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Research Article

# Photochemical fate of pharmaceuticals in the environment: Naproxen, diclofenac, clofibric acid, and ibuprofen

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**Abstract.** The aqueous photochemistry of four pharmaceutical compounds detected in surface waters (naproxen, diclofenac, ibuprofen, and clofibric acid) was investigating in purified (Milli-Q) water and in Mississippi River water (MRW). Both direct photolysis and hydroxyl radical-mediated indirect photolysis (using a combination of probe and quencher experiments) were studied. Singlet oxygenation was also investigated for naproxen. Second-order rate constants for reaction with hydroxyl radical were determined using Fenton's reagent. Naproxen was rapidly transformed via direct photolysis in sunlight in both Milli-Q and MRW. The radical quencher isopropyl alcohol (IPA), had a similar effect in both systems, and this effect was interpreted as a reaction of a carboxyl radical intermediate of naproxen. Diclofenac was found to undergo rapid direct photolysis under sunlight, confirming the results of prior studies. Addition of IPA led to more rapid transformation, possibly due to formation of other radical species or photoreduction with IPA serving as the H-source. When irradiated under natural sunlight, slow direct photolysis of clofibric acid is observed in Milli-Q water, and a combination of direct photolysis and radical mediated indirect processes appear responsible for clofibric acid photolysis in MRW. The dominant photochemical loss process for ibuprofen irradiated with a medium pressure Hg-vapor lamp was identified as reaction with photo-generated radicals. These results suggest that photolytic processes are important removal mechanisms for pharmaceutical compounds discharged into sunlit surface waters.

**Key words.** Direct photolysis; indirect photolysis; pharmaceuticals; NSAIDs; clofibric acid; diclofenac; ibuprofen; naproxen.

## Introduction

Due to incomplete removal of pharmaceuticals and personal care products (PPCPs) during the wastewater treatment process (Hignite and Azarnoff, 1977; Ternes, 1998; Ternes et al., 1998; Buser et al., 1999; Stumpf et al., 1999; Heberer, 2002; Andreozzi et al., 2003; Tixier et al., 2003), pharmaceuticals have been detected in a variety of surface and ground waters throughout the world (Buser et al., 1998; Ternes, 1998; Ternes et al., 1998; Buser et al., 1999; Stumpf et al., 1999; Kolpin et al., 2002; Tixier et al., 2003) and thus have received increased attention as an emerging class of environmental pollutants (Richardson and Bowron, 1985; Halling-Sorensen et al., 1998; Daughton and Ternes, 1999; Jorgensen and Halling-Sorensen, 2000). Because PPCPs have been designed to have a specific physiological effect on humans or animals, the compounds may pose an environmental threat

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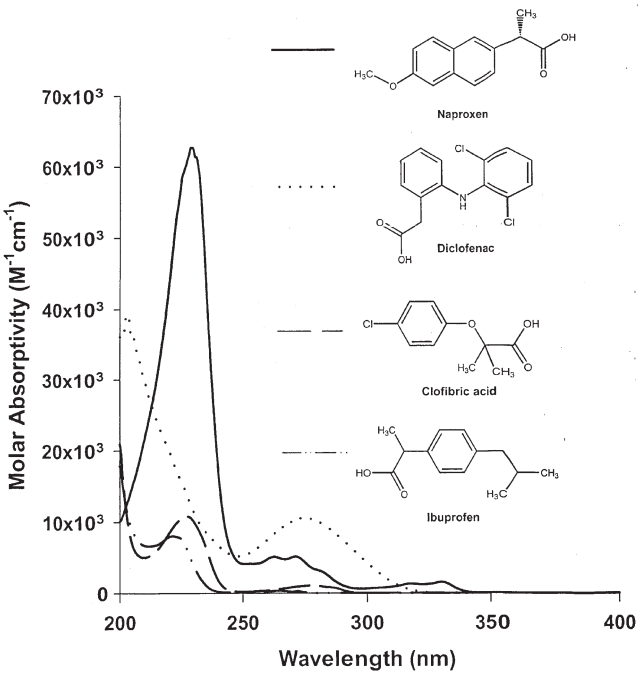


**Figure 1.** Absorption spectra at pH 7 and structures of the PPCPs used in this study. Values of $pK_a$ are 4.15 for naproxen, 4.15 for diclofenac, 3.18 for clofibric acid, and 4.91 for ibuprofen.

(Halling-Sorensen et al., 1998; Daughton and Ternes, 1999; Jones et al., 2002). PPCPs are generally designed to be lipophilic and biologically persistent to maintain therapeutic activity until their specific function has been performed (Halling-Sorensen et al., 1998; Daughton and Ternes, 1999). As a consequence, many PPCPs have been presumed to be persistent in the environment.

Four acidic PPCPs that have been widely detected and thus may be of environmental importance are the nonsteroidal anti-inflammatory drugs (NSAIDs) naproxen, ibuprofen, and diclofenac, all used worldwide as pain medications, and clofibric acid, the metabolite of the lipid regulators clofibrate, etofibrate, and theofibrate. The structures, absorption spectra, and $pK_a$ values of these compounds are given in Figure 1. Multiple studies have identified the presence of these compounds both in European and American river water samples, emphasizing the need to study the fate of these drugs (Ternes, 1998; Zuccato et al., 2000; Kolpin et al., 2002; Tixier et al., 2003). For example, a study of German rivers found diclofenac, ibuprofen, and naproxen present at median concentrations of 0.15 µg/L, 0.07 µg/L and 0.070 µg/L and maximum concentrations of 1.2 µg/L, 0.53 µg/L and 0.39 µg/L, respectively (Ternes, 1998). Clofibric acid was found to have a median river concentration of 0.067 µg/L and a maximum concentration of 0.28 µg/L. Clofibric acid has also been found in the North Sea, at concentrations up to 7.8 ng/L (Buser et al., 1998).

In surface waters, contaminants may be susceptible to direct photochemical degradation and a wide array of indirect photochemical pathways, including reaction with singlet oxygen ($^1O_2$), hydroxyl radical (·OH), peroxy radicals (·OOR), photo-excited organic matter, and other reactive species (Blough and Zepp, 1995; Mill, 1999). Because pharmaceuticals are released into surface waters via discharge of wastewater treatment plant effluent, photochemical processes may be an important removal process for these compounds. Much of the previous work on the photochemistry of naproxen and ibuprofen has focused on their phototoxicity (Castell et al., 1987; Moore and Chappuis, 1988; Bosca et al., 1990; Condorelli et al., 1993; Jimenez et al., 1997). The conditions of the studies varied widely (e.g., light source, wavelength cutoff, solvent) and have limited environmental relevance. The pathways and products of direct photolysis, however, were identified. The photo-excited pharmaceuticals can also produce either singlet oxygen or superoxide, which is believed to be one cause of the phototoxicity of NSAIDs (Moore and Chappuis, 1988; Condorelli et al., 1993).

