Antiviral pandemic risk assessment for urban receiving waters

J. B. Ellis

ABSTRACT

An 80% metabolic conversion of the Tamiflu® pro-drug (oseltamivir phosphate, OP) to its metabolite oseltamivir carboxylate (OC) and a high excretion rate combined with poor removal at sewage treatment works (STWs) means that potentially high STW OC emissions may occur in receiving waters. A risk assessment approach undertaken within the River Lee catchment in North East London indicates that predicted environmental concentrations for surface waters (PEC_{SW}) are likely to be in the general range of 40–80 $\mu g\,L^{-1}$ during a pandemic sitaution within urban catchments having low dilution capacities. This implies low risk exposure levels which confirms previous studies, but there are considerable uncertainties associated with the methodology as well as risks that might result from persistent, long term chronic exposure to low-level water and sediment concentrations which might be mobilised under subsequent extreme flow conditions.

Key words | risk assessment, sewage treatment removal, Tamiflu® pandemic, urban receiving waters

J. B. Ellis
Urban Pollution Research Centre,
Middlesex University,
The Burroughs, Hendon,
London NW4 4BT,
UK
E-mail: *b.ellis@mdx.ac.uk*

INTRODUCTION

There is now available a substantial and growing literature on a variety of pharmaceutical and personal care products (PPCPs) and their by-products in terms of their identification and quantification in surface and groundwaters (Ternes & Joss 2007; Watts & Crane Associates 2007; Mompelat *et al.* 2009). This covers the range of veterinary and human antibiotics, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and psychiatric drugs as well as lipid regulators, X-ray contrasts, steroids, hormones, antiseptics and PCPs. Although there is only limited knowledge on their ultimate fate and behaviour, the general conclusion of the majority of studies is that there is no significant environmental risk from the concentration levels currently found in receiving waterbodies (Kummerer 2008). This conclusion is primarily the result of effective removal efficiencies (>85%) by tertiary sewage treatment and the high dilution ratios (frequently exceeding 100) characterising most receiving waters (Ternes & Joss 2007). The principal remaining concerns are associated with the potential long term effects of episodic and persistent low-dose exposures characteristic of combined sewer overflows (CSOs) and municipal sewage treatment works (STW) discharges during extreme wet weather conditions (Ellis 2009), as well as the possibility of the development of anti-microbial resistance in the vicinity of STW discharges (Petrovic & Barcelo 2007).

By contrast, relatively little data exists on the incidence, concentrations and fate of antiviral medicines in urban receiving waters, despite recent studies that suggest conventional primary and secondary STW processes are largely ineffective in removing these particular pharmaceutical compounds (Fick *et al.* 2007). The effectiveness of tertiary ozone treatment with long sludge retention times has been shown to provide significant elimination of OC (Ghosh *et al.* 2009). Over 90% OC removal was demonstrated for Japanese STWs with such ozone treatment, with OC

doi: 10.2166/wst.2010.002

decreasing linearly over time following a pseudo-first order reaction. However, various workers have also demonstrated that antiviral compounds tend to inhibit biofilm formation in the *Pseudomonas aeruginosa* microorganism (Soong *et al.* 2006) and in addition, under a pandemic situation, STWs are likely to receive much higher loadings than the normal concentrations encountered in surface waters (Singer *et al.* 2008). A loss of structural floc integrity in the activated sludge process, or detrimental changes in the biofilm composition of trickling filters, could have catastrophic consequences resulting in poorly or untreated treated sewage discharging to receiving waters. In addition, the need to "fire-up" a sewage works with fresh cultures following a biofilm collapse would not be a straightforward process. There is very little experience or information to assess whether high level antiviral use associated with pandemics will seriously disrupt sewage treatment performance or predict what the magnitude of reduction in STW function is likely to be. Whilst the 1983 national strike in the UK water industry had very little effect on plant efficiency, there is no precedent for the elevated levels of antivirals ($\leq 348\,\mu g\,L^{-1}$) that have been predicted to be contained in raw sewage effluents during a pandemic (Straub 2009).

