Reactions of the amine-containing drugs fluoxetine and metoprolol during chlorination and dechlorination processes used in wastewater treatment

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Abstract

The reactivities of the amine-containing pharmaceuticals fluoxetine and metoprolol with hypochlorite were studied using conditions that simulate wastewater disinfection including neutral pH (7.0), a range of reaction times (2–60 min), and a molar excess of hypochlorite relative to the pharmaceutical concentration (5.7 times). The reactions were monitored using liquid chromatography (LC) with several detection modes including ultraviolet absorbance (UV), mass spectrometry (MS), and post-column reaction/reductive electrochemistry (EC) for determining active chlorine products. At levels of 10 \( \mu \text{M} \), both compounds reacted rapidly (<2 min) to form principally \( N \)-chloramines products that were stable in aqueous solution for at least 1 h. The reaction was also studied in wastewater, and similar reactivity was noted. These results demonstrate that the cations fluoxetine and metoprolol are likely to be rapidly transformed into neutral \( N \)-chloramines during wastewater disinfection. The reactivity of the \( N \)-chloramines was also studied with sulfite to simulate dechlorination, which is often employed in wastewater treatment. Both \( N \)-chloramines reacted slowly with sulfite. In the pure water dechlorination experiments, it was estimated that 70% and 10% of the peak areas remained after 2 min reaction time for fluoxetine and metoprolol, respectively. At longer reaction times both \( N \)-chloramines had been completely reduced by sulfite, and the product of the sulfite reduction reaction was the parent pharmaceutical amine. Since typical dechlorination times in wastewater treatment are on the order of seconds, this suggests the chloramines formed from these two basic drugs might evade dechlorination and be released into the environment. The implications of chloramine release are discussed.

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1. Introduction

Fluoxetine and metoprolol are both widely prescribed pharmaceutical compounds representing vastly different classes of drugs. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that is most commonly used to treat depression. Metoprolol is a betablocker used for treatment of a range of cardiac conditions, most commonly hypertension. Both of these compounds have been detected in a number of environmental water samples including wastewater effluents, rivers, and streams (Ternes, 1998; Kolpin et al., 2002; Huggett et al., 2003). Some studies have suggested there could be a range of potential aquatic ecosystem effects of these compounds in the environment, particularly for the SSRI drugs (see review in Fong, 2001). For example, fluoxetine and its metabolite norfluoxetine have been measured in fish samples obtained from an effluent-dominated stream (Brooks et al., 2005), indicating a potential to bioaccumulate. Reports on the toxicity of metoprolol to aquatic organisms are contradictory, but it appears that species-specific toxic effects are possible (Huggett et al., 2002; Cleuvers, 2005).
Like most pharmaceuticals, fluoxetine and metoprolol primarily enter the environment through wastewater. Wastewater treatment often involves many processes including biological treatment with activated sludge, chlorine disinfection, and dechlorination. Metoprolol is not significantly biologically degraded in activated sludge processing (Paxéus, 2004), and fluoxetine only partially absorbs to sludge (Johnson et al., 2005). However, chlorination and dechlorination are chemical processes that could transform reactive pharmaceutical compounds. Fluoxetine (I) and metoprolol (II) both contain secondary aliphatic amines and are basic drugs with pKa values of 10.1 (Ploemen et al., 2004) and 9.2 (Detroyer et al., 2001), respectively, which indicates they are predominantly protonated at neutral pH. They share this structural similarity with a wide range of other basic drugs that can react rapidly with chlorine during disinfection to form N-chloramines, which has already been demonstrated for sulfamethoxazole (Dodd and Huang, 2004). Chloramines are important in disinfection processes and the environment because they have oxidizing ability and are considered “active chlorine” compounds.