Recent work demonstrates that photochemical processes may be responsible for the degradation of PPCPs in environmental systems, as well. Direct photolysis of diclofenac has been studied in Greifensee, Switzerland (Buser et al., 1998; Poiger et al., 2001). Modeling the profiles of diclofenac, ibuprofen, and naproxen in Greifensee also suggests that there is an elimination process (potentially photolysis) for these pharmaceuticals in the epilimnion (Tixier et al., 2003). Using sunlight (Andreozzi et al., 2003) and Xe-arc lamp solar simulators (Doll and Frimmel, 2003; Lam et al., 2003), it has been demonstrated that clofibric acid is subject to photodegradation.

This study examines the photolysis of naproxen, diclofenac, clofibric acid, and ibuprofen. By conducting experiments in Milli-Q water and in Mississippi River water and using radical quenchers, the importance of direct and indirect processes for each compound are determined. Kinetic studies and calculations of quantum yields were performed, as well as an analysis of the environmental importance of direct and radical-mediated indirect photochemical processes.

## Materials and methods

### Chemicals

The following materials were used without further purification: naproxen (100.3%, ICN), diclofenac monosodium salt (99.9%, ICN), clofibric acid (99.4%, ICN), ibuprofen monosodium salt (98%, ICN), 2-acetyl-6-methoxynaphthalene (98%, Alfa Aesar), acetophenone (99%, Acros Organics), hydrogen peroxide (30%,

Mallinckrodt), $FeSO_4 \cdot 7H_2O$ (100.4%, Fisher), *p*-nitroanisole (97%, Acros Organics), *p*-nitroacetophenone (98%, Aldrich), pyridine (99+%, Aldrich), and isopropanol (IPA, 99.5+%, Aldrich).

**Photolysis experiments**

Solutions of each pharmaceutical (initial concentration of 100 μM for diclofenac, 75 μM for ibuprofen, 50 μM for naproxen, and 1–6 μM for clofibric acid) were prepared by dissolving the required mass of solid in purified water from a Milli-RO/Milli-Q plus system (Millipore Corporation) or in filtered Mississippi River water (MRW; dissolved organic carbon (DOC) = 16 mg/L, pH = 8.0, $NO_3^-N$ = 0.32 mg/L for naproxen and diclofenac; DOC = 8.9 mg/L, pH = 8.0, and $NO_3^-N$ = 0.88 mg/L for clofibric acid and ibuprofen). Mississippi River water was collected at the University of Minnesota-Minneapolis campus in acid washed Nalgene bottles and vacuum filtered through a 0.2 μm filter. The pH was adjusted to 7 using sodium hydroxide for the Milli-Q water and the pH of the MRW was returned to pH 8 with sodium hydroxide if necessary. The solutions were photolyzed in natural sunlight on August 13, 2002 (T = 20 °C), September 16, 2002 (T = 23 °C), and July 28, 2003 (T = 31°C) in Minneapolis, MN, USA (45° latitude). Pharmaceutical solutions containing 1% by volume isopropanol (IPA; DOC ≈ 4700 mg/L) as a radical scavenger in both Milli-Q water and MRW were also prepared. The samples were irradiated in cork-stoppered quartz tubes (OD = 1.3 cm, ID = 1.1 cm, $V$ = 10 mL) at an angle ~45° to normal. The tubes were not completely filled so that the solutions did not come into contact with the cork stoppers. This prevented any potential leaching of sensitizing compounds into the water from the cork or sorption of the pharmaceuticals to the cork. Sub-samples (0.25–0.5 mL) were withdrawn at various intervals and substrate loss was measured by high performance liquid chromatography (HPLC) using either an 1100 Series Hewlett Packard HPLC or a Waters LC Module 1 plus, each equipped with UV-absorbance detection and a computer-driven data acquisition system. Dark controls were prepared similarly, wrapped with aluminum foil, and exposed to the same environmental conditions. Actinometry was performed in separate, parallel quartz tubes using the *p*-nitroanisole (PNA)-pyridine or *p*-nitroacetophenone (PNAP)-pyridine method (Dulin and Mill, 1982; Leifer, 1988).

Similar preparations of ibuprofen in quartz bottles (OD = 4.2 cm, ID = 4.0 cm, $V$ = 70 mL) were also photolyzed using a merry-go-round reactor with a medium-pressure Hg-vapor lamp (450 W, Ace Glass). The lamp was placed inside a borosilicate (screening wavelengths <290 nm) cooling well (Ace Glass). A cooling fan kept the temperature near 25 °C. Samples were withdrawn and analyzed as described above. Actinometry was performed in separate, parallel bottles using the PNAP-pyridine method (Dulin and Mill, 1982; Leifer, 1988).

The rate constant for the interaction of naproxen with singlet oxygen was determined through a laser flash photolysis (LFP) experiment. Diclofenac, ibuprofen, and clofibric acid do not contain functional groups susceptible to singlet oxygenation and thus were not tested. The LFP apparatus is similar to those reported by others (Nonell et al., 1990; Nonell and Braslavsky, 2000). Samples containing perinaphthenone sensitizer and various substrate concentrations were excited by 4 ns pulses 355 nm (Nd/YAG, Continuum Minilite II). Singlet oxygen is produced through the interaction of dissolved molecular oxygen with photoexcited sensitizer. The resultant phosphorescence decay of $^1O_2$ was collected through an 1100 nm long-pass filter (CVI Laser Corp.) and a 1271 ± 18 nm interference filter (CVI Laser Corp.). The luminescent signal was focused by a collimating lens onto the Ge crystal of a liquid nitrogen cooled ultra-sensitive Ge detector (Model EI-P, Edinburgh Instruments, Ltd.). The detector output was transferred to a digital storage oscilloscope (Tektronix TDS 430A, 400 MHz) where the transients were recorded. The decay portions of the $^1O_2$ signal from the single laser shot transients were then fit to single exponential decays. The second-order rate constant for reaction with singlet oxygen was then determined from this fit as described previously (Latch et al., 2003).

