Environmental Risk Assessment Summary
Interferon alfa-2a

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 [4] 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

Interferon alfa-2a is used in the treatment of patients with chronic hepatitis C, hairy cell leukemia, and AIDS-related Kaposi's sarcoma. Interferon alfa-2a is the active pharmaceutical ingredient used in the Roche product Roferon-A [5].

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

Considering human metabolism, rapid biodegradability and acute ecotoxicological properties of Interferon alfa-2a, 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 [6].

Aquatic Toxicity Data for Interferon alfa-2a

Study	Guideline	Results	Ref.
Algal Growth Inhibition Test with *Desmodesmus subspicatus*	OECD 201	72 h EC50 (growth rate) >100 mg/L NC 72 h EC50 (yield) >100 mg/L NC 72 h NOEC 100 mg/L NC	[2] a)
Acute Immobilisation Test with *Daphnia magna*	OECD 202	48 h EC50 >100 mg/L NC 48 h NOEC 100 mg/L NC	[3]

EC50 concentration of the test substance that results in 50% effect
NC Nominal concentration
NOEC No Observed Effect Concentration
a) Precipitations occurred in the test vessels

Environmental Fate Data for Interferon alfa-2a

Study	Guideline	Results	Ref.
Ready Biodegradability Test	OECD 301 F	<u>BOD/ThOD (mineralisation)</u> 100% after 28 days 97% at the end of the 10-day window Readily biodegradable <u>DOC elimination</u> 98% after 28 days	[1] a)

BOD Biochemical oxygen demand
DOC Dissolved organic carbon
ThOD Theoretical oxygen demand
a) Tested solution incl. excipients

References

[1] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2012): Interferon alfa-2a solution. Ready biodegradability – evaluation of the aerobic biodegradability in an aqueous medium: manometric respirometry test. BMG study no. A12-00023

[2] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2012): Interferon alfa-2a. Fresh water algal growth inhibition test with *Desmodesmus subspicatus*; limit test with 100 mg/l active ingredient. BMG study no. A11-02060

[3] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2012): Interferon alfa-2a. 48-Hour acute toxicity to *Daphnia magna*; limit test with 100 mg/l active ingredient. BMG study no. A11-02059

[4] 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

[5] F. Hoffmann-La Roche Ltd (2021): Safety data sheet for Roferon-A, 19 April 2021. https://www.roche.com/sustainability/environment/global_product_strategy_and_safety_data_sheets.htm

[6] 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