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Human Pharmaceuticals in Wastewater Treatment Processes

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The presence of human pharmaceutical compounds in surface waters is an emerging issue in environmental science. In this study the occurrence and behavior of human pharmaceuticals in a variety of wastewater treatment processes is reviewed. Although some groups are not affected by sewage treatment processes others are amenable to degradation, albeit incomplete. While water purification techniques such as granular activated carbon could potentially remove these pollutants from wastewater streams, the high cost involved suggests that more attention should be given to the potential for the optimization of current treatment processes, and reduction at source in order to reduce environmental contamination.

KEY WORDS: fate, pharmaceuticals, pollution, sewage treatment plants, wastewater

I. INTRODUCTION

The term "pharmaceutical" covers a wide-ranging class of compounds with substantial variability in structures, function, behavior, and activity.[27] Developed to elicit a biological effect, they are used in both humans and animals to cure disease, fight infection, and/or reduce symptoms. Many drugs are not fully metabolized in the body and so may be excreted to the sewer system. Numerous pharmaceutical compounds have been shown to pass through sewage treatment plants (STPs) and contaminate the aquatic environment.[9,15,19,20,33,38,56,64,67,72,90,94,115,117,120,126,131]

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The use of other organic pollutants, such as pesticides, has fallen in recent years as new laws have been introduced to minimize their use.[23] However, even if they should prove problematic, pharmaceuticals are unlikely to be restricted in this way, due to their beneficial human (and animal) health effects and economic importance. Indeed, their use is expected to grow with the increasing average age of the population and the publishing of the human genome.[25] They and their metabolites are therefore likely to be found in the environment adjacent to human activity.[107]

The first reports of human drugs in the environment appeared in the late 1970s,[36,55] although it is not unreasonable to suppose that aquatic pollution from medicinal compounds dates back much further.[63] The growing importance worldwide of reducing potential impacts on water supplies has ensured that this issue has been steadily gaining attention in recent years both within the academic community and among the general public, although it is only with the comparatively recent advent of more reliable and sensitive analytical techniques that detailed research in this area has become possible.

In this article the term "drugs" is taken to exclude both natural and synthetic hormones. While these compounds are an important subgroup of pharmaceuticals, there is already an abundance of work available in the literature on this topic[4,11,14,61,80–83,95,121,124,130]

From published occurrence data, it seems probable that most if not all urban wastewater is contaminated with medicinal compounds, differing only in the type and abundance of the substances present.[24] The existence of drugs in surface waters[9,15,19,20,33,38,56,67,72,90,94,115,117,120,126,131] groundwater,[1,21,32,58,89,99,103,108] and even marine systems[18,115] has also been confirmed. It is probable that the presence of these compounds stems primarily from the consumption and use of such products rather than from manufacturing.[35]

Medicinal compounds are generally excreted after being partially or completely converted to water-soluble metabolites,[29,42,92,98] but a significant amount of the original substance may also be excreted unchanged.[57] This has previously been regarded as inconsequential because of the dilution received in the sewerage system. However, recent studies on pharmaceutical residues (primarily in Germany) have demonstrated that elimination of high to medium polar pharmaceuticals in municipal STPs is often incomplete, ranging between 60 and 90%.[116,117,120] One of the most comprehensive studies of this type was performed by Kolpin et al.[72] who chronicled the detection of over 95 organic chemicals in U.S. streams and rivers. Measured concentrations from this study were generally low (nanograms per liter) and rarely exceeded drinking-water guidelines, drinking-water health advisories, or aquatic-life criteria, although it is worth noting that no such guidelines have been established for the majority of pharmaceutical compounds detected. The detection of multiple organic pollutants was relatively common in this study, with a median of 7 and as many as 38 compounds being found

in a given water sample. These results demonstrate the importance of obtaining data on metabolites as well as parent compounds in order to fully understand the fate and transport of individual pollutants in the hydrological cycle.

Compounds having relatively short half-lives would likely survive in only the freshest of sewage sludge samples,[7] but it is important to understand the fate and behavior of these compounds during wastewater treatment in order to assess the likely concentration of contaminants in sludges and effluents, and hence their potential contribution to the pollution of the environment. Some drugs may be removed from wastewater by adsorption onto solids, but can then enter the aquatic environment, in particular groundwaters, via sludge application to land, landfilling, or soil erosion. There have been many reviews on the topic of environmental pollution by drug compounds,[6,25,44,50,64,96] all of which note that no quantitative data were found on concentrations of pharmaceuticals in sewage sludge or soil amended with sewage sludge, although some modeling has been attempted.[65,70] This is surprising, considering that this is a potential route for lipophilic substances to the terrestrial environment. However, it is most probably a consequence the extreme difficulty in extraction and analysis of pollutants from sludge samples on a quantitative basis.[70,101,106]

II. DEGRADATION WITHIN STPs

A. Biodegradation

There is an obvious potential for biological degradation (aerobic/anaerobic by micro-organisms) of drug substances leading to a reduction of the parent compounds and/or their metabolites during wastewater treatment.[128] Some biodegradation may also occur during in-pipe transport to the STP, but most will probably occur in the secondary stage of treatment when the compound is exposed to large concentrations of micro-organisms. Biodegradation tests can be performed following test protocols such as the closed bottle test (OECD 301D)[78] or the Zahn–Wellens test (OECD 302B).[77] In general, these tests are carried out with several hundred milligrams of a substance as the carbon source. Therefore, they give answers for only fairly extreme conditions, which, despite their intention, simulate only the maximum potential and not the most probable environmental outcome. Therefore, conclusions on the degradability of drugs in STPs from these tests are of limited value and further research is necessary.[76]

Al-Ahmad et al.[2] assessed the biodegradability of the clinically important antibiotics cefotiam, ciprofloxacin, meropenem, penicillin G, and sulfamethoxazole using the closed bottle test (CBT). None of the test compounds met the criteria for ready biodegradability. Of all the compounds studied, only penicillin G was found to be biodegradable to some degree,

with approximately 27% being removed after 28 days. Even when the test was prolonged to 40 days, the removal rate was only increased to 35% indicating the compound was relatively stable.

