

Photofate of Oseltamivir (Tamiflu) and Oseltamivir Carboxylate under Natural and Simulated Solar Irradiation: Kinetics, Identification of the Transformation Products, and Environmental Occurrence

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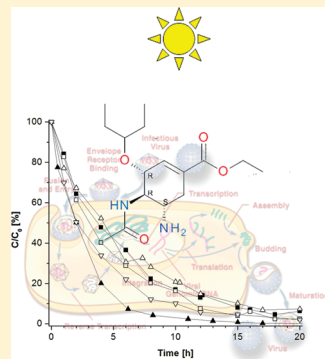
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 Supporting Information

ABSTRACT: In this work the photodegradation pathways and rates of oseltamivir ester (OE) and oseltamivir carboxylate (OC) were studied under artificial and natural solar irradiation with the goal of assessing the potential of photolysis as a removal mechanism in aquatic environments. The structures of the photoproducts of OE, elucidated by ultra performance liquid chromatography-quadrupole-time-of-flight-mass spectrometry (UPLC-QToF-MS), were proposed to originate from hydration of the cyclohexene ring (TP330), ester hydrolysis (TP284), a combination thereof (TP302), intramolecular cyclization involving the ester (TP312), and cleavage of the ethylpropoxy side chain (TP226). The only photoproduct detected in case of OC was postulated to correspond to the hydration of the α,β -unsaturated acid (TP302). Under simulated solar irradiation the degradation rate of OC was approximately 10 times slower than that of OE, with half-lives ranging from 48 h in ultrapure water to 12 h in surface water from Sant Joan Despi, Llobregat river. The photodegradation under natural solar irradiation during the season of pandemic Influenza peak incidence was about 150 days for OC and 15 days for OE. In general, the photoproducts proved to be more resistant toward further photodegradation than the parent antivirals. In a monitoring survey of surface waters from the Ebro river (NE Spain), OC and OE were detected along with the photoproducts TP330 and 312.



INTRODUCTION

Starting in March/April 2009 great concern was raised worldwide about a potential pandemic of the influenza virus H1N1. Tamiflu (Oseltamivir phosphate ester, OE) was strongly recommended by the WHO for both prevention and treatment of influenza and was considered as a first-line defense in a flu pandemic.^{1–3} Concerns about the recrudescence of influenza A resistance to such an essential antiviral used routinely in seasonal epidemics and the ecotoxicologic risks associated with its use in the case of a pandemic outbreak have put in evidence the need for studying its fate and behavior in the environment.² OE is extensively biotransformed in the human body to the active metabolite oseltamivir carboxylate (OC).¹ Approximately 60–80% of an oral dose of OE is excreted into urine as OC, whereas less than 5% is recovered unchanged in urine. In feces less than 20% is recovered in equal fractions of OE and OC while the latter is metabolically stable.¹ OC undergoes little biotransformation or physical removal in wastewater treatment plants (WWTP).³ Consequently, in case of urban areas with a large number of patients under oseltamivir medication, the risk of OC to contaminate the aquatic ecosystem was expected.^{3–5} Using (Q)SAR modeling for

2986 different compounds,⁶ the antiviral drugs were among the eighth predicted most hazardous therapeutic classes with regard to their toxicity toward algae, daphnids and fish. They also match the antibiotics in their capability to produce resistant strains of pathogens. In a recent assessment based on a wide database, Straub concluded that oseltamivir poses no significant risk, either to WWTPs or to surface water biota based on standard chronic toxicity tests, although it is admittedly persistent.⁷ Still, much is unknown about the environmental fate.

In case of a pandemic outbreak the predicted environmental concentrations (PEC) of OC in the Lee catchment (UK) could exceed 27 $\mu\text{g/L}$ for nearly 1 week whereas in the Lower Colorado catchment (U.S.) concentrations could exceed 26 $\mu\text{g/L}$ for 10 days with a maximum of 32 $\mu\text{g/L}$.² All five river catchments investigated in the UK were predicted to have concentrations of

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