

Pharmaceuticals in the environment: review of current disposal practices for medications and the influence of public perception on environmental risks

By

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## **Abstract**

There is growing public concern over the presence of trace organic contaminants, including active pharmaceutical ingredients (API), in water and the environment. Public utilities in the United States, such as water supply and wastewater treatment processes, have yet to appropriately address this problem. Although wastewater treatment plants are equipped to remove chemicals, foreign materials, and microorganisms from influent prior to discharging to natural waters, active drug compounds are not completely eliminated in the treatment process. APIs typically enter the environment when passed through the human body or when people dispose of unused medicines into the sanitary sewer system. The relative contribution of disposal practices remains uncertain, but management of disposal provides a potentially effective strategy for the reduction of API pollution. A major unknown with respect to drugs as pollutants is the proportion of drug residues found in the environment that can be attributed to discarding leftover drugs. Absence of this information inhibits the adequate assessment of the role drug accumulation and disposal plays as a contributing source of drug residues in the environment. Moreover, little is known about public awareness of the detrimental environmental consequences of APIs and how such knowledge influences personal disposal choices. By reviewing recent studies, this paper aims to shed light on the impact of current disposal practices and the public perception of environmental risks associated with pharmaceutical contamination.

## **Biography**

Elizabeth Wilcox has been employed by the City of Raleigh's Resource Recovery Division as a Chemist for the Neuse River Wastewater Treatment Plant for the past two years. She finished her bachelor's degree in Environmental Studies with a concentration in Pollution Control in spring 2006 from the University of North Carolina at Asheville. Interest in water quality and wastewater treatment design led her to pursue professional certifications within the wastewater field. Certifications include Wastewater Lab Analyst Class III, Grade II Biological Water Pollution Control System Operator, and Class III Pretreatment Program Specialist. Currently her position with the City involves conducting regulatory testing for the Neuse River Wastewater Treatment Plant and other various City managed locations. Responsibilities include upholding quality control/quality assurance, reporting data, and instrumentation maintenance.

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## **Introduction**

The presence of active pharmaceutical ingredients (APIs) in the aquatic environment, due to the improper disposal of human and veterinary pharmaceuticals, has become an issue of increasing concern in recent years. Human APIs, the focus of this paper, include compounds such as analgesics, antibiotics, anticonvulsives, cancer drugs, lipid regulators, psychiatric drugs, and recreational drugs. APIs predominantly enter the environment through the effluent of domestic wastewater treatment and are now known to be ubiquitous in surface water, groundwater, and even drinking water supplies throughout many parts of the world. While pharmaceutical pollution is most frequently detected at very low concentrations, ranging from less than 0.007 parts per billion (ppb) to roughly 150 ppb (Kolpin et al. 2002), APIs have the potential to cause damage to aquatic organisms and ecosystems and may pose significant human health risks. The review addresses the impact of pharmaceuticals on the environment and the role of current disposal practices and public risk perception on drug accumulation.

The first comprehensive study of APIs in surface waters, conducted by the U.S. Geological Survey (Kolpin et al. 2002), found trace concentrations of organic wastewater contaminants, which include prescription and nonprescription drugs, in nearly 80% of 139 streams tested across the United States. Among APIs, nonprescription drugs were detected at the highest frequencies, with caffeine detected in 71% of samples, nicotine metabolites detected in 38% of samples, and over-the-counter analgesics (e.g., acetaminophen) detected in 24% of the samples. Among prescription drugs, the most frequently detected drugs included heart medication (e.g., dehydronifedipine: 14.3%), analgesics (e.g., codeine: 10.6%), and blood pressure medications (e.g., diltiazem: 13.1%). Drugs used as both human and veterinary pharmaceuticals were detected in a high proportion of samples, including: antibiotics (e.g.,

trimethoprim: 27.4%), reproductive steroids (e.g., estriol: 21.4%), ovulation inhibitors (e.g., 19-norethisterone: 12.8%), and estrogen replacements (e.g., equilin, 2.8%).

The environmental presence of APIs is attributed primarily to wastewater effluent. Effluent-derived contaminants originate from human use of medication and personal care products that are ultimately discharged into municipal sewer systems (Doerr-MacEwen and Haight 2006). Even simple activities such as shaving, using lotions, or taking medication have been attributed to adding chemicals to the environment (Daughton and Ternes 1999). Because many wastewater treatment plants (WWTP) are not designed to remove pharmaceuticals, most APIs are not effectively removed by the wastewater treatment process. The cost of advanced treatment is prohibitive, thus the removal of individual chemical compounds in the wastewater treatment process is not a viable option for reducing APIs (Molinos-Senante et al. 2013). Pollution prevention strategies that deal with the source of the pollutants are therefore considered to be the most effective solution to date.

There are three primary pathways for household pharmaceuticals to enter the sewer system: (1) excretion after ingestion, injection, or infusion, (2) removal of topical medications during bathing, and (3) disposal of unused medications via the sewer system or trash. Excretion of APIs by humans into the sewer system and the survival of these compounds in the wastewater treatment process are considered to be the main route of APIs entering the environment. While the relative contribution of the accumulation and disposal of unused drugs in municipal sewer systems remains unknown, this may provide a unique and preventable source of potential environmental contamination (Ruhoy and Daughton 2008).

Several studies have documented observable direct, indirect, or synergistic effects from APIs in the environment; however there remains considerable uncertainty with regards to human and ecological effects of these compounds. Due to low concentrations, APIs are unlikely to elicit direct acute toxic effects but chronic, long-term exposure has the potential to affect communities or result in the decline of populations. This is especially true for aquatic organisms that are subject to continual and multi-generational exposure (Khetan and Collins 2007). The indirect effects caused by APIs in the environment may also raise considerable concern for human and ecological health. For example, the widespread use of antibiotics for both humans and animals has resulted in the emergence of antibiotic-resistant bacteria. Every year in the U.S. 2 million people acquire serious infections with bacteria that are resistant to one or more antibiotics designed to treat those infections (CDC 2013). Synergistic effects of pharmaceuticals also need to be addressed when discussing possible human and ecological toxicity because the presence of multiple APIs can produce an effect greater than the sum of their individual effects. For instance, it was demonstrated that a mixture of ibuprofen, Prozac, and ciprofloxacin produces 10 to 200-fold higher toxicity in plankton, aquatic plants, and fish than the effects of the drugs alone (Kim and Aga 2007).