Kümmerer and Al-Ahmad[77] used the CBT and the modified Zahn–Wellens test (ZWT) to examine the biodegradability of the widely used antitumor agents 5-fluorouracil, cytarabine, and gemcitabine. 5-Fluorouracil was not biodegradable in either of these tests. Gemcitabine was biodegraded by 42% in the CBT, but prolonging the test period to 40 days only improved this to 45%. Cytarabine was also partially biodegraded in the CBT (50%). In the ZWT, the biodegradation of gemcitabine was also 50% but only after an adaptation period of 20 days, which is not normally included in such tests. Prolonging the test to 40 days improved the degree of biodegradation to 80%, and in the ZWT the biodegradability was over 95%.

Henschel et al.[54] investigated the biodegradability of paracetamol and methotrexate and the two drug metabolites salicylic acid and clofibric acid. Their results were in agreement with other studies and demonstrated that salicylic acid and (to a lesser extent) paracetamol were biodegradable, whereas clofibric acid and methotrexate were not.

Kümmerer[78] studied the biodegradability of three clinically important antibiotics (ciprofloxacin, ofloxacin, and metronidazole) and found none of the compounds were biodegraded. As a consequence the genotoxicity of these compounds (as measured by the SOS chromotest) remained unaffected after treatment. A more comprehensive review of antibiotics in the environment is available in Hirsch et al.[57] This article describes the analysis of various water samples for 18 antibiotic substances, from several groups, including macrolid antibiotics, sulfonamides, penicillins, and tetracyclines. Both STP effluents and surface-water samples were frequently contaminated with sulfamethoxazole and roxithromycin (a degradation product of erythromycin) at concentrations up to 6 $\mu g\,L^{-1}$. The highest concentrations detected for tetracyclines and penicillins were 50 and 20 $ng\,L^{-1}$, respectively. Except for two sites, no contamination by antibiotics was detected from a large number of groundwater samples that were taken from agricultural areas in Germany. This suggests that contamination of groundwater by antibiotics from veterinary applications is relatively minor. Other drugs that have been investigated for their biodegradability include ifosfamide and cyclophosphamide.[79,112] Both of these compounds exhibited poor biodegradability in the CBT and the ZWT as well as in laboratory-scale activated sludge plants.

Degradation may also occur during bank filtration, if it is used. Heberer et al.[52] found clofibric acid, phenazone, propyphenazone, diclofenac, ibuprofen, and fenofibrate, and two metabolites, *N*-methylphenacetin (probably originating from phenacetin) and also a derivative of clofibric acid at concentrations up to the micrograms per liter level in groundwater samples taken from beneath a drinking-water treatment plant. These contaminants were

found to leach from the neighboring sewage contaminated surface water by bank filtration through the subsoil.[53]

Molecules with long, highly branched side chains are generally less amenable to biodegradation than unbranched compounds with shorter side chains.[105] Unsaturated aliphatic compounds are generally more accessible to biodegradation than saturated analogues or aromatic compounds with complicated aromatic ring structures and sulfate or halogen groups.[101] Examples of the latter are the x-ray contrast media. Since these compounds are exclusively utilized in human medicine, contaminated STP effluents are presumably the sole sources for these compounds in the aquatic environment. The occurrence of four iodinated x-ray contrast media (diatrizoate, iopamidol, iopromide, and iomeprol) in eight German STPs was examined by Ternes et al.[120] These compounds were found to be ubiquitously distributed in the raw sewage and were not significantly degraded or absorbed during the sewage treatment processes and so remained in the aqueous phase. The concentrations of diatrizaote, iopromide, and iomeprol frequently exceeded 1 $\mu g\,L^{-1}$ in the raw sewages, and these were found at comparable concentrations in the final effluents, with the maximum concentration measured being 15 $\mu g\,L^{-1}$ for iopamidol.

A similar study by Steger-Hartmann et al.[111] demonstrated that while these compounds are not readily biodegradable, iopromide was amenable to photodegradation. The resulting degradation product (5-amino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-*N*-methyliso-phthalamide) also exhibited a faster rate of photolysis than the parent compound and was further degraded in a test system simulating surface-water conditions. However, the predicted environmental concentration (PEC) in surface water was still high at 2 $\mu g\,L^{-1}$.

Some degradation of iopamidol in activated sludge has also been observed with 85% being transformed into two metabolites.[68] Degradation of the same compound in river water was even more significant, with a half-life of 3.1 days. However, for other, similar compounds such as diatrizoate the half-life was longer, suggesting there is potential for some compounds to reach rivers and lakes. Although of low toxicity, x-ray contrast media may contribute significantly to the absorbable organic halogen compound (AOX) load in receiving waters. This is of concern because of the high persistence, mobility, and potential of these substances to biotransform to toxic breakdown products.