Dechlorination is used in wastewater treatment following chlorination to reduce active chlorine residuals from entering the environment. Most commonly, dechlorination is achieved with sulfur dioxide or sulfite salts. Unlike chlorination, where contact times on the order of 1 h are typical, dechlorination is assumed to be instantaneous, and reaction times provided are often on the order of seconds prior to discharge. However, there have been several studies demonstrating that chloramines formed in the disinfection process exhibit vastly different rates of reaction with sulfite (Yin et al., 1987; Jensen and Helz, 1998; Jameel and Helz, 1999).

In our study, we investigated the propensity of the basic pharmaceutical compounds fluoxetine and metoprolol to react with hypochlorite in pure water using conditions that simulate wastewater disinfection. The chlorination reactions were also investigated in wastewater collected from an operating treatment plant. Additionally, the reactivity of the chlorination products with sulfite was studied to simulate wastewater dechlorination. To evaluate the reactions of these two drugs with hypochlorite and sulfite, liquid chromatography (LC) was used with multiple detectors that included ultraviolet absorbance (UV), mass spectrometry (MS), and a unique detection approach utilizing post-column reaction chemistry and reductive electrochemical detection (EC) to determine active chlorine species.

2. Materials and methods

2.1. Reagents

Fluoxetine hydrochloride and (±)-metoprolol tartrate salt (minimum 99%) were purchased from Sigma (St. Louis, MO, USA). Aqueous solutions of both fluoxetine and metoprolol were prepared to be 10 μM and 80 μM and were buffered with phosphate buffer, pH 7, to 1 mM total phosphate. The 80 μM solutions were used to obtain full-scan data for MS detection. All pharmaceutical solutions were stored at 4 °C when not being used. For chlorination experiments, a 5% solution (≥5% as Cl2) of reagent grade sodium hypochlorite (NaOCl) was obtained from Alfa Aesar (Ward Hill, MA, USA) and diluted to approximately 5 mM. The solution was standardized weekly using an iodometric titration, and the concentration was found to be stable over a period of months. At pH 7, the reactive chlorine species are distributed between hypochlorite ion and hypochlorous acid based on the pKa value of 7.5. In this paper we will refer to this equilibrium mixture as ‘hypochlorite’. Subsamples of the pharmaceutical solutions (1.0 ml) were chlorinated in amber vials by adding an appropriate aliquot of the standardized NaOCl solution and vortex mixing for 10 s. The 10 μM solutions were chlorinated to 57 μM with hypochlorite, which is equivalent to 4 ppm as Cl2, a representative disinfection dose used for wastewater treatment. The 80 μM solutions were nominally chlorinated to 456 μM to maintain the same ratio of hypochlorite to pharmaceutical as for the 10 μM solutions. All chlorination experiments were performed at room temperature, 23 °C ± 1 °C.

Water (OmniSolv, EMD Chemicals, Gibbstown, NJ, USA) and HPLC-grade methanol (Burdick and Jackson, Muskegon, MI, USA) were used for the LC mobile phases. A 1 M triethylammonium acetate buffer solution, pH 7.0, was obtained from Fluka (Buchs, Switzerland) and used to prepare the mobile phase for EC detection. For MS detection, a 1 M buffer solution was prepared from ammonium acetate and acetic acid (Mallinkrodt, Paris, KY, USA) to be pH 5.4 and was diluted to prepare the mobile phase.

For dechlorination experiments, fresh solutions of sodium sulfite (AR-grade, Mallinkrodt) were prepared in nitrogen-purged water. An aliquot was added to the pharmaceutical chlorination mixture following 1 h of reaction time and vortex-mixed. The concentration of sulfite was 84 μM (1.5 times the initial hypochlorite dose) after dilution in the reaction mixture.

2.2. Wastewater samples

Wastewater samples were collected after biological digestion and clarification but prior to disinfection from the Seneca Wastewater Treatment plant, operated by the Washington Suburban Sanitary Commission in
Germantown, MD. The conditions used at this plant as well as information about the wastewater composition, sampling, and storage have been described previously (Bedner and MacCrehan, 2006). Individual solutions of fluoxetine and metoprolol were freshly prepared in the wastewater to be 10 μM and buffered to be 1 mM phosphate, pH 7. Chlorination experiments were performed in the same manner as for the pure water experiments.