Given the way that antivirals such as Tamiflu® (Oseltamivir) and Relenza® (Zanamivir) have their effect, and the way that microbial communities in sewage treatment plants function, there is reason to question whether past experience will be an accurate guide to what will happen in a future pandemic. The variability in types of sewage treatment plant, process operating conditions, and the nature and timing of a pandemic all introduce considerable uncertainty about the nature and scale of any effect(s) that might be expected. In addition, there is only very limited information on the ecological risks that could result from STW discharges of untreated antivirals into the aquatic environment. This paper considers the environmental pathways of the antiviral drug Tamiflu® and its metabolite species and determines predicted environmental concentrations for surface waters (PEC_{sw}) receiving STW discharges for urbanised catchments in North East London under assumed pandemic conditions as a basis for evaluating exposure risks.

ANTIVIRAL ENVIRONMENTAL PATHWAYS

There are only a few antiviral compounds currently available to counter human influenza of which perhaps the most important is Tamiflu® or Oseltamivir (oseltamivir phosphate, OP). This is an ester prodrug which on consumption is metabolised into the active metabolite oseltamivir carboxylate (OC), which is excreted in urine (60%–80%) and faeces (10%–15%) in virtually unchanged form. Some basic chemical characteristics of OP and OC are given in Table 1 which emphasise the high water solubility and low sorption properties of the metabolite form. The emergence of both the H5N1 and H1N1 pandemic influenza strains has led to large national Tamiflu® stockpiling, which in the UK would cover nearly 75% of the population and exceeds some 11 metric tonnes of OP (or 14.6 M dosing courses of 75 mg/day per infected inhabitant for 10 days). It is expected that this stockpile would be fully depleted over a 10–12 week peak pandemic period (Singer *et al.* 2008). Figure 1 illustrates the predicted antiviral release pathways from infected households into the environment via wastewater effluent and waste landfill into receiving water bodies. The figure also shows the estimated percentage distributions for pathways resulting from antiviral disposal of unused drugs from domestic premises, other than associated with urine and faeces which comprise by far the majority disposal pathway. It is estimated that between 10% to 15% of prescribed medicines are disposed of via household sinks and toilets (Bound & Voulvoulis 2005) with large volumes (>60%) being released

Table 1 | Some characteristic properties of OP and OC

Property	OP	OC
Molecular weight	312.41	284.35
Water solubility ($mg\,L^{-1}$)	>200	>580
n-Octanol water partitioning; $\log K_{ow}$	1.21 ± 0.42	0.006 ± 0.7
Hydrolysis	2% loss	??
Photo- and bio-degradation	Not significant	
Excretion rate (75 mg dose)		
Urine	0.05	0.70
Faeces	0.10	0.15

Table compiled from: F.Hoffman-La Roche (2007), SciFINDER (2008) and SPARC On-Line Calculator (2008).