It is also possible that the biota of a STP may gradually become acclimatized to certain chemicals and therefore may degrade them more effectively given time.[132] For instance Zwiener et al.[133] investigated the biological degradation of pharmaceutical residues (clofibric acid, ibuprofen, diclofenac). In this study both a pilot sewage plant and biofilm reactors operating under oxic and anoxic conditions were run as model systems for municipal sewage treatment, with synthetic sewage and pharmaceuticals in

concentrations of 10 $\mu g\,L^{-1}$. Clofibric acid displayed persistence in all cases. The pilot sewage plant and the anoxic biofilm reactor showed comparable results for diclofenac and ibuprofen, which both were partially degraded. A high degree of degradation was found for ibuprofen in the oxic biofilm reactor, which was attributed to adaptation of the biofilm to the residue. This effect has also been show to occur for other compounds, for example, nitrilotriacetic acid, where a period of acclimatization has been shown to be required before biodegradation can begin.[102] In addition, the phenomenon of co-metabolism—the oxidation and degradation of nongrowth substrates by micro-organisms—is well documented.[45,46]

B. Deconjugation

Pharmaceutical compounds are often metabolized in the liver, and as a consequence gluconoride and sulfate conjugates of the parent drugs are excreted.[98] Conjugates of other organic compounds such as steroid hormones have been shown to be readily deconjugated in domestic wastewater and within STPs due to the large amounts of β-glucuridase enzyme present (produced by the fecal bacterium *Escherichia coli*).[10] It seems probable that gluconoride and sulfate conjugates of drug compounds will be degraded by the same process. The effect will be to increase the excreted contribution of the active drugs to sewage and effluents.[117]

C. Partitioning

Partitioning between the aqueous and organic biomass phases is a key component in determining the ultimate concentrations of organic pollutants.[49] Compounds with high log K_{ow} values are known to sorb to sludge,[84] while substances with lower values are more likely to stay in the aquatic phase, depending on the individual compound,[40] and substances sorbing to solids may also be remobilized if they are not strongly bound. It is also well known that bacterial, algal, and fungal cells are capable of adsorbing and accumulation organic pollutants.[10] The activated sludge biomass is able to adsorb organic pollutants such as lindane, and adsorption of these compounds generally fits the Freundlich isotherm. There is a good correlation between compound adsorption and the octanol/water partition coefficient. However, since most drugs are soluble with low log K_{ow} and K_{oc} values, they exist primarily in the aqueous phase and transfer to sewage sludge is probably of only minor concern for the majority of compounds.

There are few studies in the literature detailing potential sorption interactions of drug compounds. Hua et al.[60] studied the removal of chemical oxygen demand (COD), micro-organisms, and selected pharmaceutical compounds by trickling wastewater through a sandy soil from the Rhine valley in glass columns. The sewage contained low concentrations of at least 10 different pharmaceuticals and x-ray media. Some of the compounds

were removed by adsorption onto sand and/or biodegradation. The rate of removal varied from complete (e.g., ibuprofen and naproxen), to almost none, for several x-ray contrast media. Some of the compounds were removed as effectively by this method as by conventional sewage treatment.

Jones et al.[65] estimated physicochemical values for the top 25 pharmaceuticals in England in 2000 using a computer model. Of the top 25 compounds, 16 had low predicted sorption potential and were thought unlikely to bind to sludge solids. Five compounds had medium sorption potential and two (quinine sulfate and mefenamic acid) were predicted to have a high capacity to bind to solids (no data were available for the remaining two compounds). Although this study indicated some removal to solids for mefenamic acid, it did not demonstrate that all would be removed and in fact this compound has been found to be present in sewage effluent. The concentrations of mefenamic acid in three sewage effluents as well as upstream and downstream of the effluent discharge point have been reported by Hilton and Thomas.[56] The report does not, however, quote influent concentrations, so it is impossible to say how much was lost during treatment. For instance, if the concentration in the influent was double the concentration in the effluent, this would indicate a potentially high binding capacity (or biodegradation rate). A second paper by Soulet et al.[110] indicates a high degree of variation in the removal of mefenamic acid depending on the STP studied. Some exhibited a high removal, while others showed almost none indicating the importance of design and operational factors and/or climatic conditions. This means a definitive conclusion cannot be reached with regard to the removal rates of this drug within STPs, other than that it is potentially highly dependent on plant design, wastewater characteristics, and, most importantly, the operational regime.

Bester[8] studied the fate of the antimicrobial triclosan (2,4,4′-trichloro-2′-hydroxyphenyl ether) in a German sewage treatment plant that processed 200,000 m^3 wastewater per day. The concentrations in the influent ($\sim$1000 ng L^{-1}) were compared to those in the effluent and the sludge, and a mass balance of the works was prepared. Thirty percent of the triclosan was found to sorb to the sludge with weak bonds, but only about 5% of the influent concentration was found in the effluent. Thus, most of the incoming material was not recovered as the parent compound, and the authors suggest that it is likely that it is transformed to other metabolites or unrecovered bound residues. This compares well with a study by Singer et al.,[109] who, during a field study, attributed the fate of triclosan in a wastewater treatment plant to be 79% biological degradation, 15% sorption to sludge, with 6% being discharged to the receiving surface water. Despite the high overall removal rate, the concentration in the wastewater effluents were in the range of 42–213 ng L^{-1}, leading to concentrations of 11–98 ng L^{-1} in the receiving rivers.

A recent review of veterinary drugs by Tolls[127] suggests that mechanisms other than hydrophobic partitioning play a significant role in sorption of animal (and potentially human) medications. A number of hydrophobicity-independent mechanisms such as cation exchange, cation bridging at clay surfaces, surface complexation, and hydrogen bonding also appear to be involved. These processes are not accounted for by organic carbon normalization, suggesting that this data treatment is conceptually inappropriate and fails to describe the sorption behavior. In addition, some drug compounds may be anions at the pH values in STPs and the environment. This will lower the effective K_{ow} and decrease their sorption potential.