2.3. Chromatography

Samples were analyzed using two LC systems, LC/UV/EC and LC/UV/MS, which are described in detail elsewhere (Bedner and MacCrehan, 2006). An extensive investigation of varying isocratic and gradient elution conditions for the separation of fluoxetine and metoprolol and their chlorination products revealed only one major product for each. Isocratic separation conditions were chosen that provided some retention of the parent pharmaceutical but did not have excessive retention of the product. For analysis of fluoxetine solutions on the LC/UV/EC system, the isocratic mobile phase consisted of 80% (volume fraction) methanol, 20% (volume fraction) water containing 0.01 M triethylammonium acetate buffer, pH 7. For analysis of metoprolol solutions on the LC/UV/EC system, the isocratic mobile phase consisted of 72% (volume fraction) methanol, 28% (volume fraction) water containing 0.01 M triethylammonium acetate buffer, pH 7. For LC/UV/MS analysis of both pharmaceuticals, the same volume fractions of methanol and water were used as in LC/UV/EC, but a buffer of 0.01 M ammonium acetate/acetic acid buffer, pH 5.4 was employed. The mobile phases were delivered at 0.4 ml/min. Injections of 50 μl were used.

UV detection of fluoxetine and metoprolol and their reaction products were performed at 230 nm and 274 nm, respectively. Electrochemical detection on the LC/UV/EC system was performed using post-column reaction with acidic iodide and reductive detection at a glassy carbon electrode with an applied potential of −0.1 V versus a Ag/AgCl reference electrode, which provided active chlorine detection. Without the use of the post-column reaction, chloramines are not favorably detected by reductive EC at low applied potentials (Jersey, 1991). More details on the EC method for detecting chloramines and the reagents used may be found elsewhere (Bedner et al., 2002). Mass spectrometric detection with the LC/UV/MS system (Agilent, Palo Alto, CA) was used with positive electrospray ionization (ESI+). ESI+ used N₂ drying gas flowing at 9.0 l/min, nebulizer pressure 240 kPa, fragmentor 75 V, and a capillary voltage of +3000 V. For analysis of fluoxetine products, a gas temperature of 225 °C and a scan range of 150 to 400 m/z were used, while a gas temperature of 350 °C and scan range of 240 to 500 m/z were employed for metoprolol products.

3. Results

3.1. Chlorination and dechlorination of fluoxetine and metoprolol in pure water

In the chlorination experiments, hypochlorite doses were selected to reflect the large excess of chlorine in a typical wastewater treatment process. Reactions were studied at pH 7 using buffered solutions and monitored for 1 h, a typical contact time used in wastewater treatment. In the dechlorination experiment, sulfite was added to a new sample that had been chlorinated for 1 h, and the sample (i.e., reaction) was monitored at 2 min and 30 min (fluoxetine) or 20 min (metoprolol).