The fate and effects of APIs in the environment is a problem that is complicated by the tremendous increase of prescriptions sold in the United States. Currently in the US, over 1,000 APIs are approved for use (Kostich et al. 2013). Spending for prescription drugs has more than doubled from 1999, totaling \$234.1 billion in 2008. The percentage of persons who used at least one prescription drug in the past month increased from 44% in 1999-2000 to 48% in 2007-2008, two or more prescription drugs increased from 25% in 1999-2000 to 31% in 2007-2008, five or more prescription drugs increased from 6% to 11%. In 2007-2008, 1 out of every 5 children and



9 out of every 10 older Americans reported using at least one prescription drug in the past month (Gu et al. 2010). Some of the drivers of this growth are the expanding population and the inverting age structure in the general population, the rise of new target age groups, the discovery of new uses for existing drugs, and increased per capita consumption (see Figure 1) (Khetan and Collins 2007).

### Per Capita Expenditures for Prescription Drugs from 1960 to 2010

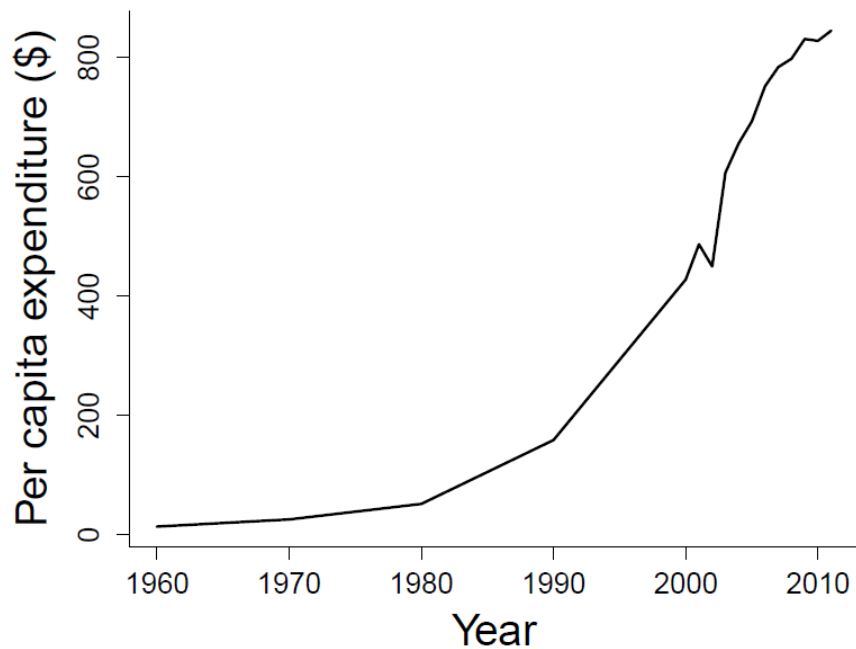


Figure 1: Per capita expenditures from 1960-2010 (Center for Medicare and Medicaid Services 2013).

Widespread occurrence of APIs in the environment has now been established. APIs introduced to the environment by means of improper disposal may prove to be an important source, especially from the perspective of pollution prevention, because actions can be designed more easily for reducing the environmental impact of this pathway relative to excretion and

bathing pathways. In this review, I address: (1) the effects of APIs observed in the environment, (2) the relative contribution of the disposal practice pathway, (3) the role that risk perception plays on pharmaceutical disposal habits, (4) the challenges associated with reducing concentrations of APIs in the environment, and (5) management strategies and potential source reduction solutions.

### **Effects of APIs in the Environment**

APIs in the environment have the potential to cause direct adverse effects to aquatic organisms. Direct effects result from a chemical acting directly at the site of action in or on the organism. For example, the appearance of new fish phenotypes near wastewater discharge areas has been attributed to high concentrations of natural and synthetic estrogens in these waters. Affected fish show gender bending with feminized male fish that lay eggs and/or that have lost their reproductive abilities (Tyler and Jobling 2008). Similarly, a seven year manipulative experiment (Kidd et al. 2007) found that chronic exposure to low concentrations of estrogenic substances adversely impact the sustainability of wild populations. Synthetic estrogen (17- $\alpha$ -ethynylestradiol) was added to a lake system at concentrations representative of wastewater effluents (5–6 ng/L). Chronic exposure of fathead minnow to potent 17 $\alpha$ -ethynylestradiol led to feminization of males, impacts on gonadal development, and altered oogenesis in females. Within one year, the fathead minnow population collapsed to near extinction in the lake. After dosing was ceased, the population rebounded within two years.

Indirect toxicity occurs when the addition of APIs to a system elicits a change of physical, chemical, or biological environment that causes adverse effects on target organisms. For instance, antibiotic APIs are a subject of special concern as they have been implicated in

facilitating the spread of drug-resistant bacteria. The genetic selection of resistant bacteria is a potentially irreversible effect that is hypothesized to be induced by low concentrations of antibiotics that are being found in environmental waters (Khetan and Collins 2007). In a study by Schwartz et al. (2003), hospital and municipal wastewater was examined for the occurrence of antibiotic-resistant bacteria; resistance was observed in several of the bacterial species that were tested. Similarly, Kim and Aga (2007) found that antibiotics, added directly to fish farm stock ponds via medicate feed and indirectly through the application of livestock manure, lead to startlingly high levels of resistance of several bacteria to antibiotics including 80% resistance to ciprofloxan, and 100% resistance to oxytetracycline and sulfamethoxazole.