D. Removal During Sludge Treatment

Drugs may also be degraded during sewage treatment processes. Many pharmaceuticals are not thermally stable[118] and so might be expected to break down during processes such as composting due to heat (as well as chemical and biodegradation). A study by Guerin[43] investigated soil composting as an alternative to incineration for the treatment of a silty clay soil that had become contaminated with residues of Probenecid (an antigout drug) and Methaqualone (a barbiturate substitute no longer available due to harmful side effects). In pilot scale trials, Probenecid was reduced from 5100 mg kg^{-1} to <10 mg kg^{-1} within 20 weeks during mesophilic treatments. The study also confirmed that thermophilic composting was effective under field conditions. In the full-scale treatment, 180 tons of soil were composted. Initial concentrations of the major contaminants in the full-scale compost treatment facility for Probenecid and Methaqualone were 1160 mg kg^{-1} and 210 mg kg^{-1}, respectively. Probenecid concentration reached the target level of 100 mg kg^{-1} in 6 weeks, and removal of Methaqualone to <100 mg kg^{-1} was achieved after 14 weeks. The study concluded that composting was effective in reducing soil concentrations of Probenecid and Methaqualone residues to acceptable values and hence is a technology that has potential application in the remediation of pharmaceutical contaminants in sludge/soil, although further testing using other drug compounds and soils would be necessary.

E. Photodegradation

Several pharmaceutical compounds have been shown to degrade due to the action of sunlight.[12,97] The most extensively studied of these compounds is the analgesic/anti-inflammatory drug diclofenac, which has been shown to degrade in the aquatic environment due to ultraviolet (UV) light. Other compounds such as the topical antimycotic drugs naftifine, sulbentine, cloxiquin, tolnaftate, and chlorphenesin have also been shown to be light sensitive,[125] and an overall elimination rate of 0.03 day^{-1} due to photochemical degradation was observed for triclosan in the epilimnion of Lake Greifensee by Singer et al.[109]

Andreozzi et al.[5] carried out a monitoring survey of STP effluents in Italy, France, Greece, and Sweden and found more than 20 individual pharmaceuticals. The photodegradation of six compounds (carbamazepine, diclofenac, clofibric acid, ofloxacin, sulfamethoxazole, and propranolol) was tested. Carbamazepine and clofibric acid were found to have the longest half-lives (of the order of 100 days at the most northerly areas sampled), whereas sulfamethoxazole, diclofenac, ofloxacin, and propranolol were found to undergo faster degradation with half-lives of 2.4, 5.0, 10.6, and 16.8 days, respectively. For almost all the studied compounds, except propranolol, the presence of nitrate ions in aqueous solutions resulted in a reduction of the measured half life. This effect may be ascribed to the formation of HO radicals due to photolysis of nitrate. The authors point out that besides pharmaceutical residues, other species targeted by OH radicals, such as naturally occurring organic constituents, are present in rivers and lakes. For this reason, the effect caused by nitrate on the degradation rates of the pharmaceuticals found in this study should be interpreted only as a tendency if no other organic molecules but the substrate are present in the test solution.

A more complex situation arose when humic acids were added to the solutions containing the pharmaceuticals. Humic acids are known to exert two opposite effects on the rate of photodegradation of organic molecules in water. Due to their capability to absorb UV radiation in a broad range of wavelengths, they can reduce the available energy for the organic molecules present in the solution, thus acting as an inner filter (thus decreasing photodegradation). At the same time, the molecules of humic acids submitted to UV irradiation are promoted to a transient, excited state, in which they may react with oxygen in the solution, forming reactive species as singlet oxygen, or react directly with other organic species, thus promoting their phototransformation. The overall effect of humic acids on the phototransformation rate of an organic substance will therefore depend on the balance between these two opposite contributions. In the study, humic acids were found to act as inner filters toward carbamazepine and diclofenac, but as photosensitizers toward sulfamethoxazole, clofibric acid, oflaxocin, and propranolol.

Buser et al.[19] established that up to 90% of diclofenac entering a Swiss lake was degraded with a half-life of less than 1 h^{-1}. Incubation of lake water, fortified with diclofenac, exhibited no reduction in the dark, suggesting minimal chemical and biological degradation. However, when the fortified water was exposed to sunlight, rapid degradation was observed that indicated that this was the result of photodegradation. The use of sewage lagoons may therefore increase the removal of light sensitive compounds as demonstrated by Kreuzinger et al.,[74] who showed that removal rates of diclofenac were only 14% with just activated sludge treatment, while after further polishing in a sewage lagoon concentrations decreased to below the limits of detection. Adsorption and biodegradation were ruled out as the

cause of the decrease, as there was no developed/active sludge flock in the lagoon, leaving photodegradation as the most likely cause.

Latch et al.[85] studied the photochemical fates of the histamine H_2-receptor antagonists cimetidine and ranitidine. Each displayed high rates of reaction with both single oxygen and hydroxyl radicals, with two transient oxidants being formed in sunlit natural waters. Ranitidine was degraded in direct photolysis experiments with a half-life of 35 min under noon summertime sunlight at 45° latitude, while cimetidine was shown to be resistant to direct photolysis. The results of these experiments, combined with the expected steady state near-surface concentrations of single oxygen and hydroxyl radicals, indicate that photo-oxidation mediated by single oxygen radicals is the likely degradation pathway for cimetidine in most natural waters, while photodegradation by direct photolysis is expected to be the major pathway for ranitidine. However, the extent of photo-induced degradation of pharmaceuticals can vary significantly for different pharmaceuticals, and it strongly depends on the aqueous constituents (such as humic and fulvic acids) present in solution.[28] In addition, light levels within STPs are likely to be much lower than in the environment (effectively zero), due to the higher solids content. Indeed, Koutsouba et al.[73] found diclofenac to be widespread in Greek domestic sewage effluent, with concentrations in effluent ranging from 10 to 365 ng L^{-1}. Given the inherent photosensitivity of this compound, its presence in sewage effluent would seem to indicate that photodegradation is highly unlikely to take place within STPs where light penetration is minimal at best.