UV-visible spectra were obtained using a Shimadzu UV-1601 PC spectrophotometer, and quantum yields were calculated using the procedure described by Dulin and Mill (1982). For diclofenac and naproxen, tabulated sunlight $L_\lambda$ values (Leifer, 1988) for August 13 at 45° latitude were estimated from averaging summer 40° and 50° latitude values, whereas sunlight $L_\lambda$ values for September 16, at 45° latitude were estimated from averaging the 40° and 50° latitude and the summer and autumn values. For clofibric acid, light intensities for July 28 were determined using SMARTS (A Simple Model of the Atmospheric Radiative Transfer of Sunshine; Gueymard, 1995; Gueymard, 2001) because the tabulated $L_\lambda$ values did not provide the discretization necessary for the overlap between the absorbance spectra of clofibric acid and the solar spectrum. Light intensities for the emission wavelengths of the Hg-vapor lamp were obtained from Murov et al. (1993). Photolysis rates were corrected for light screening (Zepp and Cline, 1977) by the MRW and the pharmaceutical compounds themselves because the pharmaceutical concentrations employed resulted in some solutions that were not optically dilute. These rates were then used to calculate quantum yields (Dulin and Mill, 1982).

### Fenton reaction

The second-order rate constant for the reaction of the selected pharmaceuticals with hydroxyl radical was determined using Fenton's reagent, as described previously for a variety of pollutants (Haag and Yao, 1992). Reactors (125 mL serum bottles) contained a solution of the pharmaceutical of interest and acetophenone at comparable concentrations (35–100 µM), $Fe^{2+}$ (0.2 mM), and hydrogen peroxide (5 mM) adjusted to pH 3.5 with sulfuric acid (Tang and Huang, 1996). The reactor was wrapped in aluminum foil to exclude light and prevent photo-Fenton chemistry. Incubations were performed at room temperature (22 ± 1°C). Samples (0.5 mL) were withdrawn at predetermined intervals, and the reactions were quenched with an equivalent volume of methanol (Chen and Pignatello, 1997). Samples were then analyzed via HPLC.

### HPLC analyses

All analyses were conducted with a Supelco Discovery RP-Amide $C_{16}$, 150 × 4.6 mm, 5 µm particle size column. Absorbance was monitored at 219 nm for the pharmaceutical compounds. The mobile phase consisted of a 60:40 ratio of acetonitrile and 25 mM $KH_2PO_4$ buffer (pH 3) at a flow rate of 1.0 mL/min. The *p*-nitroanisole and *p*-nitroacetophenone actinometers were analyzed under identical conditions except the detector was set to 313 nm and 300 nm, respectively. Acetophenone was measured using the phosphate buffer (pH 3) and either acetonitrile or methanol in a 50:50 ratio as the mobile phase, and the absorbance was recorded at 254 nm.

## Results

### Photolysis experiments

Table 1 contains a summary of the sunlight photolysis results obtained including the first order photolysis rate constants ($k$) and quantum yields ($\Phi$) determined in Milli-Q water, the first order rate constants in Milli-Q water with IPA, and the first order rate constants in MRW (with and without IPA) for naproxen, diclofenac, and clofibric acid. The degradation of ibuprofen could not be quantified under sunlight irradiation under the conditions employed. The rate constants in Table 1, therefore, are for irradiation by the Hg-vapor lamp.

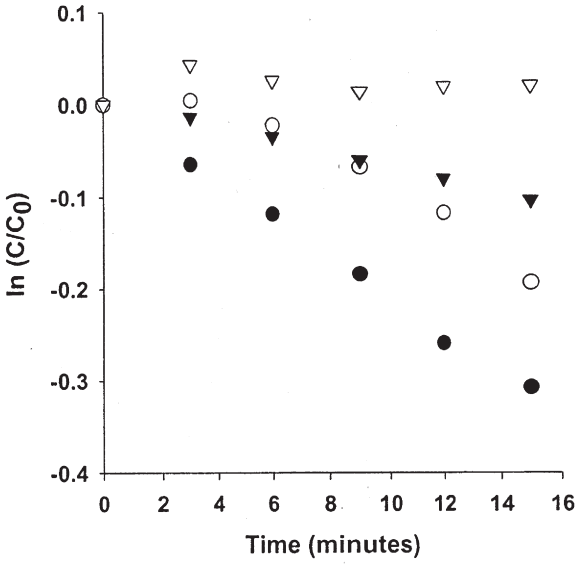


**Figure 2.** Direct photolysis of naproxen in $H_2O$ in sunlight. Conditions are as follows: ● = substrate in Milli-Q water, ○ = Mississippi River water (MRW), ▼ = MRW with 1% isopropanol, ▽ = dark control. Reprinted with permission from Packer et al., 2003.

The photolysis of naproxen in Milli-Q water and in MRW by natural sunlight is shown in Figure 2. In MRW, naproxen was photodegraded slightly more slowly than in Milli-Q water ($k_{MRW}/k_{MQ}$ = 0.78). In the MRW, degradation of the naproxen did not begin until two minutes had elapsed. Thus, the first-order rate constant was determined from the data collected at t ≥ 2 min. The radical inhibitor IPA reduced the photodegradation rate in MRW ($k_{MRW\text{-}IPA}/k_{MRW}$ = 0.43). Subsequent work with 1% IPA in Milli-Q water showed similar inhibition (data not shown). The rate constant for reaction of singlet oxygen with

**Table 1.** Observed first-order rate constants and calculated quantum yields

| Compound | Milli-Q water | | | Mississippi River Water | |
|---|---|---|---|---|---|
| | $k_{MQ}$ ($min^{-1}$) × $10^2$ | $k_{MQ\text{-}IPA}$ ($min^{-1}$) × $10^2$ | $\Phi$ | $k_{MRW}$ ($min^{-1}$) × $10^2$ | $k_{MRW\text{-}IPA}$ ($min^{-1}$) × $10^2$ |
| Naproxen | 2.08 ± 0.14[a] | not measured | 0.036 | 1.64 ± 0.54 | 0.71 ± 0.08 |
| Diclofenac | 1.97 ± 0.30 | 2.86 ± 0.25 | 0.094 | 1.97 ± 0.16 | 3.32 ± 0.34 |
| Clofibric Acid | 0.008 ± 0.001 | 0.014 ± 0.002 | 0.002 | 0.023 ± 0.007 | 0.009 ± 0.002 |
| Ibuprofen[b] | 0.10 ± 0.02 | 0.06 ± 0.01 | – | 0.45 ± 0.03 | 0.10 ± 0.01 |

[a] Errors represent 95% confidence limits.
[b] Results with ibuprofen were obtained with a medium pressure Hg-vapor lamp with intensity approximately 5 times greater than sunlight. Because the borosilicate incompletely blocks wavelengths < 290 nm, no quantum yield is reported.