A synergistic effect pertains to an effect whereby two or more chemicals together have more of the toxicological impact than the cumulative effects of the individual pollutants alone. Because concentrations of APIs in the environment are typically much lower than toxic doses, a direct effect of exposure to humans has not been observed (Ducey and Sapkota 2010). However, most of these findings involve single drug studies that ignore the risk of synergistic effects of cumulative chronic exposure to a combination of drugs (Leal et al. 2010). The synergy of various chemicals in the environment has been shown to increase individual effects. For instance, one study used yeast estrogen screen (YES), which detects the ability to bind to the alpha human estrogen receptor and implicates binders as chemicals that can affect reproductive endpoints. The investigators tested mixtures of eight chemicals, each at a concentration below the level of observable effects. In combination, their effects were additive and produced a detectable effect (Leal et al. 2010). There are multiple questions yet to be answered concerning the health effects of chronic exposures to low levels of multiple bioactive substances.

## **Pathways of APIs to the environment and the significance of disposal**

WWTPs are only designed to handle human waste, mainly of natural origin primarily through acclimated biodegradative action of microorganisms and the coagulation/flocculation of suspended solids and are not designed to remove pharmaceuticals (Doerr-MacEwen and Haight 2006). The efficiency of removing pharmaceuticals varies depending on the treatment plant and chemical type and, overall, the ability of the wastewater treatment process to remove these chemical compounds is limited. An extensive study performed in Germany reported removal from WWTPs from five broad physiologic categories. Removal of the parent compounds ranged from 7% (carbamazepine, an antiepileptic) to 96% (propranolol, a beta-blocker), with most removal efficiencies averaging 60% (Ternes 1998). Kostich et al. (2013) measured concentrations of 56 active pharmaceuticals and seven API metabolites in wastewater effluent samples from 50 large municipal wastewater plants across the United States. Of the 63 pharmaceuticals measured, 43 were detected at least once, further illustrating the expanse of APIs entering the environment and the need for better source control. These studies illustrate that conventional treatment is inefficient in achieving the complete elimination of APIs from raw wastewater. The utility of wastewater treatment in reducing APIs is complicated by the high number of substances of concern. The high investment, operation, and maintenance cost associated with wastewater treatment solutions of APIs make relying on treatment strategies for API removal unfeasible (Molinos-Senante et al. 2013).

APIs may also be introduced to the environment by landfills when household medications are discarded to trash though the environmental impact of disposing medications via the trash is still inconclusive. In a study performed by Maine Department of Environmental Protection (DEP), the concentrations of drugs in samples of leachate from landfills only receiving

household waste were measured. The amount of yearly leachate emissions equated to ‘hundreds of pounds’ of APIs from over the counter (OTC) and prescription drugs. For example, acetaminophen was present in samples from one landfill at concentrations of 117mg/L (Lubrick 2010). In contrast, other studies have concluded that landfill contribution to API in the environment may be of little consequence. Cook et al. (2012) estimates that a 100% trash disposal program would have similar results to a take back program with 50% participation, coupled with lower financial cost and higher convenience and compliance. Such results make it difficult to determine whether disposal in landfills is a safe option for disposal of unused medications (Lubrick 2010).

### *Drug Accumulation*

Because advanced treatment technologies are currently cost prohibitive or insufficient for reducing API pollution, strategies that address the consumption and accumulation of APIs are much more likely to be an effective means of reducing the pollutants in the environment (Doerr-MacEwen and Haight 2006). The entry of APIs via the disposal pathway is dependent on the habits of individuals and the efficiency of prescription practices leading to fewer unfinished prescriptions. Many factors cause medications to remain unused, creating leftover drugs that can accumulate and eventually become subject to disposal. Knowledge of the motivation behind different disposal methods and drug accumulation is useful in determining the best management to reduce the release of APIs in the environment (Bound and Voulvoulis 2005).

Leftover medications tend to accumulate after being set aside, stored or forgotten. Accumulated or stockpiled medications are eventually either disposed of by a formal collection program or by the end user discarding directly into sewer systems or trash. In order to reduce or eliminate API’s entry to the environment by improper disposal, a better understanding of the

many and varied origins and sources of leftover drugs will need to be developed. Ruhoy and Daughton (2008) define the possible reasons why drugs accumulate which include: (1) the method of prescribing, (2) the practice of pharmaceutical promotions, (3) the form of drug delivery and (4) patient non-compliance and non-adherence (Ruhoy and Daughton 2008).

One of the many reasons for drug accumulation involves the method of prescribing. Often, there is not one perfect method of treating a chronic ailment and optimal prescribing can be complicated and time-consuming. There is a potential for increased misuse, mismanagement, ineffectiveness, and non-compliance with the medication and this leads to the accumulation of unused medication (Ruhoy and Daughton 2008). Pharmaceutical promotional items and programs can also play a role in drug accumulation. A 2008 study by York University estimated that the US pharmaceutical industry spends almost twice as much on promotion than it does on research and development. Surveys report that direct-to-consumer advertising will lead a patient to ask their doctor about medications solely based on viewing an advertisement. In turn, physicians then consider prescribing such medication as a result of patient's request (Ruhoy and Daughton 2008).

The form of drug delivery (e.g., pill, liquid, cream, gel, or intramuscular injection forms) often affects the patient's perception, willingness, and comfort in consuming the medication. Consumption patterns associated with each of these pose challenges with regards to drug accumulation. For example, cream and gel forms of delivery often result in the disposal of unused portions of the product. Likewise, drugs used to treat chronic ailments are often provided to patients in forms and quantities meant to last for multiple months. While this can be seen as a convenience to the consumer, the large quantity of drugs stored in the home increases the

potential of having unused medication, especially if that treatment is altered by the physician or in the event of their death (Ruhoy and Daughton 2008).