III. FATE OF COMPOUNDS WITHIN SEWAGE WORKS

Because of the complexity of most environmental matrices (i.e., wastewater and sludge samples), analytical techniques with very high resolving power are needed to provide the required sensitivity and detection limits.[34] Metcalfe et al.[93] analyzed for residues of selected prescription and nonprescription drugs in samples of influent and effluent from 18 STPs across 14 municipalities in Canada. Several neutral and acidic drugs were detected in effluents, including analgesic/anti-inflammatory agents, lipid regulators, and antiepileptics. Drugs such as ibuprofen and naproxen, as well as salicylic acid (the metabolite of aspirin), were often detected in final effluents at micrograms per liter concentrations. The rates of elimination of ibuprofen and naproxen appeared to be elevated in STPs with hydraulic retention times of over 12 h, indicating that this could be a factor in increasing drug removal rates, although it is more likely factors that affect HRT (such as SRT) were responsible for the observed effect. The lipid regulator clofibric acid and the analgesic drug diclofenac were not detected in any final effluent samples. This is not consistent with data from European

studies which often report their presence. This may reflect different prescribing practices in the two areas. For instance, the precursors to clofibric acid (e.g., clofibrate) are not widely prescribed for use as lipid regulators in Canada.[93]

Soulet et al.[110] studied five acidic drugs (clofibric acid, ibuprofen, ketoprofen, mefenamic acid, and diclofenac) at three STPs in order to determine their behavior during treatment. Each plant consisted of a physical and a biological treatment stage, with one of the plants also having additional treatment before the biological treatment stage. In addition, two of the three received wastewater from the pharmaceutical industry. The results demonstrated that four of the pharmaceuticals (clofibric acid, ketoprofen, mefenamic acid, and diclofenac) are not well removed by treatment in Swiss STPs. Indeed, although recovery rates in the influent were low (35 ± 10%, versus 86 ± 8% for the effluent), possibly due to interferences during detection, the maximum concentration for mefenamic acid in the effluent determined was 1.0 $\mu g/L^{-1}$. This level of contamination indicates it would also be present in surface waters. However, it should be noted that the removal efficiencies for this compound (as well as the others in the study) varied depending on the STP in question. In one instance there was more than twice the amount in the influent as there was in the effluent, while in other cases more of the compound was found in the effluent than in the influent, perhaps because of remobilization of previously absorbed material from biological solids retained in the system. This indicates that removal of these compounds is not uniform and may be dependent on a number of factors.

Kanda et al.[69] utilized a number of analytical procedures to investigate the presence of a number of pharmaceuticals in six UK sewage treatment works. The work established that many pharmaceuticals occurred in influent at nanograms per liter levels and were removed by wastewater treatment processes. Ibuprofen was detected in all influent sample as well as in all but one effluent sample. Removal of ibuprofen by the different STPs was generally between 80 and 100%, with the exception of one STP where removal was poor (14.4 to 44%). Similar results were also reported by Jones et al.,[62] who found five drug compounds (ibuprofen, paracetamol, salbutamol, propranolol HCl, and mefenamic acid) present at nanograms per liter levels in a large English STP.

Samples from eight STPs in southern Ontario, Canada were analyzed by Lee et al.[86] for 11 acidic drug compounds: salicylic acid, clofibric acid, ibuprofen, acetaminophen, gemfibrozil, fenoprofen, naproxen, ketoprofen, diclofenac, fenofibrate, and indomethacin, as well as the antibacterial agent triclosan. While clofibric acid, acetaminophen, fenoprofen, and fenofibrate were not detected, the other eight compounds were found in nearly all the influent and effluent samples, from low micrograms to low nanograms per liter levels. Eight STPs removed from 0 to 98% of these drugs from the influent.

Measured concentrations of nine pharmaceutical and personal care products (PPCPs) in samples from two surface-water bodies, a sewage treatment plant effluent, and various stages of a drinking-water treatment plant in Louisiana, and from one surface-water body, a drinking-water treatment plant and a pilot plant in Ontario, Canada, were reported by Boyd et al.[15] Naproxen was detected in Louisiana sewage treatment plant effluent at 81–106 ng L^{-1} and in Louisiana and Ontario surface waters at 22–107 ng L^{-1}. Triclosan was detected in Louisiana sewage treatment plant effluent at 10–21 ng L^{-1}. Of the three surface waters sampled, clofibric acid was detected in Detroit River water at 103 ng L^{-1}, but not in Mississippi River or Lake Pontchartrain waters. None of the other target analytes were detected above their method detection limits.

Based on results at various stages of treatment, conventional drinking-water treatment processes (coagulation, flocculation and sedimentation) plus continuous addition of powdered activated carbon at a dosage of 2 mg L^{-1} did not remove naproxen from Mississippi River water. However, chlorination, ozonation, and dual-media filtration processes reduced the concentration of naproxen below the limit of detection in Mississippi River and Detroit River waters and reduced clofibric acid in Detroit River waters. Results of this study demonstrate that existing water treatment technologies can effectively remove certain pharmaceuticals. In addition, the study demonstrates the importance of obtaining data on removal mechanisms and by-products associated with pharmaceuticals and other endocrine-disrupting chemicals in drinking-water and sewage treatment processes.