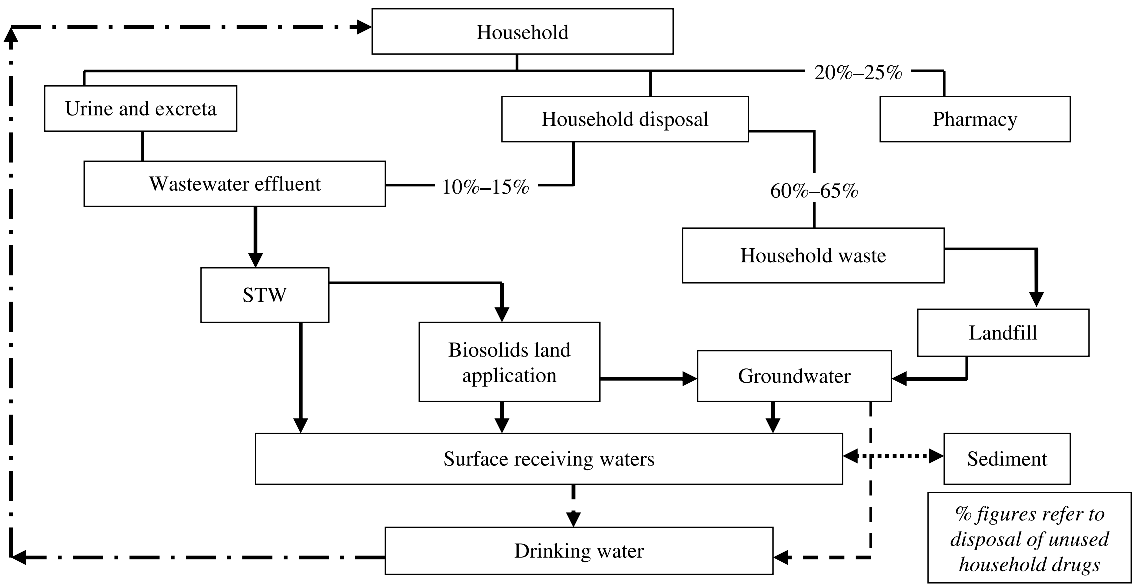

Figure 1 | Environmental pathways for antiviral drugs in the urban water cycle.

to the environment via household waste and landfill, with at least 2–5 units of every 100 nonsteroidal anti-inflammatory drug (NSAID) units prescribed ultimately entering the drinking water cycle as indicated in Figure 1.

However, unlike most antibiotic NSAID compounds, which have between 85% and 95% removal rate in STWs, the throughput of antivirals within this urban water cycle would be subject to very low removal rates by both STW and natural biodegradation processes according to the laboratory batch tests conducted by Fick *et al.* (2007), who noted only some 15%–20% decrease over 8 days and half-lives of 18–30 days in river water. This assertion of minimal removal has been questioned by more recent field and experimental studies by Accinelli *et al.* (2007) and Bartels & von Tumpling (2008), with both studies demonstrating biological and photo-degradation of OC in surface waters as well as low chronic ecotoxicity potential, with no-effect-environmental-concentrations (NOEC) being consistently below 1 mg L^{-1}. Other studies such as those of Singer *et al.* (2008) have failed to confirm any specific disruption of STW function resulting from amendment or modification of bacterial biofilm production or inhibition of nitrification (Straub 2009) in the treatment process stream. There is therefore considerable disagreement and concern over the removal processes, their efficiency and release pathways for antiviral medicines into the receiving environment.

RISK ASSESSMENT

A generic approach

The environmental risk assessment (ERA) of PPCPs for human use is primarily based on the guidelines of the European Agency for the Evaluation of Medicinal Products (EMEA 2006). The lowest tier of this ERA approach derives a predicted average environmental concentration value for receiving surface waters (PEC_{sw}; mg L^{-1}) based on a generic formula:

$$PEC_{sw} = [Dd \times Mp]/[Wv_d \times D]$$

where Dd is the maximum daily dose consumed per inhabitant; mg hd^{-1} d^{-1}, Mp is market penetration; % (and assumed to be 1%), Wv_d is the daily wastewater volume; l hd^{-1} d^{-1}, and D is the dilution factor; assumed to be 10. For this first tier assessment phase, the calculated value is based on a number of working assumptions including a lack of metabolism, biodegradation or retention of the compound which derives a worst-case risk outcome. If the predicted PEC value exceeds a threshold value of 0.01 μg L^{-1}, a further tier of risk assessment is required to be undertaken under the EMEA protocol.

Continuous STW discharges

The EMEA generic model can be adapted to consider the STW removal rate (STWr) to derive both daily and maximum PEC_{sw} values during a pandemic situation:

$$PEC_{sw}\ (\text{ng l}^{-1}\ \text{day}^{-1}) = [\text{Dd} \times \text{Ef} \times (1 - \text{STW}_r)]/[\text{Wv}_d \times \text{P} \times D]$$