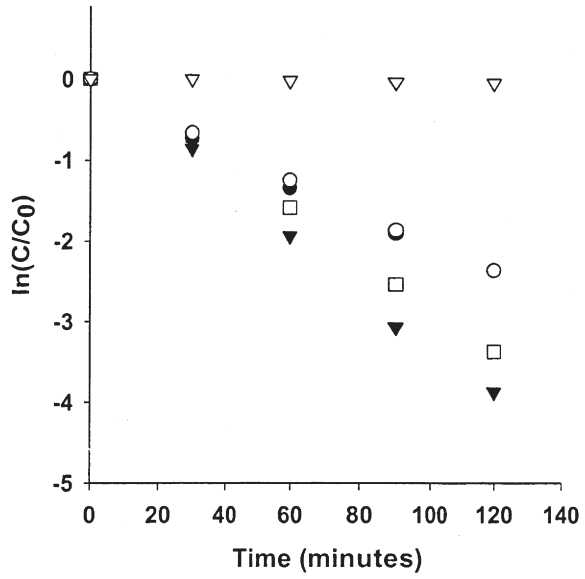


**Figure 3.** Direct photolysis of diclofenac in $H_2O$ in sunlight. Conditions are as follows: ● = substrate in Milli-Q water, ○ = Mississippi River water (MRW), □ = Milli-Q water + 1 % isopropanol, ▼ = MRW with 1 % isopropanol, ▽ = dark control. Reprinted with permission from Packer et al., 2003.

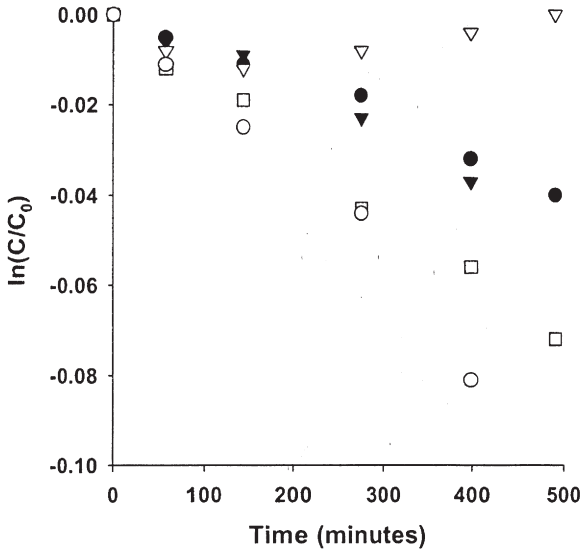


**Figure 4.** Direct photolysis of clofibric acid in $H_2O$ in sunlight. Conditions are as follows: ● = substrate in Milli-Q water, ○ = Mississippi River water (MRW), □ = Milli-Q water + 1 % isopropanol, ▼ = MRW with 1 % isopropanol, ▽ = dark control.

naproxen was determined by LFP to be $(1.1 \pm 0.1) \times 10^5$ $M^{-1}$ $s^{-1}$ in ethanol. One previously observed product of naproxen photolysis, 2-acetyl-6-methoxynaphthalene (Moore and Chappuis, 1988; Bosca et al., 1990; Jimenez et al., 1997), was identified by comparison of HPLC retention time with an authentic standard. This product was produced in 27% yield.

The results for diclofenac photolysis by natural sunlight are shown in Figure 3. Sunlight photolysis of diclofenac in natural water proceeded at a rate that is equivalent to that in Milli-Q water ($k_{MRW}/k_{MQ} = 1.00$). The IPA (added to serve as a radical inhibitor) actually increased the photodegradation rate in Mississippi River water ($k_{MRW\text{-}IPA}/k_{MRW} = 1.68$). Further study revealed that IPA also increased the photodegradation rate of diclofenac in deionized water by a similar amount ($k_{MQ\text{-}IPA}/k_{MQ} = 1.45$).

In Figure 4, the photolysis of clofibric acid in sunlight is depicted. The rate of disappearance in MRW is 2.9 times faster than in Milli-Q water. IPA slows the photolysis rate in MRW ($k_{MRW\text{-}IPA}/k_{MRW} = 0.39$) and the resulting rate is the same as that in Milli-Q water. Addition of IPA to the Milli-Q water resulted in a photolysis rate 1.7 times that observed in Milli-Q water alone. This is attributed to experimental variation as only 8–10% of the clofibric acid was degraded during the experiments.

Because the limited transformation of ibuprofen observed in sunlight made determination of quantum yields and comparison between experimental treatments difficult, further experiments were performed with a Hg-vapor lamp. The photolysis kinetics of ibuprofen are shown in Figure 5. Ibuprofen was negligibly degraded in Milli-Q water (with or without IPA). In MRW, however, transformation did occur, and this reaction was quenched by the addition of IPA.

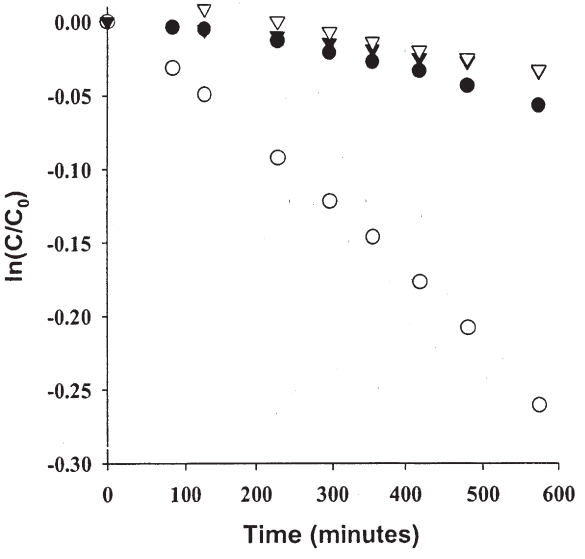


**Figure 5.** Direct photolysis of ibuprofen in $H_2O$ by a Hg-vapor lamp. Conditions are as follows: ● = substrate in Milli-Q water, ○ = Mississippi River water (MRW), ▼ = Milli-Q water with 1% isopropanol, ▽ = MRW with 1% isopropanol.