The most pressing concern with regard to antibiotics in the environment is, at present, the continued spread of resistance of bacterial pathogens to the many compounds presently used to control infections,[104] a phenomenon that may be assisted by repeated doses at the low concentrations found in the environment.[66] Antibiotics also have the potential to affect the microbial community in sewage treatment systems, and the inhibition of wastewater bacteria has the potential to seriously affect organic matter degradation as well as nitrification and denitrification. Although one study has shown that bacteria isolated from treated sewage and digested sludge were generally not significantly more resistant to antibiotics than isolates from raw sewage, others have shown the opposite.[22,41,88,100,104] Therefore, the occurrence of antibiotics in sewage effluent and receiving waters, as well as their potential effects on exposed microbial populations, is of interest and concern.

Certain antibiotics may also have a toxic effect. For instance, Hartmann et al.[47] identified fluoroquinolone antibiotics as the main source of genotoxicity in hospital wastewater using a bacterial short-term genotoxicity assay, based on a umuC:lacZ fusion gene (umuC assay). The ratio of theoretical mean wastewater concentrations (derived from consumption data) and

lowest-observable-effect concentrations of selected pharmaceuticals were used to calculate umuC induction probabilities. The fluoroquinolone antibiotics ciproxin and noroxin exhibited the highest induction probabilities and exceeded all other investigated drugs by at least one order of magnitude in significance. Antineoplastic drugs, originally thought to be the main effectors, were found to be of marginal significance using this technique. These findings were further supported by investigation of urine samples from hospital patients with the umuC assay. The determination of ciprofloxacin in hospital wastewater by reverse-phase high-performance liquid chromatography and fluorescence detection revealed concentrations from 3 to 87 $\mu g\,L^{-1}$. Ciprofloxacin concentrations and umuC induction factors in 16 hospital wastewater samples exhibited a log-linear correlation. The authors suggest that the previously measured umuC genotoxicity in the wastewater of the hospital under investigation is caused mainly by fluoroquinolone antibiotics, especially by ciprofloxacin. However, follow-up work by Hartmann et al. suggested this could also be due to the presence of additional mutagens that are yet to be identified.[48]

Ternes et al.[123] assessed the removal of pharmaceuticals, iodinated x-ray contrast media, and musk fragrances from municipal wastewater using a pilot ozonation and UV-disinfection plant recieving effluent from a German STP. In the original STP effluent, 5 antibiotics (0.34–0.63 $\mu g\ L^{-1}$), 5 beta-blockers (0.18–1.7 $\mu g\ L^{-1}$), 4 antiphlogistics (0.10–1.3 $\mu g\ L^{-1}$), 2 lipid regulator metabolites (0.12–0.13 $\mu g\ L^{-1}$), the antiepileptic drug carbamazepine (2.1 $\mu g\ L^{-1}$), 4 ICMs (1.1–5.2 $\mu g\ L^{-1}$), the natural estrogen estrone (0.015 $\mu g\ L^{-1}$), and 2 musk fragrances (0.1–0.73$\mu g\ L^{-1}$) were detected. X-ray contrast media were present with the highest concentrations (diatrizoate, 5.7 $\mu g\ L^{-1}$; iopromide, 5.2 $\mu g\ L^{-1}$).

By applying 10–15 mg L^{-1} ozone (contact time 18 min), all the pharmaceuticals investigated as well as musk fragrances (HHCB, AHTN) and estrone were no longer detected. However, ICMs (diatrizoate, iopamidol, iopromide, and iomeprol) were still detected in appreciable concentrations. Even with a 15 mg L^{-1} ozone dose, the ionic diatrizoate exhibited a maximum removal efficiency of only 14%, while the nonionic media were removed by more than 80%. Advanced oxidation processes (O_3/UV-low-pressure mercury arc, O_3/H_2O_2), which were nonoptimized for wastewater treatment, did not lead to a significantly higher removal efficiency for the x-ray media than ozone alone.

This work demonstrated that it may be possible to remove pharmaceuticals and other organic contaminants from sewage using available technologies. It is not clear, however, how much upgrading STPs in this way would cost. Capital and operational costs are high for ozonation plants and other tertiary treatment options,[87] and if water companies do not see a benefit to such investment they are unlikely to be inclined to treat wastewater in this way.

IV. DISCUSSION

Drugs in the environment are an emerging environmental issue.[56] Although some contamination may come from landfill leachates or via the incorrect disposal of waste drugs, these are likely to be relatively small sources of pollution.[13] Most human pharmaceuticals are released after excretion from the patient or, to a lesser extent, in aqueous waste produced by manufacturing. Sewage treatment plants may therefore be reasonably expected to be the main point of collection and subsequent release into the environment. However, conventional sewage treatment facilities were never designed to deal with pharmaceutical compounds, and due to their highly variable physical and chemical properties, the efficiencies by which they are removed may vary substantially. It is also not known if sewage treatment facilities could be cost-effectively modified to reduce pharmaceutical emissions.