where Dd is expressed as the daily dosage (ng) of active OC, Ef is the excreted fraction of OC, STWr is the OC fraction discharged from the STW (i.e the STW capacity) and P is the total population served by the STW. This equation has been applied for average dry weather flow (DWF) conditions to the 399 km^2 sewered urban catchment of the Thames Water Deephams STW in NE London. The works receives an average wastewater flow of 200 ML day^{-1} serving a population of 836,000 and discharging (at an average rate of 5.96 $m^3\,s^{-1}$) into the receiving waters of the Salmons Brook which has a DWF dilution capacity of 1.79. The Salmons Brook itself discharges into the parent River Lee catchment to the north of the 2012 Olympic Park site at Stratford, East London. Previous studies have confirmed persistent, long term chronic PPCP receiving water exposure at this discharge location, with various NSAID compounds and in particular ibuprofen occurring at elevated levels (Ellis 2006). Given an assumed 35% of the total population infected during the course of the pandemic period, an 80% OP/OC conversion rate and 0.8 excretion and STW treatment release rates, the calculated worst-case PEC_{sw} is equivalent to 83 $\mu g\,L^{-1}\,d^{-1}$ over the estimated 10 week pandemic period. These assumed values are consonant with those used in related antiviral studies such as Singer *et al.* (2008) and Straub (2009). Assuming a higher 0.43 STW removal fraction as suggested by the experimental data for STW discharges to the River Elbe in Straub (2009), this PEC_{sw} value reduces to 47 $\mu g\,L^{-1}\,d^{-1}$ which would be well below the threshold 100 $\mu g\,L^{-1}$ 21 day NOEC level for chronic daphnid and fish reproduction inhibition. On the other hand, Soderstrom *et al.* (2009) have reported that OC levels in the range of 80–230 ng L^{-1} are sufficient to cause 50% inhibition (IC_{50}) in cell cultures.

Table 2 compares the PEC_{sw} values calculated for the Salmons Brook with those of the 1,412 km^2 parent River Lee catchment having a total 1.78 M population and a 2.18 dilution capacity as determined by Boucard in Singer *et al.* (2008), Singer *et al.* (2007) and Straub (2009). The calculated PEC_{sw} values for the more polluted and urbanised Salmons Brook are towards the higher end of the parent Lee predicted data but generally provide mutual confirmation of the expected upper range of surface water concentrations that can be expected during a pandemic in such highly urbanised receiving waters having minimal dilution ratios. There is an assumption in all modelling approaches that a NOEC condition will apply to intermittent discharges such as those characteristic of STW combined sewer overflows (CSOs). This assumption may be invalid for CSO wet weather flows which pass untreated to receiving waters, as has been demonstrated for NSAID compounds within the Salmons Brook catchment (Ellis 2006, 2009), and the assertion remains to be robustly tested.

The range of predicted values given by the various approaches also emphasises the uncertainties and unreliability associated with current PEC modelling approaches

Table 2 | Surface water PEC_{sw} values for the Urban River Lee and Salmons Brook catchments

	Surface water concentration (PEC_{sw}; $\mu g\,L^{-1}$)	
Catchment	**Pandemic**	**Infection rate**
Salmons Brook (this study)		
15% STW OC removal	83	35% (T + P)
43% STW OC removal	47	35% (T + P)
Lee (maximum values, Singer *et al.* (2007))	0.3–27.0	35%
Lee (Straub 2009 based on data in Singer *et al.* 2007)	82.6	50% (T + P)
Lee (Straub 2009 based on EUSES data)	39.4–50.2	50% (T + P
Lee (T.Boucard in Singer *et al.* 2008)	98.1	50% (T + P)

Note: T + P = Treatment + Prophylaxis.

which primarily reflect the lack of knowledge on STW OC removal processes and infection rates. These uncertainties are so large that such modelling approaches can only really offer at most a first-order screening level for receiving water risk assessment and need calibrating against actual measured environmental concentrations (MECs) under varying flow conditions.

Many of the variables used in the calculation of PECs have poorly defined sources and levels of uncertainty; observed differences can be particularly marked where local conditions differ from assumed average values and thus specific site outcomes may be very different from the predicted values, especially as k_{ow}/k_d partitioning values are highly site specific. The application of adaptive neural network fuzzy logic approaches might offer enhanced prediction performance in terms of reducing the parameter uncertainty (Pai *et al.* 2009).