The chlorination and dechlorination reactions of fluoxetine were initially evaluated using a liquid chromatographic separation with UV absorbance and EC detection using the LC/UV/EC system. To simplify the presentation, the UV data will be described first, which are presented as the upper chromatograms (labeled UV) in Fig. 1. The solvent-front events in these separations produced significant positive and negative deviations from the baseline and are not shown. Chromatogram A in Fig. 1 is a hypochlorite blank, which reveals no detectable interferences in the separation. Chromatogram B is of standard fluoxetine, which illustrates the purity and retention time (5.8 min) of fluoxetine under these separation conditions. Fig. 1C presents a chromatogram of the solution of fluoxetine that has been reacting with hypochlorite (from here, termed fluoxetine/hypochlorite) for 1 h. The lack of a peak at 5.8 min indicates that fluoxetine has reacted completely to form one major product of notably increased hydrophobicity eluting at 21.2 min. Complete disappearance of the parent fluoxetine peak was also noted for 2 min and 30 min chlorination times (data not shown), indicating the chlorination reaction is rapid under the conditions of this experiment. Chromatograms D and E present separations of the fluoxetine/hypochlorite solution that had been reacting with sulfite for 2 min and 30 min, respectively. After 2 min, the peak area of the product has decreased to about 70% of the peak area at 1 h chlorination time (shown in chromatogram 1C), indicating only a portion has been chemically reduced with this reaction time. Also, a peak has appeared at 5.8 min, which corresponds to the retention time of fluoxetine. After 30 min, the chlorination product peak has completely disappeared, and the peak at 5.8 min has continued to intensify. This provides evidence that the chlorination product is converted back to fluoxetine upon dechlorination, although the peak area only reaches approximately 70% of the area found prior to reaction with hypochlorite and sulfite. This is most likely attributable to undetected products that have formed during chlorination and are not reduced back to fluoxetine during dechlorination.

As previously mentioned, the separations that were obtained using UV detection were concurrently detected using tandem EC with active chlorine detection chemistry,
and the results are presented in the lower chromatograms of Fig. 1 (labeled EC). The hypochlorite blank (A) produces a large electrochemical detection peak at 5.3 min (displayed off-scale) and several smaller peaks. These “blank” peaks arise from the triethylammonium acetate mobile phase buffer, which may contain some di- and mono-ethylammonium impurities that have formed chloramines due to reaction with hypochlorite. The standard fluoxetine chromatogram (Fig. 1B, EC) reveals no peaks, which is also expected given that the parent fluoxetine does not contain active chlorine. However, the separation of the fluoxetine/hypochlorite mixture at 1 h (Fig. 1C, EC) reveals a more hydrophobic reaction product at 21.8 min. Given the 0.6 min time delay between the UV and EC detectors, this product is the same one observed in the UV analysis (see Fig. 1C, UV). Detection of this product with EC/post-column chemistry strongly indicates that it is an active chlorine compound. However, it is also possible for easily reduced compounds that do not contain active chlorine to be detected with EC under these conditions. To investigate this possibility, EC detection was performed without the post-column reaction chemistry, and no signal was observed for the chlorination product of fluoxetine (data not shown). The evidence therefore indicates that the product does contain active chlorine. Given the structure of fluoxetine, this active chlorine product is most likely an N-chloramine formed from chlorination of the amine functional group, N-chlorofluoxetine (III). The remaining two chromatograms (D and E) in the EC chromatograms in Fig. 1 show the results from the sulfite dechlorination experiment. At 2 min dechlorination time, the active chlorine product has a reduced peak area relative to the 1 h chlorination experiment. At 30 min, the product was completely reduced by sulfite. As noted in the UV chromatograms in Fig. 1, the chloramine product was likely reduced back to the parent pharmaceutical (amine).

![Fluoxetine Chromatogram](image)