Non-adherence and non-compliance to prescribed treatment may also be a significant source of drug accumulation. Non-adherence is when a patient attempts to follow the directions of the physician but is unable to adhere to all the directions for proper use and consumption. Non-compliance refers to when a patient willingly chooses to not comply with treatment as prescribed. For instance, there is high incidence of non-compliance for clinical depression and for drugs that are prescribed for long-term treatment for a chronic disorder. Non-compliance and non-adherence are often used synonymously because the end results for having unused medications are the same. According to the World Health Organization (WHO) 2003 report on long term therapies, 50% of patients in the US, treated for chronic diseases, failed to complete the course of treatment. Reasons for non-compliance and non-adherence are countless and highly complex and may include ineffectual delivery systems, adverse side effects, numerous psychosocial factors, and even sensory aversion (Ruhoy and Daughton 2008). These unwanted and unused drugs indicate the growing problem of what to do with unused and unwanted medications (Ruhoy and Daughton 2007).

### *Importance of Disposal*

To date, the pathway of excretion has long been considered to be the major contributor to environmental APIs. Environmental models of API loading often consider the excretion pathway as the only contributory factor. While excretion is likely the primary pathway, such assumptions are unlikely to adequately characterize APIs in the environment. For instance, while excretion pathways may have the largest contribution to API concentrations, disposal pathways may lead to short term high concentrations of APIs with significant consequences for environmental

systems. Release by disposal is expected to result in brief, episodic, transient spikes in concentrations of API's to the sewer system that are significantly higher than the more constant "ambient" levels resulting from continual, low-level release through excretion. The times of drug disposal can therefore be "compressed" compared with those for excretion and bathing. Confluences of similar facilities, such as Long-Term Care Facilities (LTCF) that routinely practice drug disposal and are served by the same wastewater treatment plant could amplify episodic releases. LTCFs often dispose of drugs in mass quantities during particular days or times of day after a certain amount has been accumulated. The season of the year could also make disposal more significant when those medications that tend to be taken during certain seasons are disposed when usage is lowest (Ruhoy and Daughton 2009).

The types and quantities of APIs released by disposal may be more significant for certain drugs compared to their release by excretion or bathing. For instance, some medications have universally poor compliance rates and therefore are disposed of at greater quantities (Ruhoy and Daughton 2008). For example, according to the *Canadian Community Health Survey: Mental Health and Well-being* (Bulloch and Patten 2009), an estimated 45.9% of patients prescribed anti-depressants do not comply with their treatment regime. In an earlier study, 28% of patients stopped taking anti-depressants during the first month of treatment and 44% stopped taking medications by the third month (Lin et al. 1995). Patients' non-compliance and non-adherence is one of the leading reasons for pharmaceutical wastage and accumulation.

Disposal may also be a primary source of environmental contamination of drugs recommended to be disposed into the sewer system because they are subject to abuse. Drug diversion, the use of licit drugs for purposes that differ from their original use, is an important public health and safety concern. The possibility of unintentional poisonings or diversion for



abuse must be minimized from medications that pose extraordinary and imminent hazards to humans (i.e. those subject to abuse and addiction or those having high acute toxicity). The White House Office of the National Drug Control Policy has a limited list of these medications that are recommended to be disposed of directly into the sewer system to minimize human exposure (Glassmeyer et al. 2008). Environmental contamination by these drugs therefore represents a trade-off between human health and environmental risk.

Some drugs have been observed at high concentrations in the aquatic environment despite being metabolized at rates that would otherwise be reduced by excretory pathways of these substances. For instance, the disposal of one dose of carbamazepine (CBZ) is capable of contributing the equivalent mass of roughly 29-87 ingested CBZ doses (Daughton and Ruhoy 2009). The high prevalence of API pollutants that would otherwise be removed by metabolic processes has drawn some to question the dominance of the excretion pathway. One study reported several APIs (Table 1) with high environmental concentrations relative to the efficiency of excretion of APIs in their unmetabolized, parent form and their occurrence in the environment. All but three of the pharmaceuticals are available over-the-counter and are purchased in large quantities, which make them prone to expiration and subsequent disposal. The negative correlation between expected and observed occurrence of these APIs suggests that excretion is not the source of the contamination of these systems (Daughton and Ruhoy 2009).

**Pharmaceuticals with Reported Negative Correlation between Efficiency of Excretion and Occurrence in the Environment**

| Compound                       | OTC or Prescription | Excretion Type      |
|--------------------------------|---------------------|---------------------|
| acetylsalicylic acid (aspirin) | OTC                 | poorly excreted     |
| Ibuprofen                      | OTC                 |                     |
| acetaminophen                  | OTC                 |                     |
| Carbamazepine                  | Prescription        |                     |
| sulfamethoxazole               | Prescription        | moderately excreted |
| diclofenac                     | OTC                 |                     |
| primidone                      | Prescription        |                     |
| ranitidine                     | OTC                 |                     |

Table 1: List of APIs compounds found to have a negative correlation between expected and observed rates of occurrence (Daughton and Ruhoy 2009).

*Determining the relative influence of the disposal pathway*

Direct measure of whether pharmaceuticals present in wastewater effluent originate from disposal of unwanted medications or from excretion and bathing is next to impossible. However, studies are emerging on ways to indirectly determine the significance of the contributions from disposal. Ruhoy and Daughton (2007) utilized a unique study design to determine the types and amounts of drugs accumulated by consumers. The researchers investigated coroner records from Clark County Coroner’s Office (CCCO). Many times, coroner offices maintain detailed inventories of medications from sites visited for investigation and acquisition of decedents. These accumulated medications can serve as a means of obtaining maximum and minimum ranges on the quantities and types of drugs that might ordinarily be disposed. The 13-month dataset contained greater than 5,000 discrete entries, averaging approximately four APIs per decedent. Data inventory from coroners may be a data source that enables the measurement of disposal as a source of environmental contaminations.

Ruhoy and Daughton's study also provides an accurate measure of pharmaceuticals that are disposed into sewer systems by coroners. The most prevalent method of disposal for the CCCO was to flush the inventoried medications into the sewer system. Greater than 92% of the medications were disposed of in the sewer system, 7% were disposed of in the household trash and less than 1% was incinerated by law enforcement service. Incineration usually occurred when pills were unable to be identified. During the 13-month study, 325,000 doses of a wide array of drugs, representing 102kg of APIs, were disposed directly to the sewer system. By extrapolating the death rates between Nevada and the US, it is estimated that 17.9 metric tons of APIs are disposed of annually by coroners into sewer systems from deceased population alone (Ruhoy and Daughton 2007).