Receiving water-sediment concentrations

Sacca *et al.* (2009) have determined an OC half-life of 15 days in a sediment-water mixture with more than 30% OC residue remaining after a three week incubation period. This would suggest that sediment adsorption does not reduce the potential bioavailability to microbial degradation and indirect photolysis. The EMEA (2006) model for determining the predicted receiving water OC sediment concentration (PEC_{sed}; $mg\,kg^{-1}$) is given by:

$$PEC_{sed} = [(ks_w/TSbd) \times PEC_{sw} \times 1000]$$

where ks_w is the water-sediment partitioning coefficient; $m^3\,m^{-3}$, and TSbd is the solids bulk density; $kg\,m^{-3}$. Assuming a bulk density of 2.18 and ks_w value as given in Table 1, applied to the mixing zone of the Deephams STW on the Salmons Brook, this equation at worst-case PEC_{sw} concentration yields a PEC_{sed} OC value of $0.228\,mg\,kg^{-1}$. This contained pollutant mass could serve as a long term reservoir for future slow release into the overlying water column at ultra-low concentrations. However, it has been asserted that oseltamavir is not known to be carcinogenic, mutagenic or an endocrine disrupter (Hoffman–La Roche 2007). It is also the case that with OC partition coefficients (expressed as log k_d) of between 1.5–0.36 at neutral pH levels there may be relatively little concern for bioaccumulation.

CONCLUSIONS

The current work provides a novel contribution to studies on the pathways and risk exposure of antiviral releases from STWs to urban receiving waters. The work confirms related studies undertaken within the urbanised River Lee catchment, all of which indicate PNEC values below the $1\,mg\,L^{-1}$ threshold level for aquatic life. Based on the PEC_{SW}:NOEC risk ratios, all studies would suggest that no significant risks are evident to receiving waters during high Tamiflu® pandemic use even for those situations having low dilution capacities. Nevertheless, whilst the studies indicate low risk antiviral exposure levels, there still remain considerable uncertainties associated with the risk evaluation methodology and the working assumptions. These uncertainties are compounded by the possibility of long term, chronic effects from persistent episodic CSO discharges and inoculated benthal sediment which might stimulate the growth of antiviral resistance in foraging wild duck populations and which might then recombine with viruses that can potentially endanger human health. Current approaches for the calculation of antiviral receiving water PEC values are predicated by high levels of parameter uncertainty and much more reliable field data is required on infection rates, environmental pathways and STW removal processes to improve both aquatic and human health risk assessment. In addition, further work is needed on the significance of untreated CSO discharges that may bypass the STW process stream during wet weather conditions and on long term in-stream sediment OC uptake and release.

REFERENCES

Accinelli, C., Caracciolo, A. B. & Grenni, P. 2007 Degradation of the antiviral drug oseltamivir carboxylate in surface water samples. *Int. J. Environ. Anal. Chem.* **87**, 579–587.

Bartels, P. & von Tumpling, W. 2008 The environmental fate of the antiviral drug oseltamivir carboxylate in different waters. *Sci. Total Environ.* **405**, 215–225.

Bound, J. P. & Voulvoulis, N. 2005 Household disposal of pharmaceuticals as a pathway for aquatic contamination in the UK. *Environ. Health Perspect.* **113**(12), 1705–1711.

Ellis, J. B. 2006 Pharmaceutical and personal care products (PPCPs) in urban receiving waters. *Environ. Pollut.* **144**, 184–189.

Ellis, J. B. 2009 PPCP sources and pathways in the urban water cycle. In *Proc. Int. Conf. Xenobiotics in the Urban Water*

Cycle; XENOWAC2009. 11–13 March 2009. Cyprus. ISBN 978 9963 671 892.

EMEA 2006 *Guidance on Environmental Risk Assessment of Medicinal Products for Human Use*. CHMP/SWP/4447/00. European Agency for the Evaluation of Medicinal Products (EMEA), London, UK.