Another factor to consider is the sheer number of compounds involved. A pharmaceutical may be described as any chemical used for the diagnosis, treatment (cure/mitigation), alteration, or prevention of disease, health condition, or structure/function of the body.[20] There are literally thousands of compounds that maybe taken for medicinal purposes throughout the world, with more than 3000 individual pharmaceutical substances currently licensed for use in the United Kingdom alone.[6] Thus the terms "pharmaceutical," "pharmaceutically active compounds" (PhAC), and "pharmaceuticals and personal care products" (PPCP) are somewhat general, catch-all terms for an extremely broad group of compounds with wide-ranging physical and chemical properties. Clearly it is not feasible to monitor sewage for all the compounds that might potentially be found. Therefore, some form of selection process is needed to narrow down interest to those compounds likely to do most harm, through either their sheer volume of use (e.g., painkillers such as ibuprofen) or their potential for toxicity (e.g., anticancer drugs). This could conceivably be achieved via computer modeling.

Although there is a paucity of data on the behavior of pharmaceuticals, their fate is likely to be dependent on their physicochemical properties (e.g., chemical structure, aqueous solubility, octanol/water partition coefficient, and Henry's law constant). Their behavior during wastewater treatment will therefore comply with the pathways outlined by Meakins et al.,[91] and there have been attempts to model fate and behavior in the literature.[65,70,71]

In general, the more hydrophobic a chemical is, the greater the amount that will accumulate in the solid phase (e.g., sludge), and the more hydrophilic, the greater the amount that will stay in the aqueous phase. The following guide to the significance of sorption can be used.[101]:

- Log K_{ow} <2.5 Low sorption potential
- Log K_{ow} >2.5 but <4.0 Medium sorption potential
- Log K_{ow} >4.0 High sorption potential

For instance, some polybrominated diphenyl ethers with high log K_{ow} values[26] of around 9 are known to partition to sludge,[84] whereas steroid estrogens with lower log K_{ow} values of 2–4 may sorb to solids or stay in the aquatic phase depending on the individual compound.[40] Some workers, however, have expressed doubts over the usefulness of this method with regard to pharmaceuticals.[127]

The K_{oc} is also an important parameter which can be used when considering potential losses of a chemical due to sorption. As with K_{ow} values, the higher the log K_{oc}, the higher is the likelihood that a compound will sorb to matter containing organic carbon such as suspended solids as well as the nonpolar fats and lipids, mineral oils, greases, and surfactants generally present in domestic sewage.[75] Those with lower values will tend to remain in the liquid phase and may be more easily leached from sludge or sediments.[3] However, it is worth noting that predicted concentrations of drug compounds in sludge based on K_{ow}, sludge-water partition coefficients (K_d), or acid–base constants (pKa) and measured in effluent vary extensively.[65,114] This may be because the values were calculated using equations originally designed for lipophilic compounds containing no functional groups.[119]

The extent to which individual compounds are accumulated or degraded will be influenced both by the properties of the compound in question and of the unit treatment process employed at the STP itself; individual compounds may be lost at any one of several treatment stages.[106] Typical sewage treatment usually consists of primary sedimentation followed by secondary (biological) treatment and final sedimentation. There may also be facilities for removing nutrients (e.g., nitrogen and phosphorus) and/or pathogens. This may include processes with anaerobic and anoxic zones or tertiary treatment processes such as slow sand filtration and in some cases UV disinfection or chlorination. Treatment of sewage sludge to reduce pathogens and pollutants is also often mandatory.[59]

Typically, there is very little elimination of organic micropollutants from the preliminary treatment of wastewater,[91,101] and it is also unlikely that many pharmaceutical compounds will be removed during screening or primary sedimentation. As there is little biological activity, any pollutant removal at this stage will rely on both the tendency of the individual drug to adsorb to solids and the degree of suspended solid removal from the primary sedimentation tank.[17] The removal of organic compounds may also be affected by factors such as pH, retention time, temperature, and amount of solids present, as has already been demonstrated for metals.[113] Normally there is little change in dissolved polar organics, such as pharmaceuticals, at this point,[87] so little to no loss of polar drugs may be expected here.

Activated sludge and trickling, filters are the principle types of secondary biological treatment usually used following primary sedimentation.[87] Losses

of drugs in both processes may be by the same mechanisms as other organic micropollutants and include adsorption to and removal in waste sludge and/or biological or chemical degradation and biotransformation. Little loss by volatilization during aeration is expected, but field data suggest that activated sludge removes greater amounts of pharmaceutical compounds than percolating filters,[117] probably due to the greater bacterial activity in the former.

Since sewage treatment plants are the principal method by which human pharmaceuticals enter the environment there are, theoretically at least, a number of potential opportunities to control their release. For example, certain compounds have been shown to be removed more efficiently by reducing the sludge loading rate (SLR) and/or increasing the hydraulic retention time (HRT).[93] Both these factors are ultimately determined by the sludge age (θc) of the plant. Increasing sludge age results in a reduction of the SLR and an increase in HRT. This enables populations of slower growing bacteria to develop and also serves to increase the potential for the acclimatization of the population to the compounds encountered. This change in the bacterial population with time means any chemicals in the sewage are exposed to a greater array of bacteria and bacterial enzymes, increasing the likelihood that they will be degraded to less harmful compounds; however, recalcitrant polar organics may still pass through.[129]

STPs employing nitrification and denitrification also exhibit significantly lower concentrations of drugs such as ibuprofen and naproxen in their effluent.[30] This is probably a consequence of the diverse bacterial compositions within a nitrifying and denitrifying system. Nitrification is a highly oxygenated process, while denitrification requires anoxic and anaerobic conditions. These differences give rise to a sequence of differing bacterial populations, which may act synergistically and result in a greater degree of degradation being achieved. For example, a compound may be partially biodegraded during nitrification, with the resulting product then degraded fully in the denitrified system.