A commonly used strategy is consumer questionnaires and surveys designed to assess the most commonly used disposal methods and the reason behind consumer choices (Glassmeyer et al. 2008). To investigate household disposal of unused pharmaceuticals as a source of APIs in the environment, a survey of 400 households was carried out in Southeastern England. Information from the survey was used to construct a conceptual model to assess the pathways of human pharmaceuticals into the environment. The survey data, coupled with estimations of compound elimination in the human body and wastewater treatment removal efficiencies were used to model the relative importance of pathways to the environment (Bound and Voulvoulis 2005). Consider 100 units of metoprolol, a succinate of  $\beta$ -blockers used to treat high blood pressure (Figure 2). Only 46.8% of respondents who had been prescribed  $\beta$ -blockers said they finished the prescription. Assuming that those people took half of the medication, then 26.6 units were disposed and 73.4 units of active ingredients were consumed. Only 7.3 units of active ingredients were introduced to the sewer system because 90% of the medication taken is

modified in the body. When combined with the 4.4 units of drugs that were put down the drain, these result in a total of 11.7 units entering a wastewater treatment plant. At the WWTP, 83% is removed, leaving 2 units to be discharged to surface waters. Of the 26.6 units that are unused, 17.7 units (nearly 10 times as much as released into the environment through the WWTP) are put into the landfill. Once there, some will be removed by biologic and chemical degradation, some will be collected as leachate and be subjected to similar treatments as in the WWTP and then released to surface water, and some may leach directly into surrounding groundwater and surface water.

### Pathway of Metoprolol by Units Used

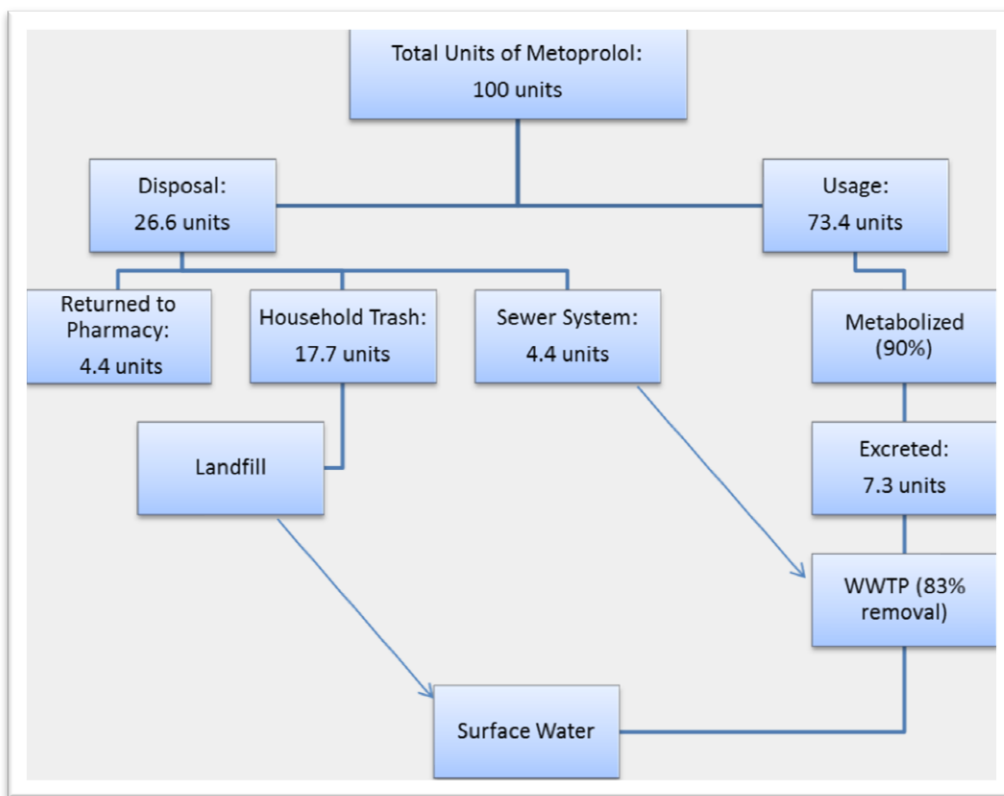


Figure 2: Model of the relative importance of pathways to the environment illustrated by the fate of metoprolol by units used (Bound and Voulvoulis 2005).

## **Regulation of APIs**

A lack of uniform federal and state regulations governing the proper disposal of pharmaceuticals may contribute to the hoarding of medication and improper disposal methods. Several governmental parties regulate different aspects of the pharmaceutical industry. The FDA regulates the introduction and approval of new drugs that come on the market. The Drug Enforcement Administration (DEA) enforces the controlled substances laws and regulations to prevent drug diversion through the Controlled Substance Act (CSA). The US Environmental Protection Agency protects the environment and human health from chemical exposure via a series of laws such as the Resource Conservation and Recovery Act (RCRA), the Clean Water Act, and the Safe Drinking Water Act (Glassmeyer et al. 2008).

The US Food and Drug Administration (FDA) require an environmental review process for new drugs as part of the New Drug Applications (NDA). First the manufacturer is required to estimate the expected introductory concentration (EIC) entering the environment based on total 5 year production estimates. If the EIC of a drug or any of its metabolites at point of entry is shown to be less than 1µg/L the drug is considered to be acceptable and no further assessment is needed. If the EIC is over 1µg/L then a formal environmental assessment is required. The assessment is usually based on effects on microbial respiration and acute toxicity on algal, invertebrate, and fish species. Chronic testing is only considered under certain circumstances like when a drug has the potential to bioaccumulate. The main criticism of this procedure include the difficulty in obtaining EIC, the level of threshold EIC that triggers assessment, the lack of consideration for terrestrial compartments, the specificity of the toxicity assessment and the bias toward acute rather than chronic toxicity (Jones et al. 2004). Standard acute ecotoxicity alone may not be suitable for addressing the question of environmental impact.