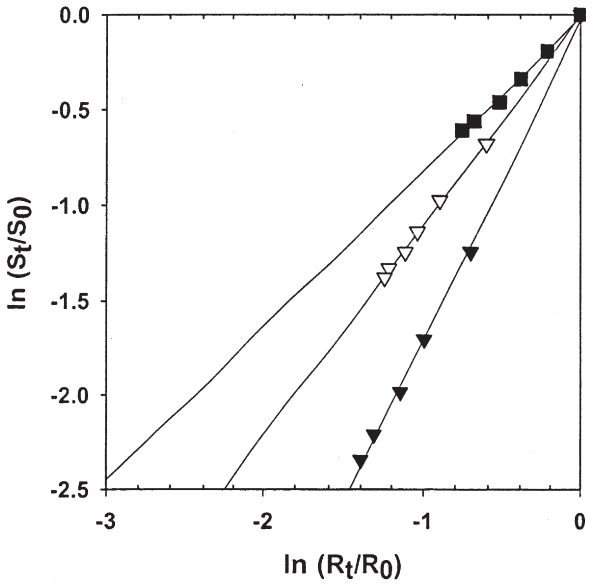


**Figure 6**. Competitive oxidation of PPCPs and acetophenone in aqueous solution by hydroxyl radicals generated using Fenton's reaction. Substrates are as follows: ▽ = ibuprofen, ▼ = naproxen, ■ = clofibric acid. Reprinted with permission from Packer et al., 2003.

### Fenton reaction: ·OH $k_{rxn}$ measurements

Second order rate constants for reaction with hydroxyl radical were determined using competition kinetics according to eq. 1 (Haag and Yao, 1992):

$$k^{S}_{\cdot OH} = \frac{\ln([S_t]/[S_0])}{\ln([R_t]/[R_0])} k^{R}_{\cdot OH} \quad (1)$$

where $S$ is the substrate and $R$ is the reference compound with a known hydroxyl radical rate constant (acetophenone, $5.9 \times 10^9$ $M^{-1}$ $s^{-1}$; Buxton et al., 1988). A plot of ln ($[S_t]/[S_0]$) versus ln ($[R_t]/[R_0]$) has a slope of 1.63 ± 0.09 for naproxen, 0.80 ± 0.06 for clofibric acid, and 1.10 ± 0.03 for ibuprofen as shown in Figure 6. The reported errors are the calculated 95% confidence limits of the regressed slopes. No transformation of diclofenac was observed in the Fenton system, and thus no rate constant could be determined. Using the slopes derived from Figure 6 and eq. 1, the hydroxyl radical rate constants for reaction with the selected pharmaceuticals shown in Table 2 were determined.

## Discussion

### Naproxen

Naproxen is subject to direct photolysis with a half-life in MRW of 42 minutes under the conditions studied (summer sunlight, 45° latitude). The UV-visible spectrum (Fig. 1) of naproxen helps explain its photolability. Although the major maximum is at 230 nm, the spectrum of naproxen does have smaller absorbance maxima at 273 and 330 nm. Calculation of the light screening factor reveals that screening of the wavelengths >300 nm by the MRW causes the slight decrease in transformation rate in the MRW. The quantum yield found (0.036) is higher than that reported previously (0.012; Moore and Chappuis, 1988). The difference is likely due to different light sources, as Moore and Chappuis (1988) used a filter to block wavelengths <310 nm from their Hg-vapor lamp. The measured rate constant for interaction with singlet oxygen was found to be $(1.1 \pm 0.1) \times 10^5$ $M^{-1}$ $s^{-1}$ in ethanol, which is similar to rate constants measured for $^1O_2$ reaction with dialkyl-substituted naphthalenes (van den Heuvel, 1980; Cazin, 1986). For instance, 1,4-dimethylnaphthalene was reported to have a reaction rate constant with $^1O_2$ of $1.3 \times 10^5$ $M^{-1}$ $s^{-1}$ in 86 % EtOH: 14% $H_2O$ (Cazin, 1986). The total singlet oxygen quenching rate constant (the sum of chemical reaction and physical quenching) as determined by LFP suggests that $^1O_2$ is unimportant in the photochemical fate of naproxen in natural waters.

The decrease in reaction rate in the presence of IPA in both Milli-Q water and MRW cannot be explained by the quenching of ·OH. At a typical value of $10^{-16}$ M for ·OH, <1% of the quenched transformation in MRW can be attributed to hydroxyl radical based on the second-order rate constant determined for naproxen. Another possibility for the observed effect of IPA is the quenching of a radical form of the naproxen itself. Support for this possibility arises from previous phototoxicity work, in which the direct photolysis products of naproxen were identified in the presence and absence of molecular oxygen (Moore

**Table 2.** Hydroxyl radical rate constants and expected environmental half lives of PPCPs based solely on hydroxyl radical concentrations.

| Compound | $k_{\cdot OH}$ ($M^{-1}$ $s^{-1}$) × $10^{-9}$ | Half-life corresponding to hydroxyl radical concentration | | |
|---|---|---|---|---|
| | | $10^{-15}$ M | $10^{-16}$ M | $10^{-17}$ M |
| Naproxen | 9.6 ± 0.5 [a] | 20 h | 202 h | 2020 h |
| Clofibric Acid | 4.7 ± 0.3 | 41 h | 408 h | 4080 h |
| Ibuprofen | 6.5 ± 0.2 | 29 h | 296 h | 2960 h |

[a] Errors represent 95% confidence limits.

and Chappuis, 1988; Bosca et al., 1990; Jimenez et al., 1997). Under aerobic conditions, the first product observed is 1-(6-methoxy-2-napthyl)ethanol, which is subsequently oxidized to 2-acetyl-6-methoxynaphthalene (Moore and Chappuis, 1988; Bosca et al., 1990; Jimenez et al., 1997). Under anaerobic conditions, 1-(6-methoxy-2-napthyl)ethanol and 1-ethyl-6-methoxynaphthalene are observed. The first step is conversion of the carboxylate (RC(=O)O-) group to a carboxyl radical (RC(=O)O·) by photoionization. Such a photochemically activated electron transfer is well established for a variety of substituted 2-arylacetic acids (Joschek and Grossweiner, 1966; Crosby and Tang, 1969). Decarboxylation, resulting in carbon dioxide and a benzylic radical, is then proposed to occur. The resulting benzylic radical then abstracts a hydrogen atom from a suitable donor resulting in the product with an ethyl side chain, or reacts with molecular oxygen, eventually leading to the alcohol or ketone moiety in place of the carboxylate group. The 27% yield of 2-acetyl-6-methoxynaphthalene in this work is consistent with the 34% obtained by Jimenez et al. (1997) using a medium pressure Hg-lamp. The identification of this product also provides support for the formation of the carboxyl radical and is consistent with the effect of the IPA.

