

Environmental Risk Assessment Data Summary

<u>Active Pharmaceutical Ingredient</u>	<u>Medical Product</u>
Bupropion hydrochloride	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 our pharmaceuticals and use these data in risk assessments to evaluate potential for harm to the environment. We post summaries of our Environmental Risk Assessments on the GSK website as part of our commitment to data transparency.

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. Bupropion 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.

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

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 (PEC)

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 based on patient consumption in the European Union and UK in 2020 (IQVIA 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 = Population of European Union + UK. Per capita use of drug substance A/P = 5.88E-05 kg/inhabitant (IQVIA Data).

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

D = factor for dilution of wastewater 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 = 0.081 µg/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

$$\text{PEC/PNEC} = 0.081/10$$

$$\text{PEC/PNEC} = 0.0081$$

The PEC/PNEC is ≤ 0.1 which means the use of bupropion 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 ^{14}C -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 ^{14}C 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, April 2022.
<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