Analogous chlorination and dechlorination experiments were performed with metoprolol, and the results obtained from the UV and EC analyses are presented in the upper and lower portions of Fig. 2, respectively. The chromatograms labeled A are from the hypochlorite blank. Fig. 2A, EC shows that the primary active chlorine compound formed from the hypochlorite/buffer reaction is retained longer (6.5 min) in this weaker solvent mobile phase than it was in the fluoxetine experiment shown in Fig. 1A, EC. This compound has some UV absorbance at 274 nm, as indicated by the small peak at 5.9 min in Fig. 2A. The chromatograms labeled B in Fig. 2 represent metoprolol blanks, and the retention time of metoprolol is 4.4 min under these conditions as determined by UV detection. The 1 h chlorination experiment shown in chromatogram C indicates that only one major product with greater hydrophobicity than the parent amine is formed with a retention time of 11.3 min (Fig. 2, UV), and the product contains active chlorine (Fig. 2, EC). As with fluoxetine,
the metoprolol/hypochlorite mixture was analyzed at 2 min and 30 min (data not shown). Complete disappearance of the parent metoprolol peak was noted for both reaction times, indicating the chlorination reaction is rapid on the timescale of this experiment. For reasons similar to fluoxetine, this product is most likely a metoprolol chloramine, N-chlorometoprolol (IV). After 2 min dechlorination time (Fig. 2D, UV), the peak area of the chloramine has decreased to about 10% of the peak area at 1 h chlorination time (shown in chromatogram 2C, UV), indicating that it has been partially chemically reduced with this reaction time. The chloramine has been completely reduced by 20 min (chromatogram 2E, UV). Also, the UV chromatograms in Fig. 2D and E clearly show that reduction by sulfite converts the chloramine product back to the parent metoprolol. After 20 min dechlorination time, the peak area of metoprolol is approximately 90% of its value prior to reaction with hypochlorite and sulfite. This indicates there are probably some minor, undetected products formed during chlorination that are not reduced back to metoprolol upon dechlorination.

MS detection with ESI+ was used to further confirm the identities of the chloramine products. A mass spectrum was obtained for the chlorination product of fluoxetine and is shown in Fig. 3A. There are prominent ions in the spectrum at m/z 344 and m/z 346 with relative intensities indicative of one chlorine atom (as 35Cl or 37Cl) in the molecule. Given that the nominal relative molecular mass of fluoxetine is 309, an [M + H]+ at m/z 344 corresponds to a mono-chlorinated fluoxetine molecule. Since the product contains active chlorine as evidenced from the EC detection, the product can be identified as N-chlorofluoxetine. However, the most prominent ion in the mass spectrum occurs at m/z 310, which corresponds to [M + H]+ for fluoxetine. This indicates that the chloramine of fluoxetine exhibits some instability in the ESI source and gets reduced back to the parent. The use of a lower gas temperature (225 °C) helped reduce this instability. It was also notable that there were three other reaction product peaks detected with the mass spectrometer (data not shown) that were not visible in the UV and EC chromatograms. These peaks probably are minor reaction products that have lost the chromophoric structure of fluoxetine, but they were unable to be identified. The mass spectrum obtained for the chlorination product of metoprolol is presented in Fig. 3B. The spectrum contains two major ions at m/z 302 and m/z 304, and their relative intensities indicate the compound has a chlorine atom. For reasons analogous to the fluoxetine chloramine, the product spectrum corresponds to N-chlorometoprolol. No additional reaction products were detected with the mass spectrometer for the metoprolol/hypochlorite reaction.

Fig. 2. Separations of chlorinated and dechlorinated metoprolol solutions (as well as appropriate blanks) in pure water determined with UV detection and EC detection utilizing post-column reaction chemistry. A: 57 μM OCl− in pure water (blank). B: 10 μM metoprolol, 1 mM phosphate buffer, pH 7, in pure water (blank). C: 10 μM metoprolol, 57 μM OCl−, 1 mM phosphate buffer, reaction time 1 h. D: same conditions as for chromatogram C, plus addition of 84 μM SO32− for 2 min. E: same as chromatogram D except for dechlorination time of 20 min. All concentrations represent initial reactions conditions. All reactions studied at room temperature 23 °C ± 1 °C.
the similarity of the results obtained, only examples of data for each compound in wastewater will be presented and discussed.

The chlorination of fluoxetine was studied in wastewater, and the results obtained using UV detection are presented in Fig. 4. Chromatogram A in this figure is a wastewater blank that had been chlorinated for 30 min. Chromatogram B presents a blank of fluoxetine that was prepared in wastewater at 10 M. The chromatographic separation of the fluoxetine/hypochlorite reaction mixture in wastewater after 1 h is shown in chromatogram C in Fig. 4. The formation of N-chlorofluoxetine is apparent, demonstrating that fluoxetine exhibits similar reactivity in this wastewater as it does in pure water.

