# Environmental Risk Assessment Summary
# Ocrelizumab

## 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.

The EMA Guideline on Environmental Risk Assessment (ERA) for Non-GMO Human Medicinal Products [5] requires an ERA for the Marketing Authorisation Application (MAA) of all new medicinal products in the European Union. For proteins and peptides, however, the 'ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment'.

## Summary

Ocrelizumab is a humanised monoclonal antibody designed to target CD20-positive B cells, a specific type of immune cell thought to be a key contributor to myelin (nerve cell insulation and support) and axonal (nerve cell) damage. This nerve cell damage can lead to disability in people with multiple sclerosis (MS). Based on preclinical studies, Ocrelizumab binds to CD20 cell surface proteins expressed on certain B cells, but not on stem cells or plasma cells, and therefore important functions of the immune system may be preserved [6].

Ocrelizumab is the active pharmaceutical ingredient used in the Roche product OCREVUS [7]. It is approved for primary progressive and relapsing forms of multiple sclerosis [6].

A Manometric Respirometry Test according to OECD guideline no. 301 F showed that formulated Ocrelizumab (including excipients) is readily biodegradable [1]. Additionally, as supporting information, acute ecotoxicity limit tests with green algae [2], daphnids [3] and fish [4] consistently showed no adverse effects at the only tested concentration of 100 mg/L nominal concentration relating to the active substance Ocrelizumab.

Considering human metabolism, rapid biodegradability and acute ecotoxicological properties of Ocrelizumab, no exposure levels of concern to the environment are to be expected. This confirms the general finding that monoclonal antibodies and other protein or peptide active pharmaceutical substances are not expected to pose any risk to the environment [8].

## Aquatic Toxicity Data for Ocrelizumab

| Study | Guideline | Results | Ref. |
|---|---|---|---|
| Algal Growth Inhibition Test with *Desmodesmus subspicatus* | OECD 201 | 72 h EC50 (growth rate) >100 mg/L NC<br>72 h EC50 (yield) >100 mg/L NC<br>72 h NOEC 100 mg/L NC | [2] |
| Acute Immobilisation Test with *Daphnia magna* | OECD 202 | 48 h EC50 >100 mg/L NC<br>48 h NOEC 100 mg/L NC | [3] |
| Acute Toxicity to guppy (*Poecilia reticulata*) | OECD 203 | 96 h LC50 >100 mg/L NC | [4] |

EC50 concentration of the test substance that results in 50% effect
LC50 concentration of the test substance that results in 50% mortality
NC Nominal concentration
NOEC No Observed Effect Concentration

## Environmental Fate Data for Ocrelizumab

| Study | Guideline | Results | Ref. |
|---|---|---|---|
| Ready Biodegradability Test | OECD 301 F | <u>BOD/ThOD (mineralisation)</u><br>93% after 28 days<br>76% at the end of the 10-d window<br>Readily biodegradable<br><br><u>DOC elimination</u><br>98% after 28 days | [1] |

BOD Biochemical oxygen demand
DOC Dissolved organic carbon
ThOD Theoretical oxygen demand

## References


[1] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2008): Ocrelizumab. Ready biodegradability – evaluation of the aerobic biodegradability in an aqueous medium: manometric respirometry test. BMG study no. A08–00132

[2] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2008): Ocrelizumab. Fresh water algal growth inhibition test with *Desmodesmus subspicatus*; limit test with 100 mg Ocrelizumab/l. BMG study no. A08–00134

[3] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2008): Ocrelizumab. 48-Hour acute toxicity to *Daphnia magna*; limit test with 100 mg Ocrelizumab/l. BMG study no. A08–00135

[4] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2008): Ocrelizumab. 96-Hour acute toxicity to *Poecilia reticulata* (guppy); limit test with 100 mg Ocrelizumab/l. BMG study no. A08–00284

[5] European Medicines Agency (EMA) (2006/2015): Guideline on the environmental risk assessment of medicinal products for human use. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), 01 June 2006, EMA/CHMP/SWP/447/00 corr 2

[6] F. Hoffmann-La Roche Ltd (2017): Media Release, 28 September 2017. https://www.roche.com/dam/jcr:1f07813c-0934-46f6-9da7-ee68c9e808ce/de/170928_MR_OCREVUS_CH_en.pdf

[7] F. Hoffmann-La Roche Ltd (2019): Safety data sheet for Ocrevus, 4 July 2019. https://www.roche.com/sustainability/environment/global_product_strategy_and_safety_data_sheets.htm

[8] Straub JO (2010): Protein and Peptide Therapeuticals: An Example of "Benign by Nature" Active Pharmaceutical Ingredients. *In* Kümmerer K, Hempel M, eds: Green and Sustainable Pharmacy. Springer, Heidelberg, pp 127–133