The CSA regulates the importation, manufacture, distribution, possession and improper use of any chemical that can be abused for intoxication (21 USC 811). The CSA establishes five schedules to classify drugs of abuse which regulate how a drug can be written and filled. Schedule I classifies drugs that cannot be prescribed at all and Schedule V represents drugs with the lowest potential for abuse (21 USC 829). Any person who possesses a CSA without a prescription is subject to monetary fines or imprisonment (21 USC 823). The CSA can have impact on how pharmaceutical take back programs are conducted. For example, a scheduled drug that is taken to a collection event may only be handled by law enforcement to avoid violating the CSA. The CSA is a major factor that has led the US away from using pharmacies or other locations as collection sites (Glassmeyer et al. 2008).

The US RCRA Subtitle C is the framework for the proper management of hazardous waste. Hazardous wastes are wastes that are considered dangerous or potentially harmful to human health or the environment. To be hazardous, waste must meet one of four characteristics—ignitability, corrosivity, reactivity, or toxicity. Once a pharmaceutical is dispensed or purchased by a member of the public, any unwanted medications are classified as household waste, and their disposal is not subject to any controls. Currently, hazardous household waste, including hazardous pharmaceuticals are not subject to the federal RCRA hazardous waste regulations, as household wastes are exempt from Subtitle C regulations (Glassmeyer et al. 2008).

Instructions on proper disposal are often times confusing and send out conflicting messages. For instance, poison control centers have long advised against discarding medications via the trash, and instead recommend discarding into the sanitary sewer system. This advice was perceived as the easiest means available for protecting humans and pets from accidental and

purposeful poisonings (Glassmeyer et al. 2008). Similarly, the White House Office of National Drug Control Policy (ONDCP) issued federal guidance that listed 13 specific hazardous drugs that should be discarded directly to the sewer system because of the potential for abuse and acute toxicity (Glassmeyer et al. 2008). The ONDCP also recommends returning unused medications to pharmacies for safe disposal; these drug-specific disposal guidelines have the potential to confuse participant regarding the proper methods of disposal. Additionally, few pharmacies facilitate proper disposal of unused medication likely due to the difficulties posed by the CSA (Seehusen and Edwards 2006).

Shortly after the release of federal guidance for disposal, the US Fish and Wildlife and the American Pharmacists Association (APhA) partnered for a program called SMARxT Disposal to address proper disposal practices. These two organizations have recognized the need for public awareness on the potential hazards associated with the discarded unused medication in to the sewer system. Education that accompanied this effort focused on environmental impacts, as well as health impacts associated with the practice of storing or flushing unused medications. The recommended disposal steps are identified in Table 2. However, these recommendations are not always disseminated or discussed with consumers, and may be difficult to comply with or cause more problems than they solve. According to SMARxT Disposal, landfills are safe for disposal of pharmaceuticals. However, as previously mentioned, impacts from drug disposal in to landfills are not yet understood and few studies have been conducted on landfills and leachate (Lubrick 2010).

## **SMARxT Disposal Guidelines Issued in 2007 by the US Fish and Wildlife and the American Pharmacists Association**

- One option is to check for approved state and local collection alternatives such as community based household hazardous waste collection programs. Please understand that different regions and states have different ways of addressing this issue, so it is important to follow the laws that are in place in your part of the country for medication disposal.
- Another option involves participating in the DEA National Prescription Drug Take Back Day; these events always include law enforcement officials.
- Also, you can safely dispose of your unused and expired medications in your household trash. When discarding unused medications, ensure you protect children and pets from potentially negative effects:
- Pour medication into a sealable plastic bag. If medication is a solid (pill, liquid capsule, etc.), add water to dissolve it.
- Add kitty litter, sawdust, coffee grounds (or any material that mixes with the medication and makes it less appealing for pets and children to eat) to the plastic bag.
- Seal the plastic bag and put it in the trash.
- Remove and destroy ALL identifying personal information (prescription label) from all medication containers before recycling them or throwing them away.
- Consult your pharmacist with any questions.

Table 2: SMARxT Disposal Guidelines Issued in 2007 by the US Fish and Wildlife and the American Pharmacists Association found on <http://www.smarxtdisposal.net/>

### **Public Perceptions of API Disposal**

The extent to which the public is adherent to drug disposal guidelines is not well understood. The motivation behind the selection of different disposal methods could be based on several factors. The primary method of disposal is the sewer system or waste management. These methods of disposal are often chosen due to concerns that drugs that are not discarded may end up in the hands of children. Additionally, many people feel that disposing pharmaceuticals via the sewer systems or municipal waste streams is unlikely to cause much harm to the environment. For most people the most straight forward and least time-consuming approach is to



discard unused medication in to the trash or sewer system. Several survey efforts have sought to determine the motivation for different disposal practices in order to determine the most effective ways to communicate methods of proper disposal.

In a survey completed by patients from the Institutional Review Board of Madigan Army Center, more than half the respondents reported storing unused or expired medications in their homes and more than half reported flushing medications into the sewer system. More than 35% of respondents believed that it was acceptable to flush medications down the toilet and 21% thought it acceptable to rinse them down a sink (Seehusen and Edwards 2006). Respondents who were counseled to return unused medications to a pharmacy or medical provider were significantly more likely to dispose medications in this manner. However, less than 20% of respondents reported being advised by a health care provider regarding proper disposal of medications (Seehusen and Edwards 2006). Only fourteen percent reported returning unused medications to a health care provider and 22.9% reported returning medication to a pharmacy. Proper communication regarding disposal practices by health care providers can be an effective tool for promote correct disposal. The Seehusen an Edwards (2006) survey actually reported a relatively high rate of returning medications. Comparatively, an older study Kuspis and Krenzelok (1996) surveyed 500 callers to a US poison information center, finding that only 1.4% reported returning unused medication to a pharmacy. The most typical disposal methods were household trash (54%), discarding to the sewer system (35.4%), and not disposing of them at all (7.2%).