We attribute the lower degradation rate of naproxen in the presence of IPA in both Milli-Q and MRW as arising from quenching of the carboxyl radical by IPA. This process would result in re-formation of naproxen and lead to a lower overall degradation rate in the presence of IPA. The overall effect on reaction rate would be dependent on the relative rates of quenching by IPA and decarboxylation. The participation/quenching of other radical species (e.g., peroxy radicals, DOC radicals) in the MRW, however, cannot be ruled out. Note that such a quenching effect by the DOC in the MRW (16 mg/L) would be minimal compared to that by 1% IPA (≈4700 mg/L DOC).

**Diclofenac**

Diclofenac reacts rapidly via direct irradiation. It has a half-life of 39 minutes in both natural water and in Milli-Q water in the experiments performed. Because the solutions of diclofenac were not optically dilute, the light screening by diclofenac itself dominates over that caused by the organic matter in MRW. Thus, additional screening by MRW is minimal, resulting in similar degradation rates in MRW and Milli-Q water. The quantum yield found in this study, 0.094, is very close to that reported in the literature (0.12–0.2) (Buser et al., 1998). Quantum yields at pH 5.5 (0.03–0.04) have recently been reported, as well (Andreozzi et al., 2003). Diclofenac has an absorbance maximum at 273 nm that tails well over 300 nm. The significant amount of absorbance in the solar region helps to explain the rapid direct photodegradation of diclofenac. An acceleration of the reaction in the presence of IPA occurred in both Milli-Q water and in MRW, indicating that either a reaction with or mediated by IPA takes place. The acceleration may be due formation of a carbon centered radical from the IPA which could react with molecular oxygen resulting in superoxide and hydroperoxyl radicals (von Sonntag, 1987), acceleration of the ring closure to previously observed photoproducts (Moore et al., 1990; Buser et al., 1998; Poiger et al., 2001), or photo-initiated reduction between isopropanol (an H-donor) and diclofenac (Poiger et al., 2001). The results of this study and of previous researchers (Moore et al., 1990; Buser et al., 1998; Poiger et al., 2001; Andreozzi et al., 2003), however, indicate that direct photolysis is the dominant degradation mechanism for diclofenac.

**Clofibric acid**

In the natural water irradiated by sunlight, the half-life of clofibric acid was 50 hours under the conditions employed, and the quantum yield found in Milli-Q (0.002) water is comparable to the 0.005 recently reported by Andreozzi et al. (2003). Andreozzi et al. (2003) also found that the presence of nitrate and humic acids increased the degradation rate which argues that radicals play a role in clofibric acid transformation. In addition, both the more rapid reaction observed in MRW versus Milli-Q water and the quenching by IPA in MRW in this work suggest a role of indirect photochemical processes. At a typical, upper-range value of $10^{-16}$ M for ·OH, ~20% of the quenched transformation can be attributed to hydroxyl radical based on the second-order rate constant determined for clofibric acid. This analysis suggests that other radical species are also likely involved. Previous work by Lam et al. (2003) did not see any acceleration of the degradation rate of clofibric acid upon addition of Suwannee River fulvic acid and/or nitrate. These authors noted, however, that the solar simulator used in their experiments incompletely screened wavelengths <290 nm, and thus likely overestimated the importance of direct photolysis. Thus in sunlit natural waters, it appears that direct and radical-mediated indirect photolysis may play approximately equal roles in the transformation of clofibric acid.

**Ibuprofen**

Ibuprofen is transformed only minimally via direct irradiation using the Hg-vapor lamp. The photostability of ibuprofen is explained by its UV-visible spectrum, which exhibits a maximum at 223 nm and shows little absorbance in the wavelength region of the solar spectrum. Because the borosilicate well incompletely screens wavelengths <290 nm, no quantum yield is reported. The degradation of ibuprofen in the MRW and the quenching

of this reaction by IPA argues for a radical-mediated mechanism of degradation in MRW. Based on the $k_{OH}$ value for ibuprofen and the observed degradation rate that can be attributed to radical processes ($k_{MRW} - k_{MRW\text{-}IPA} = 3.5 \times 10^{-4}$ min$^{-1}$), the calculated steady state hydroxyl radical concentration would be $5.4 \times 10^{-14}$ M in the irradiated MRW. This value is 5–10 times greater than that obtained previously using this Hg lamp for similar waters collected in Minnesota (Brezonik and Fulkerson-Brekken, 1998). It is likely that photogenerated radicals other than hydroxyl radical are also involved in the transformation of ibuprofen. This analysis indicates that indirect photolysis mediated by radicals is the primary photolysis process for ibuprofen in surface waters. Given the overall slow photodegradation of ibuprofen, however, other loss processes such as biodegradation (Richardson and Bowron, 1985), may be responsible for its removal from the environment and explain its lower detection frequency in surface waters.

**Fenton's reaction: ·OH reaction measurements**

Naproxen, clofibric acid, and ibuprofen exhibit bimolecular rate constants for reaction with hydroxyl radical near the diffusion-controlled limit. In the Fenton system, diclofenac was not susceptible to hydroxyl radical attack over timescales that the acetophenone reference was present. Either the Fenton system is unsuitable to study diclofenac, or the rate of reaction with hydroxyl radicals is relatively slow (second order rate constant of order $10^7$ or less). The first explanation is more likely given the nonspecific nature of hydroxyl radical attack. The rate constant for ibuprofen found in this work is similar to that reported by Huber et al. (2003) ($(7.4 \pm 1.2) \times 10^9$ M$^{-1}$ s$^{-1}$) in a study evaluating advanced oxidation processes for the treatment of waters containing pharmaceuticals. The predicted half-lives of the pharmaceuticals assuming that reaction with hydroxyl radical is the only loss process are given in Table 2 at typical ·OH concentrations. It is necessary to note that the nitrate concentration in the Mississippi River is increased substantially in the region where the Mississippi merges with the Minnesota River (south of Minneapolis/St. Paul), an agriculturally impacted river. Hydroxyl radicals would likely play a much more important role in this stretch of the river due to the increased nitrate concentration (Brezonik and Fulkerson-Brekken, 1998; Mill, 1999).