Fick, J., Lindberg, R. H., Tysklind, M., Haemig, P. D., Waldenstrom, J., Wallensten, A. & Olsen, B. 2007 Antiviral Oseltamivir is not removed or degraded in normal sewage water treatment: Implications for development of resistance by Influenza A virus. *PLoS ONE*, **2**(10), e986, 1–5. (www.plosone.org)

Ghosh, G. C., Nakada, N., Yamashita, N. & Tanaka, H. 2009 Oseltamivir carboxylate: The active metabolite of Tamiflu® detected in sewage discharge and river water in Japan. *Environ. Health Perspect.* (In Press). doi:10.1289/ehp0900930.

Hoffman–La Roche Ltd, 2007 *Safety Data Sheet for Oseltamivir*, Basel, Switzerland.

Kummerer, K. (ed.) 2008 *Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks*. Springer, Berlin, Germany, ISBN 978 3 540 74663 8.

Mompelat, S., Le Bet, B. & Thomas, O. 2009 Occurrence and fate of pharmaceutical products and by-products from resource to drinking water. *Environ. Int.* **35**, 803–814.

Pai, T. Y., Wan, T. J., Hsu, S. T., Chang, T. C., Tsai, Y. P., Lin, C. Y., Su, H. C. & Yu, L. F. 2009 Using fuzzy inference system to improve neural network for predicting hospital wastewater treatment plant effluent. *Comput. Chem. Eng.* **33**(7), 1272–1278.

Petrovic, M. & Barcelo, D. (eds) 2007 *Analysis, Fate and Removal of Pharmaceuticals in the Water Cycle*, *Series on Comprehensive Analytical Chemistry* (Vol. 50). Elsevier Science, London, ISBN 978 0 444 53052 3.

Sacca, M. L., Accinelli, C., Lindberg, R. & Olsen, B. 2009 Environmental fate of the antiviral drug Tamiflu® in two aquatic ecosystems. *Chemosphere* **75**(1), 28–33.

SciFINDER 2008 *SciFINDER online database*. Amer. Chem. Soc. (https://scifinder.cas.org)

Singer, A. C., Nunn, M. A., Gould, E. A. & Johnson, A. C. 2007 Potential risks associated with the proposed widespread use of Tamiflu®. *Environ. Health Perspect.* **115**(1), 102–106.

Singer, A. C., Howard, B. M., Johnson, A. C., Knowles, C. J., Jackman, S., Accinelli, C., Cararriolo, A. B., Bernard, I., Bird, S., Boucard, T., Boxall, A. *et al.* 2008 Risk assessment of Tamiflu under pandemic conditions. Meeting Report. *Environ. Health Perspect.* **116**(11), 1563–1567.

Söderström, H., Järhult, J. D., Olsen, B., Lindberg, R. H., Tanaka, H. & Fick, J. 2009 Detection of the antiviral drug Oseltamivir in aquatic environments. *PLoS ONE* **4**(6). doi:10.1371/journal.pone.0006064.

Soong, G., Muir, A., Gomez, M. I., Waks, J., Reddy, B., Planet, P., Singh, P. K., Kanetko, Y., Wolfgang, M. C., Hsiao, Y-S., Tong, L. & Prince, A. 2006 Bacterial neuraminidase facilitates mucosal infection by participating in biofilm production. *J. Clin. Invest.* **116**(8), 2297–2305.

SPARC On-Line Calculator 2008 University of Georgia, Atlanta, Georgia, US. (www.sparc.chem.ug.edu)

Straub, J. O. 2009 An environmental risk assessment for oseltamivir (Tamiflu) for sewage works and surface waters under seasonal influenza and pandemic use conditions. *Ecotoxicol. Environ. Saf.* **72**(6), 1625–1810.

Ternes, T. A. & Joss, A. (eds) 2007 *Human Pharmaceuticals, Hormones and Fragrances: The Challenge of Micropollutants in Urban Water Management*. IWA Publishing, London, UK, ISBN 978 1843390930.

Watts & Crane Associates 2007 *Desk-based Review of Current Knowledge on Pharmaceuticals in Drinking Water and Estimation of Potential Levels*. Final Report, DWI 70/2/213. UK Drinking Water Inspectorate, London, UK.