In a more recent study in England, results showed that around half of the respondents (52.8%) finish their medications, and hence have none to dispose of, a third (30.7%) keeps them until their expiration, and 12.2% dispose of them when treatment is done (Bound et al. 2006).

When a pharmaceutical needs to be discarded, two-thirds (63.2%) disposed of medication in the trash, 21.8% returned them to pharmacies, and the remainder discarded them in to the sewer system (11.5%). Although 82.2% felt that disposal of pharmaceuticals was a problem, many expressed concerns regarding the safety of children rather than environmental problems (Bound et al. 2006). Likewise, a study performed in 2012 in the countries of Malta and the Republic of Ireland showed that the most common disposal practices were disposal in the trash (57% liquid, 14% pills), followed by disposal in the sewer system (28% liquids, 14% pills). Less than 10% of respondents reported returning unused pharmaceuticals (Fenech et al. 2013).

Leal et al. (2010) sought to evaluate the public's current knowledge of pharmaceuticals in drinking water. The study differentiated between health care employees and non-health care employees because it was expected that respondents that worked in health care may be more likely to know about pharmaceuticals in the environment. Of the respondents who worked in health care, 13 (72%) had previous knowledge of pharmaceutical medications being found in local water supply. Of respondents not employed in health care, only 42 (54%) had previous knowledge (Leal et al. 2010). Table 3 summarizes study results of disposal methods for unused pharmaceuticals.

### Summary of Methods Used to Depose of Unused Medications by Peer-Reviewed Literature

| Year of Study and Author(s) | Country                           | Method of Disposal              |                                  |                    |                            | Number surveyed |
|-----------------------------|-----------------------------------|---------------------------------|----------------------------------|--------------------|----------------------------|-----------------|
|                             |                                   | Sewer System                    | Household Trash                  | Return to Pharmacy | Other                      |                 |
| 2010 Leal et al.            | U.S.                              | 7% (with previous knowledge)    | 38% (with previous knowledge)    | <1%                | 36% (multiple methods)     | 96              |
|                             |                                   | 3% (with no previous knowledge) | 35% (with no previous knowledge) | none               | 42% (multiple methods)     |                 |
| 2006 Seehusen and Edwards   | U.S.                              | 35.2% (sink)                    | --                               | 22.90%             | --                         | 301             |
|                             |                                   | 53.8% (toilet)                  |                                  |                    |                            |                 |
| 1996 Kuspis and Krenzelok   | U.S.                              | 35%                             | 54%                              | 1.40%              | 7.2% (storing)             | 500             |
| 2005 Bound and Voulvoulis   | U.K.                              | 11.50%                          | 63.20%                           | 21.80%             | 52.8% (finish medications) | 392             |
| 2012 Fenech et al.          | Malta and the Republic of Ireland | 28% (liquids)                   | 57% (liquid)                     | <10%               | --                         | --              |
|                             |                                   | 14% (pills)                     | 14% (pills)                      |                    |                            |                 |

Table 3: Methods used to dispose of unused medication as reported by peer-reviewed literature.

Household waste and discarding into the sewer system are the most favored methods of disposal of unused pharmaceuticals according to recent surveys. However, patients with knowledge about the impact of pharmaceuticals in the environment coupled with the information of correct disposal techniques are more likely to return medications for proper disposal and destruction. This indicates the paramount importance that a formalized protocol for patient disposal of pharmaceuticals be implemented.

## *Risk perception*

Assessment of public awareness and risk perception of API pollution may be used to instruct and improve risk assessment and management. Because environmental effects could be avoided through better handling of unused pharmaceuticals and drug accumulation, it is important to examine the kinds of judgments people make when they balance choices regarding personal health and environmental risk. Risk is defined as the product of a hazard and the probability of its occurrence. Risk perception is the way an individual evaluates hazard, most commonly through intuitive risk judgments. Risk perception can be influenced by a number of factors including trust, feelings of control, and trade-off between benefits and risk (Bound et al. 2006). An influential study by Bickerstaff (2003) analyzed data on behavioral patterns associated with risk perception. The study concluded that people were inclined to accept risks where exposure was voluntary rather than imposed. Study subjects reacted negatively to imposed risk due to a perceived lack of individual control over personal decision-making processes. Willingness to accept risk was especially heightened in cases in which risks were perceived to be proportionate to the benefits gained from the activity. Conversely, those activities or situations where risk exposure was involuntary or where the risks were perceived to clearly outweigh the benefits were avoided. If a clear benefit can be derived, people are more likely to accept a risk in their environment. These beliefs about risk behavior are reflected in views of pharmaceuticals in the environment and disposal choices.

To further examine people's risk perception and choices in regard to environmental risks of APIs in the environment, Dohle et al. (2010) evaluated tradeoffs between human and environmental health. This study was used to assess awareness that human or agricultural medicine can be a threat to the environment. A second aim was to investigate how satisfied

respondents would be with an environmentally friendly pharmaceutical if it was the only one available to them. Thirdly, was to examine if environmental protection plays a role in people's drug use choices. In the case where the drugs were used for the treatment of a rather harmless disease, respondents valued environmentally friendly options or preferred to refrain from taking medication altogether when they realized that drugs have a considerable impact. However, in the case of severe disease such as cancer, it was demonstrated that a policy requiring doctors to prescribe the drug with the lowest environmental impact was not supported and probably perceived as too paternalistic. When weighting human health and the environment, people in general feel that the patient's health should be considered first (Dohle et al. 2010). This study shows how the perception of environmental risk is viewed to be less than that of health benefits received.

When the medicine is familiar, such as with painkillers and antihistamines, the perceived risk is lower. These drugs are used regularly and available over the counter and therefore perceived as "weaker," less potent, and less threatening to the environment. For unfamiliar medicines, such as lipid regulators and antiepileptic's that are present in a small number of households, opinions are not as well-formed. A Canadian study found that 90% of people said that unused and expired prescription medications required "special disposal," but the figure for non-prescription medications was lower at 81%. This difference may reflect the perception that "weaker" drugs are less harmful to the environment. However, even with the high level of recognition of the importance of proper disposal, 60% of respondents disposed of these drugs via trash or sewer system (Bound et al. 2006).