**Environmental significance**

The experiments described in this work demonstrate that naproxen and diclofenac are photolabile in Mississippi River water, a surface water in which pharmaceuticals have been detected (Kolpin et al., 2002). Direct photolysis is the dominant loss process for diclofenac and naproxen, and both compounds will behave comparably at 45° latitude in the summer with expected half-lives of 78 and 84 minutes respectively in surface waters after correcting for lens effects of the test tubes (Dulin and Mill, 1982; Haag and Hoigne, 1986). These estimates are for noontime, full-sun, and near-surface conditions, and should be viewed as the minimum half-lives at this latitude. Using tabulated winter light intensity values (Leifer, 1988), the half-life of diclofenac is expected to increase to approximately 8 hours due to the decrease in light intensity, while naproxen should increase to about 7 hours. Using tabulated summer and winter solar intensity values at 30° latitude (Leifer, 1988), the expected half-life of diclofenac is 67 minutes, and in the winter it is expected to be about 3 hours. The half-life for naproxen at 30° latitude in summer sunlight should be 79 minutes, and it will increase to 3 hours in the winter.

For clofibric acid, the summer half-life at 45° latitude is expected to be ~100 hours if the lens effect of the test tube influences direct and indirect photochemical processes similarly. Overall, 60% of clofibric acid transformation in MRW is attributed to indirect photolysis processes, indicating that the persistence of this compound in natural waters will be highly dependent on the sensitizing species (e.g., dissolved organic matter, nitrate) present. Hydroxyl radical concentration may range from $10^{-16}$ M in agriculturally impacted waters containing high nitrate levels to $10^{-18}$ M for pristine waters (Brezonik and Fulkerson-Brekken, 1998; Mill, 1999). Based on these low steady-state concentrations, the degradation of the pharmaceuticals targeted in this study by ·OH is expected to be slow, but for ibuprofen and clofibric acid, this and other radical mediated processes may be the dominant photochemical loss mechanisms.

These estimated environmental half-lives represent only photochemical degradation and do not account for other loss processes. Furthermore, as mentioned above, they correspond to maximum environmental photodegradation rates and will need to be corrected for light absorption and scattering in the water column. In the environment, these pharmaceuticals are detected at concentrations approximately four to five orders of magnitude lower than those used in this study. Thus, the fraction of light absorbed by these compounds will be reduced by dissolved organic matter and other constituents present in natural waters, and the direct photolysis rates would be proportionately reduced. In addition, indirect photolysis rates could be decreased by competition with dissolved organic matter and carbonate for photogenerated radicals.

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## References

Andreozzi, R., M. Rafaele and N. Paxeus, 2003. Pharmaceuticals in STP effluents and their solar phtotodegradation in aquatic environment. Chemosphere **50:** 1319–1330.

Blough, N. V. and R. G. Zepp, 1995. Reactive oxygen species in natural waters. In: C. S. Foote, J. S. Valentine, A. Greenberg and J. F. Liebman (eds.), Active Oxygen in Chemistry, Chapman and Hall, New York, pp. 280–333.

Bosca, F., M. A. Miranda, L. Vano and F. Vargas, 1990. New photodegradation pathways for naproxen, a phototoxic nonsteroidal anti-inflammatory drug. Journal of Photochemistry and Photobiology A: Chemistry **54:** 131–134.

Brezonik, P. L. and J. Fulkerson-Brekken, 1998. Nitrate-induced photolysis in natural waters: controls on concentrations of hydroxyl radical photo-intermediates by natural scavenging agents. Environmental Science and Technology **32**(19)**:** 3004–3010.

Buser, H.-R., M. D. Mueller and N. Theobald, 1998. Occurrence of the pharmaceutical drug clofibric acid and the herbicide mecoprop in various Swiss lakes and in the North Sea. Environmental Science and Technology **32**(1): 188–192.

Buser, H.-R., T. Poiger and M. D. Mueller, 1998. Occurrence and fate of the pharmaceutical drug diclofenac in surface waters: rapid photodegradation in a lake. Environmental Science and Technology **32**(22): 3449–3456.

Buser, H.-R., T. Poiger and M. D. Mueller, 1999. Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. Environmental Science and Technology **33**(15): 2529–2535.

Buxton, G. V., C. L. Greenstock, N. P. Helman and A. B. Ross, 1988. Critical review of rate constants for reaction of hydrated electrons and hydroxyl radicals in aqueous solution. Journal of Physical and Chemical Reference Data **17:** 513–886.

Castell, J. V., M. J. Gomez-L., M. A. Miranda and I. M. Morera, 1987. Photolytic degradation of ibuprofen, toxicity of the isolated photoproducts on fibroblasts and erythocytes. Photochemistry and Photobiology **46**(6): 991–996.

Cazin, B., J. M. Aubry and J. Rigaudy, 1986. Is water the best or the worst solvent for [2 + 4] cycloadditions of singlet oxygen to aromatic compounds? Journal of the Chemical Society, Chemical Communications **12:** 952–953.

Chen, R. and J. J. Pignatello, 1997. Role of quinone intermediates as electron shuttles in Fenton and photoassisted Fenton oxidation of aromatic compounds. Environmental Science and Technology **31**(8): 2399–2406.

Condorelli, G., G. D. Guidi, S. Giuffrida and L. L. Costanzo, 1993. Photosensitizing action of nonsteroidal antiinflammatory drugs on cell membranes and design of protective systems. Coordination Chemistry Reviews **125:** 115–128.

Crosby, D. G. and C.-S. Tang, 1969. Photodecomposition of 1-naphthalene acetic acid. Journal of Agricultural and Food Chemistry **17**(6): 1291–1293.

Daughton, C. G. and T. A. Ternes, 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change? Environmental Health Perspectives Supplements **107**(6): 907–938.

Doll, T. E. and F. H. Frimmel, 2003. Fate of pharmaceuticals-photodegradation by simulated solar UV-light. Chemosphere **52:** 1757–1769.

Dulin, D. and T. Mill, 1982. Development and evaluation of sunlight actinometers. Environmental Science and Technology **16**(11): 815–820.

Gueymard, C. A. 1995. SMARTS, A simple model of the atmospheric radiative transfer of sunshine: algorithms and performance assessment. Cocoa, FL, Florida Solar Energy Center. Technical Report No.FSEC-PF-270-95.

Gueymard, C. A., 2001. Parameterized transmittance model for direct beam and circumsolar spectral irradiance. Solar Energy **75:** 325–346.