Utilization of nitrification–denitrification and increasing the sludge age of the majority of sewage treatment plants would (along with most other options) be likely to involve a number of associated environmental costs in terms of resource and energy consumption, which would need to be balanced against the potential benefits of a reduced pharmaceutical load in the effluent. However, most modern treatment facilities already have these systems in place (often in conjunction with biological phosphorus removal) to control nutrient release. Therefore the cost would be offset somewhat by existing legal requirements. It may be that moves to limit nutrients to receiving waters have also reduced pharmaceutical and other related contaminants. However, there may be scope to optimize pharmaceutical removal at little extra cost.

In order to develop effective management strategies to minimize the risks of the release of compounds to the environment, it is necessary to fully understand the potential sources and the subsequent fate and behavior of the compounds in question, as well as the associated costs and benefits of effecting a change in treatment options.[37] This necessarily includes consideration of how local conditions are likely to influence their impact. Strategies that are developed also need to be evaluated in terms of their overall effectiveness, including both environmental and economic considerations. While the latter are likely to be easily identified (although at present there are no economic or legal incentives for water companies to remove medicinal compounds from wastewater), the environmental aspects are more difficult to determine.

Drugs left in the effluent after primary and secondary treatment may be eliminated by tertiary treatment. However, in most countries only a small proportion of sewage treatment facilities have these adaptations. Advanced treatment techniques such as ozonation and membrane treatment have been shown to remove pharmaceuticals to below detection limits in a water treatment works,[122] but how effectively they do so varies with the treatment conditions employed. In addition, these processes have not been applied to the treatment of wastewater and would prove costly and pose maintenance problems if they were used.[59]

Those compounds not removed in sludge or degraded during treatment will be released in the final effluent with unknown effects on the receiving aquatic systems. Compounds that do sorb to the solid phase (such as the fluoroquinolone antibiotics[39]) still have the potential to return to the environment via the landfilling of sludge or the application of biosolids as a fertilizer/soil conditioner.[70] In each case, compounds could be removed via leaching and enter groundwater and/or surface water. This scenario is likely to be mitigated to some extent by the treatment that sewage sludge must undergo before disposal. Various techniques are utilized, all of which may influence the loss, or potential formation, of organic contaminants. The main form of treatment is digestion (anaerobic or aerobic).[87] Temperatures are usually elevated during these processes, and nonthermally stable compounds (such as many drugs) may be broken down at this point; however, there is no evidence regarding the fate of pharmaceutical compounds before and after sludge digestion. While disposal of sludge to land is desirable for a variety of reasons, both environmental and economic, concern over pollutants has led many to be cautious over its use, and as yet the data are inadequate to assess the need for land utilization guidelines for organic contaminants such as pharmaceuticals. As analytical surveys for organic residues are expensive, environmental modeling may assist in identifying pharmaceuticals, that should potentially be analyzed in sewage sludge and/or treated soils.[31]

Where pharmaceuticals are released into the environment there is the risk of exposure to humans via potable water supplies. Although the associated risks are likely to be relatively minor, the increasing demands on the worlds freshwater supplies will likely lead to greater incidences of indirect and direct water reuse situations, and the potential for adverse effects should not be overlooked,[51] especially since little is known regarding the environmental or human health hazards that might be posed by chronic, subtherapeutic levels of pharmaceutical substances or their transformation products. In addition, the presence of pharmaceuticals, however small, will likely increase the general public's already negative attitude to water reuse. This is because it is impossible to prove there will never be any negative effects from their presence. For example, a water reuse scheme in San Diego, California, recently failed precisely because the onus was put on the operator to prove the negative regarding quality, health, and local media effects, even though none were detected during the scheme.[16]

To conclude, if pharmaceuticals are proved to be problem pollutants, it is theoretically possible that contemporary STPs can be upgraded to deal with them but in practice it is very unlikely that this will be economical. Therefore, controlling pollution sources (such as disposal practices and therapeutic usage) may prove a more effective tool to control this problem, since prevention of contamination is generally preferable to remediation.

V. CONCLUSIONS

- Pharmaceuticals are used in large amounts in human (and veterinary) medicine and reach the aquatic environment mainly through sewage treatment systems, where their concentrations can reach micrograms per liter levels.
- Although some predictions can be made based on their physical and chemical properties, pharmaceuticals display a variety of removal efficiencies during wastewater treatment and their fate and behavior are not clear.
- There is little experimental evidence showing levels of pharmaceutical compounds in sewage effluent or sludge and even less showing they should be of concern. However, their biological activity alone may support ecotoxicity assessments of chemicals with high production volumes, especially in view of the increasing importance of freshwater resources and use of drug compounds.
- If receiving waters are used for potable supplies, the presence of these compounds (although this is unlikely) may represent a potential hazard to human health, especially in areas without advanced water treatment.
- Despite the increasing research activities in this field, there is still a considerable need for future work and further investigation in order to assess the significance of residues in terms of their persistence and potential

environmental impact. The development of markers for wastewater contamination of surface waters with pharmaceuticals would also be useful.

- A possible recommendation to protect the aquatic and terrestrial environment is that hazard, biodegradability, and fate assessment should be required for all new synthetic chemicals, irrespective of their purpose or end use, in order to determine the potential for them to transfer to wastewater or sewage sludge and the subsequent implications for the environment. Specified criteria regarding toxicity and biodegradation could be set for compounds that exhibit a propensity to enter STWs, and restrictions could be enforced regarding production and use if these criteria were not met.
- Any changes to sewage treatment parameters would need to be offset against the economic costs. Likewise, any restrictions or drug use must be balanced against the potential loss of health benefits derived from the administration of those drugs.

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