The reactivity of metoprolol was also investigated in wastewater. Fig. 5 presents results obtained from the chlorination of metoprolol using EC/active chlorine detection. Chromatogram A in Fig. 5 is a sample of wastewater that had been chlorinated for 1 h. It is notable that the chlorine in wastewater blank looks significantly different than the chlorine in pure water blank shown in Fig. 2A, EC. This wastewater contains significant quantities of ammonia and organic-N compounds that consume the majority of the chlorine by forming chloramines. The chloramines

Fig. 3. Mass spectra of N-chlorofluoxetine (A) and N-chlorometoprolol (B) obtained with ESI+. Chloramines were formed by reaction of 80 μM pharmaceutical and 456 μM OCl⁻, 1 mM phosphate buffer, reaction time 1 h.

Fig. 4. Chlorination of fluoxetine in wastewater determined by LC with UV detection. A: 57 μM OCl⁻ in wastewater (blank). B: 10 μM fluoxetine, 1 mM phosphate buffer, pH 7, in wastewater (blank). C: 10 μM fluoxetine, 57 μM OCl⁻, 1 mM phosphate buffer, reaction time 1 h.

Fig. 5. Chlorination of metoprolol in wastewater determined by LC with EC detection. A: 57 μM OCl⁻ in wastewater (blank). B: 10 μM metoprolol, 1 mM phosphate buffer, pH 7, in wastewater (blank). C: 10 μM metoprolol, 57 μM OCl⁻, 1 mM phosphate buffer, reaction time 1 h.
formed in the wastewater inhibited formation of the mobile phase buffer chloramines that produced the peak at 6.5 min in the pure water experiment (Fig. 2A, EC), which is not evident in the chlorinated wastewater blank (Fig. 5A). Chromatogram B in Fig. 5 is a blank of metoprolol in wastewater, which has no notable features. Chromatogram C presents chlorination of metoprolol in wastewater for 1 h. The N-chlorometoprolol product is evident at 11.6 min, indicating favorable formation of this product in wastewater.

Dechlorination experiments for fluoxetine and metoprolol were also performed in wastewater. The results of the experiment were exactly the same as those obtained for the pure water experiments, where reduction of the chloramine products back to the parent amines was noted (data not shown).

4. Discussion

The basic drugs fluoxetine and metoprolol both readily react with hypochlorite in pure water and in wastewater using conditions simulating wastewater treatment. After 2 min of chlorination time, both pharmaceuticals were transformed completely to single major products. Through the use of multiple LC detection modes, these products were unequivocally identified as N-chloramines. Chloramines have significant but often controversial roles in wastewater disinfection. For example, the principal chloramine of ammonia, monochloramine, is generally considered to be a “useful” chloramine in that it has notable disinfection ability. However, organic chloramines are also important contributors to active chlorine but are often considered “nuisance” chloramines because their parent amines consumed large quantities of reactive chlorine (i.e., present a large “chlorine demand”), and the resulting chloramines have widely varying disinfection ability (Mattice and Tsai, 1983; Jameel and Helz, 1999). Although the basic drugs fluoxetine and metoprolol form chloramines that will contribute to the active chlorine in wastewater disinfection, their concentrations are very low in comparison to the other reactive organic amines present. For example, the amine metoprolol has been measured in wastewater effluents in both Germany (Ternes, 1998) and the United States (Huggett et al., 2003), although the concentrations found are typically in the ng/l to µg/l range. A number of studies have found the amine fluoxetine in the low ng/l range (Metcalfe et al., 2003; Kinney et al., 2006) or to be not detectable in wastewater effluents (Metcalfe et al., 2003; Jones-Lepp et al., 2004). However, the formation of the chloramines of both metoprolol and fluoxetine is highly favored even when other wastewater amines are present, and therefore it is also important to measure the chloramine products. While preconcentration procedures for reactive chloramines have not been developed, the LC/EC and LC/MS analytical methods detailed in this paper would be suitable for measuring the chloramines of these two compounds in environmental samples.