Haag, W. R. and J. Hoigne, 1986. Singlet oxygen in surface waters. 3. Photochemical formation and steady-state concentrations in various types of waters. Environmental Science and Technology **20**(4): 341–348.

Haag, W. R. and C. C. D. Yao, 1992. Rate constants for reaction of hydroxyl radicals with several drinking water contaminants. Environmental Science and Technology **26**(5): 1005–1013.

Halling-Sorensen, B., S. Nors Nielsen, P. F. Lanzky, F. Ingerslev, H. C. Holten Lutzhoft and S. E. Jorgensen, 1998. Occurrence, fate and effects of pharmaceutical substances in the environment – a review. Chemosphere **36**(2): 357–393.

Heberer, T., 2002. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicology Letters **131**(1–2): 5–17.

Hignite, C. and D. L. Azarnoff, 1977. Drugs and drug metabolites as environmental contaminants: chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. Life Science **20**(2): 337–341.

Huber, M. M., S. Canonica, G.-Y. Park and U. V. Gunten, 2003. Oxidation of pharmaceuticals during ozonation and advanced oxidation processes. Environmental Science and Technology **37**(5): 1016–1024.

Jimenez, M. C., M. A. Miranda and R. Tormos, 1997. Photochemistry of naproxen in the presence of β-cyclodextrin. Journal of Photochemistry and Photobiology A: Chemistry **104:** 119–121.

Jones, O. A. H., N. Voulvoulis and J. N. Lester, 2002. Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. Water Research **36:** 5013–5022.

Jorgensen, S. E. and B. Halling-Sorensen, 2000. Drugs in the environment. Chemosphere **40**(7): 691–699.

Joschek, H.-I. and L. I. Grossweiner, 1966. Optical generation of hydrated electrons from aromatic compounds. II. Journal of the American Chemical Society **88:** 3261–3268.

Kolpin, D. W., E. T. Furlong, M. T. Meyer, E. M. Thurman, S. D. Zaugg, L. B. Barber and H. T. Buxton, 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. Streams, 1999–2000: a national reconnaissance. Environmental Science and Technology **36**(6): 1202–1211.

Lam, M. W., K. Tantuco and S. A. Mabury, 2003. PhotoFate: a new approach in accounting for the contribution of indirect photolysis of pesticides and pharmaceuticals in surface waters. Environmental Science and Technology **37**(5): 899–907.

Latch, D. E., B. L. Stender, J. L. Packer, W. A. Arnold and K. McNeill, 2003. Photochemical fate of pharmaceuticals in the environment: cimetidine and ranitidine**.** Environmental Science and Technology **37**(15): 3342–3350.

Leifer, A., 1988. The Kinetics of Environmental Aquatic Photochemistry: Theory and Practice; American Chemical Society, Washington D.C.

Mill, T., 1999. Predicting photoreaction rates in surface waters. Chemosphere **38**(6): 1379–1390.

Moore, D. E. and P. P. Chappuis, 1988. A comparative study of the photochemistry of the non-steroidal anti-inflammatory drugs, naproxen, benoxaprofen and indomethacin. Photochemistry and Photobiology **47**(2): 173–180.

Moore, D. E., S. Roberts-Thomson, D. Zhen and C. C. Duke, 1990. Photochemical studies on the anti-inflammatory drug diclofenac. Photochemistry and Photobiology **52**(4): 685–690.

Murov, S. L., I. Carmichael and G. L. Hug, 1993. The Handbook of Photochemistry. New York, Marcel Dekker.

Nonell, S., S. E. Braslavsky and K. Schaffner, 1990. Quantum yield of production of singlet molecular oxygen ($^1\Delta g$) in aqueous dispersions of small unilamellar lipid vesicles. A time-resolved near-IR phosphorescence study. Photochemistry and Photobiology **51**(5): 551–556.

Nonell, S. and S. E. Braslavsky, 2000. Time-resolved singlet oxygen detection. Methods in Enzymology **319:** 37–49.

Packer, J. L., D. E. Latch, K. McNeill and W. A. Arnold, 2003. Photochemical fate of pharmaceuticals in the environment: naproxen, ibuprofen, diclofenac and clofibric acid. *Preprints of Extended Abstracts,* Division of Environmental Chemistry, American Chemical Society, **43**(1): 396–400.

Poiger, T., H.-R. Buser and M. D. Muller, 2001. Photodegradation of the pharmaceutical drug diclofenac in a lake: pathway, field measurements, and mathematical modeling. Environmental Toxicology and Chemistry **20**(2): 256–263.

Richardson, M. L. and J. M. Bowron, 1985. The fate of pharmaceuticals in the aquatic environment. Journal of Pharmacy and Pharmacology **37:** 1–12.

Stumpf, M., T. A. Ternes, R.-D. Wilken, R. Silvana Vianna and W. Baumann, 1999. Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. Science of the Total Environment **225**(1–2): 135–141.

Tang, W. and C. P. Huang, 1996. Effect of chlorine content of chlorinated phenols on their oxidation kinetics by Fenton's reagent. Chemosphere **33**(8): 1621–1635.

Ternes, T. A., 1998. Occurrence of drugs in German sewage treatment plants and rivers. Water Research **32**(11): 3245–3260.

Ternes, T. A., M. Stumpf, B. Schuppert and K. Haberer, 1998. Simultaneous determination of antiseptics and acidic drugs in sewage and river water. Vom Wasser **90:** 295–309.

Tixier, C., H. P. Singer, S. Oellers and S. R. Mueller, 2003. Occurrence and fate of carbamazepine, clobiric acid, diclofenac, ibuprofen, ketoprofen and naproxen in surface waters. Environmental Science and Technology **37**(6): 1061–1068.

Van den Heuvel, C. J. M., H. Steinberg and T. J. De Boer, 1980. The photooxidation of mono- and dimethylnaphthalenes by singlet oxygen. Recueil des Travaux Chimiques des Pays-Bas **99**(4): 109–13.

von Sonntag, C., 1987. The Chemical Basis of Radiation Biology. Philadelphia, PA, Taylor & Francis Inc.

Zepp, R. G. and D. M. Cline, 1977. Rates of direct photolysis in aquatic environment. Environmental Science and Technology **11**(4): 359–66.

Zuccato, E., D. Calamari, M. Natangelo and R. Fanelli, 2000. Presence of therapeutic drugs in the environment. Lancet **355**(9217): 1789–1790.