharmacological activity, it is most unlikely that they contribute to paroxetine's therapeutic effects. Metabolism does not compromise paroxetine's selective action on neuronal 5-HT uptake. Urinary excretion of unchanged paroxetine is generally less than 2% of dose whilst that of metabolites is about 64% of dose. About 36% of the dose is excreted in faeces, probably via the bile, of which unchanged paroxetine represents less than 1% of the dose. Thus paroxetine is eliminated almost entirely by metabolism binding [1].

## References

1. Summary of Product Characteristics Seroxat (paroxetine hydrochloride hemihydrate) Oral Suspension. GlaxoSmithKline, January 2014. <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](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](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](http://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>