In order for risk management measures to reduce the quantity of improper pharmaceuticals disposal, there is a need to understand the motivation behind the behavior. It is

important to consider that environmental stewardship may play a key role in gaining participation in proper disposal practices. For respondents who considered themselves to be environmentally friendly, the proportion of pharmaceuticals thrown in household trash (40.8%) was considerably less than those who did not consider environmental protection a priority (71%) (Bound et al. 2006). Appealing to moral sensibilities and environmental stewardship may therefore have an effect on changing current disposal practices. In a drug take-back program launched in Maine, participants noted that they felt the service was the best solution for the environment. Similarly, Thach et al. (2013) found that the most salient reason for participation in take-back programs was to protect the environment. It may be therefore be effective to promote return programs as part of an “environmentally friendly” lifestyle. Communicating the cumulative effects of individual decisions may assist in modifying behaviors in situations in which individual actions have a negligible effect.

### **Management Strategies**

Three different approaches for managing risks of APIs in the environment can be distinguished: (1) drug handling, (2) emission control or the optimization of treatment options in wastewater treatment, and (3) drug development or designing pharmaceuticals that are optimized for efficacy and degradability. Emission control and drug development depend largely on scientific research and technological capabilities. In contrast, drug handling relates to change in current prescription utilization, and disposal practices (Dohle et al. 2010). Drug handling is governed by prescription practices and personal behavior. The improper disposal of medication represents an easily preventable source of pharmaceuticals entering the environment (Bound et al. 2006). Strategies focused on waste reduction and pollution prevention can be optimized to

reduce these pathways of APIs entering the environment. Some management strategies include drug take-back programs and low-dose prescribing.

Many state and local governments have established pharmaceutical collection programs. These initiatives provide the legal framework and the logistical resources required to allow the general public to turn in unwanted drugs for safe disposal. Types of collections range from small-scale, one-day events to sustained collection programs involving either drop-off sites, mail-back (pilot basis only), or regularly scheduled collection days and events (Glassmeyer et al. 2008). Drug take-back programs coupled with education regarding drug disposal was ranked third as effective management strategies by expert stakeholders. While disposal is considered a minor contributor to environmental loading of APIs, return programs increase public awareness, are very feasible to organize, and address other concerns such as public safety (Doerr-MacEwen and Haight 2006).

Drug return programs are hindered by a lack of monetary incentive and require more effort than other methods of disposal but may be a viable means of reducing the disposal pathway (Bound et al. 2006). Of respondents from the Thach et al. (2012) study, almost all respondents participated or would participate in the medication-take back program to protect the environment, while over half said they would to make their home safer. Most respondents were likely to choose a pharmacy that provided take-back services and the majority positively viewed paying for medication disposal on a per weight basis. In fact, Kotchen et al. (2008) found that the mean willingness to pay is \$1.53 per prescription to support proper disposal programs. These studies demonstrate favorable public perception of medication take-back services and suggest the importance of establishing more community-based take back programs as an effective strategy to engage the public in reducing API pollution.

Historically, drug dose has been excluded from consideration in reducing APIs in the environment. Environmental risk can be reduced and public health be better protected by communicating the impacts of API in the environment to healthcare practitioners. Imprudent or inappropriate prescribing (i.e., over-prescribing or mis-prescribing) with higher-than-necessary dose strengths and larger-than-needed dose quantities or durations contribute to the accumulation of unused medications. By reducing dose (to levels below on-label guidance), therapeutic goals can still be met. Campaigns for dose reduction gained traction in the 1980s/1990s. Since then, evidence has evolved to show that therapeutic effectiveness of off-label, low doses often match the on-label drug doses. In fact, recommended doses for many drugs are often readjusted more often downward than upward. For example, an evaluation of the 71% (354) of the new molecular entities approved by the FDA from 1980 to 1999 revealed that 21% later experienced on-label dose changes. Among the 73 that were changed, 79% were adjusted downward (Daughton and Ruhoy 2012). When interviewing expert stakeholders, Doerr-MacEwen and Haight (2005) found that reducing the consumption of pharmaceuticals through education of medical professionals, to minimize over prescription, was rated the second most effective strategy for reducing APIs in the environment. This option addresses the problem in a direct way, both by reducing APIs pathway of excretion and disposal.

## **Conclusion**

Entry to the environment of APIs used in pharmaceutical products is a complex issue. A major question not yet answered is the overall importance of drug disposal practices as a contributing source of API residues in the environment. The current evidence suggests that improper disposal of pharmaceuticals may be a significant contributor that is worth receiving attention. The most widely used disposal methods observed in many of the studies (i.e.,



discarded into the sewer system or trash) have the potential to detrimentally pollute the environment beyond the expectations of models that exclude or diminish the importance of this pathway. The expanding pharmaceutical industry and the current prescribing, dispensing, and consumption practices that lead to the accumulation of surplus drugs make pollution prevention strategies increasingly important and regulation of the pharmaceutical waste stream may provide an achievable means by which to reduce API pollution. This is especially true since advanced wastewater treatment is not feasible in all areas and does not account to the potential contamination caused by landfills.

Decisions concerning the appropriate approach to communicating potential risks posed by APIs to the environment and human health remain particularly complex. Studies on risk perception suggest that knowledge of the adverse environmental effects posed by API residues may not be enough to motivate the public to practice correct disposal methods. In addition, confusion over the methods of disposal still exists because of conflicting or incomplete guidelines for the proper disposal of unused medications. Public services, including government and private sectors, need to be more proactive about educating people on how to use and dispose of medication in a more environmentally acceptable manner. Greater emphasis on the importance of drug disposal and the integration of drug disposal into a more routine, environmentally friendly activity may be more effective than education about the risks associated with their presence in the environment. Ultimately, uniform disposal guidelines, more informed public outreach efforts, and widely available drug take-back programs will reduce disposal pathways and decrease the prevalence of API contamination in the environment.

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