Another important property of chloramines is that they vary widely in their reactivity toward reduction by dechlorination agents such as sulfite. While monochloramine reacts rapidly with sulfite (Yin et al., 1987), many organic chloramines such as those produced from peptides and proteins are slowly reduced by sulfite (Jensen and Helz, 1998; Jameel and Helz, 1999). We investigated the reactivity of the chloramines of fluoxetine and metoprolol with sulfite in pure water and in wastewater, and the reductions were found to be slow on the timescale of wastewater dechlorination. After 2 min dechlorination time, approximately 70% and 10% of the N-chloramines of fluoxetine and metoprolol, respectively, remained in the pure water experiments. Since typical dechlorination times are on the order of seconds, this indicates that these chloramines may evade complete dechlorination and likely will be discharged into the environment. The sluggishness of these reduction reactions with sulfite is consistent with the behavior of other organic chloramines, which represent sources of refractory active chlorine that has been detected in wastewater effluent (Helz and Nweke, 1995). Also, for treatment plants that use chlorine disinfection but do not practice dechlorination, it is highly likely that metoprolol and fluoxetine will be released in the effluent as their chloramines.

The release of the chloramine forms of these pharmaceuticals into the environment is important for several reasons. First, chloramines have increased hydrophobicity relative to the parent amine. At neutral pH conditions, both the parent compounds fluoxetine and metoprolol will be protonated (pKₐ values of 10.1 and 9.2, respectively), which enhances their hydrophilicity. After they are chlorinated, the resulting chloramine will be neutral (unprotonated) as pKₐ values of chloramines are ≤2 (Antelo et al., 1997). Also, an increase in hydrophobicity arises from the replacement of a hydrogen atom with a chlorine atom in the parent amine. The increased hydrophobicity arising from these properties was observed in our experiments, where both chloramines eluted at significantly greater chromatographic retention times than the parent amines. An implication of increased hydrophobicity may be a greater tendency of the chloramines to sorb to surfaces such as sediments, soils, and biological membranes. For example, a recent study found that fluoxetine was highly retained in soil that had been irrigated with chlorinated wastewater with a very low feed concentration. It was concluded that the high retention in the soil correlated with the hydrophobicity of fluoxetine (log Kᵢw 4.05) and the soil organic carbon content (Kinney et al., 2006). It is unclear what effects the formation of N-chlorofluoxetine had on the measurements and conclusions of this study.

Another important characteristic of chloramines is that they can transfer their active chlorine to other reducants, reversing the chlorination reaction. For example, both N-chlorofluoxetine and N-chlorometoprolol were reduced back to the parent pharmaceutical amines by dechlorination with sulfite. Similar reactions can occur if a chloramine
is assimilated within a biological cell, where it can transfer its active chlorine to other reductants such as thiols (Peskin and Winterbourn, 2001), freeing the bioactive parent pharmaceutical. Chloramines formed from basic drugs will also encounter and react with chlorine demanding reductants present in effluent receiving waters, sediments, and soils. Even though the reversibility of the reaction is not fast enough to evade discharge, if given sufficient reaction time ($\leq 30$ min) N-chlorofluoxetine and N-chlorometoprolol were completely reduced by sulfite. On an environmental timescale, N-chloramines would be considered quite reactive toward reduction, and it seems unlikely that these chlorination products will have a very long persistence in the environment. Thus, the primary impact of the chloramines will be limited to the immediate receiving water and sediment near treatment operations, to the soil where chlorinated wastewater is used for irrigation, and in effluent-dominated bodies of water.

Disclaimer

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