

Environmental Risk Assessment Data Summary

<u>Active Pharmaceutical Ingredient</u>	<u>Medical Product</u>
Bupropion hydrochloride	Wellbutrin Zyban

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 bupropion 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

Bupropion is not readily biodegradable but is inherently biodegradable and has been shown to be chemically unstable in water. It is expected not 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. Significant removal from the aquatic environment by biodegradation in wastewater treatment plants is expected. 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 bupropion 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 bupropion 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 = 0.041 $\mu\text{g/L}$

Predicted No Effects Concentration (PNEC)

PNEC ($\mu\text{g/L}$) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for fathead minnow (= 100 $\mu\text{g/L}$) has been used for this calculation since it is the most sensitive of the three tested species.

$$\text{PNEC} = 100/10 = 10 \mu\text{g/L}$$

PEC/PNEC Risk Characterisation

$$\text{PEC/PNEC} = 0.041/10$$

$$\text{PEC/PNEC}_{(\text{European Union})} = 0.0041$$

The PEC/PNEC is ≤ 0.1 which means the use of bupropion 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

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 bupropion 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 bupropion 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.

$$\text{PEC} = 0.0034 \mu\text{g/L}$$

Predicted No Effects Concentration (PNEC)

PNEC ($\mu\text{g/L}$) = lowest NOEC/10, where 10 is the assessment factor applied for three long-term NOECs. NOEC for fathead minnow (= 100 $\mu\text{g/L}$) has been used for this calculation since it is the most sensitive of the three tested species.

$$\text{PNEC} = 100/10 = 10 \mu\text{g/L}$$

PEC/PNEC Risk Characterisation

PEC/PNEC = 0.0034/10

PEC/PNEC (United States of America) = 0.00034

The PEC/PNEC is ≤ 0.1 which means the use of bupropion in the United States of America is considered to result in insignificant environmental risk, in accordance with the Fass environmental classification scheme [4].

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

Following oral administration of 200mg of ¹⁴C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and faeces, respectively. The fraction of the dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion. Less than 10% of this ¹⁴C dose was accounted for in the urine as active metabolites [1].

References

1. Summary of Product Characteristics Zyban® 150 mg prolonged release film-coated tablets (Bupropion hydrochloride). GlaxoSmithKline, September 2012.
<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.
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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.

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