

Pharmaceuticals and Personal Care Products in the Environment
Environmental Chemistry

ENVIRONMENTAL FOOTPRINT OF PHARMACEUTICALS: THE SIGNIFICANCE OF
FACTORS BEYOND DIRECT EXCRETION TO SEWERS

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Abstract—The combined excretion of active pharmaceutical ingredients (APIs) via urine and feces is considered the primary route by which APIs from human pharmaceuticals enter the environment. Disposal of unwanted, leftover medications by flushing into sewers has been considered a secondary route—one that does not contribute substantially to overall environmental loadings. The present study presents the first comprehensive examination of secondary routes of API release to the environment and for direct but unintentional human exposure. These include bathing, washing, and laundering, all of which release APIs remaining on the skin from the use of high-content dermal applications or from excretion to the skin via sweating, and disposal of unused and partially used high-content devices. Also discussed are the health hazards associated with: partially used devices, medication disposal practices of consumers, and interpersonal dermal transfer of API residues. Understanding these secondary routes is important from the perspective of pollution prevention, because actions can be designed more easily for reducing the environmental impact of APIs compared with the route of direct excretion (via urine and feces), for reducing the incidence of unintentional and purposeful poisonings of humans and pets, and for improving the quality and cost-effectiveness of health care. Overall, unintentional exposure to APIs for humans via these routes is possibly more important than exposure to trace residues recycled from the environment in drinking water or foods.

Keywords—Disposal Excretion Pharmaceuticals Poisoning Sweat

INTRODUCTION

Pharmaceuticals and personal care products (PPCPs) as environmental pollutants is a subject that has received exponentially growing attention since the late 1990s. The U.S. Environmental Protection Agency (U.S. EPA) maintains a large, publically available literature citation database for PPCPs [1] (<http://www.epa.gov/ppcp/lit.html>). It currently catalogs over 8,000 citations covering aspects that are directly or peripherally related to the entire spectrum of the risk paradigm—from origin and sources, to fate and transport, source control and waste treatment, ecological and human exposure, biological effects, pollution prevention, risk management, risk perception/communication, modeling, and others. Among these thousands of publications, however, fewer than 200 address any of the aspects of leftover (expired or unwanted) drugs and their disposal. None discusses the secondary routes by which active pharmaceutical ingredients (APIs) enter the environment (those beyond direct excretion to sewers) or that serve as source terms for modeling human exposure. The present study is the first comprehensive examination of the hazards of drug disposal and the potential significance of the secondary routes by which APIs enter the environment. This includes summarizing what the published literature covers, as well as highlighting the data gaps and needs, and a framework, termed pharmEcoKinetics (PEK), as the umbrella under which these processes and their relative significance might be better understood.

Widespread occurrence of APIs in the environment is now well established. Published reports of the occurrence of APIs in

sewage, surface and groundwaters, sediments, sewage sludge, biota, and elsewhere in the environment total over 1,000 as of September 2009 [1] (<http://www.epa.gov/ppcp/lit.html>); many of these studies were catalyzed after the seminal 2002 publication of the initial nationwide monitoring study by the U.S. Geological Survey (USGS) [2].

The environmental presence of APIs is attributed primarily to raw or treated sewage (for human drugs) and to manure and lagoons (for veterinary drugs used in animal feeding operations); additional, less obvious sources also exist, which can sometimes play important localized roles [3]. The major route by which APIs enter sewage is commonly accepted to be via urine and feces, with each contributing different relative amounts depending on the pharmacokinetics and structure of the individual API [4]. Although other contributory routes, such as personal hygiene bathing or washing and the disposal of leftover medications by consumers, have been considered minor or inconsequential [5–7], no empirical evidence has been published yet to support this supposition.

Specifically, with respect to the disposal route, prior work regarding leftover, unwanted medications has covered the following aspects: the broad spectrum of locales in society where unused drugs accumulate and from where they must be disposed of or stockpiled [3,8]; the many factors that lead to the accumulation of leftover medications, which then in turn eventually result in the need for their disposal [8]; the many approaches having the potential to minimize or reduce the accumulation of unused, leftover drugs and therefore reduce the need for disposal [8–10]; disposal of consumer drugs via collection programs in the United States [11]; the factors that encourage disposal to sewers versus other means of disposal such as trash or formal means of collection (e.g., take-back events) [12–14]; the first methodology by which accurate and

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comprehensive empirical data on the actual types and quantities of individual APIs that are disposed of can be collected for a particular, defined population, namely, coroner records from decedent investigations [15]; and the human health, medical, and environmental ramifications and consequences of accumulated, leftover drugs [16,17].

As for bathing or washing as a route of release and the hazards of leftover medications and the disposal process, no formal discussion has ever been presented to our knowledge, other than brief mentions [3].

In the present study, disposal is placed into a formal context for assessing its significance. The potential significance of washing and dermal transfer to other surfaces as contributory routes also is examined. Disposal and washing or bathing are discussed as the two most important secondary alternative routes of API release to the environment. The context required to assess their relative significance as contributory routes is developed. Understanding these routes is important from the perspective of pollution prevention, because actions then can be designed more easily for reducing their environmental impact compared with the route of direct excretion (via urine and feces) and for reducing the incidence of unintentional and purposeful poisonings of humans and pets. It is worth noting that although the literature on the larger topic of PPCPs as pollutants has grown dramatically since the mid-1990s [1], few publications (beginning in the late 1980s) tackle the questions surrounding disposal from a scientific perspective. This means that the single aspect of the problem involving environmental and human exposure having the greatest potential for control (i.e., disposal) has received the least attention. This bias has arisen perhaps because disposal has been assumed generally to contribute little to environmental residues compared with excretion.

Also introduced here is the concept of PEK. In simple terms, conventional pharmacokinetics (PK) deals with how a drug is processed in an organism (mainly, the time course of drug concentration), with the prime focus being on the eventual concentration that becomes bioavailable, so that therapeutic effect can be optimized and side effects minimized: "The activity of drugs in the body over a period of time, including the processes by which drugs are absorbed, distributed in the body, localized in the tissues, [transformed], and excreted" [18] (http://www.cancer.gov/templates/db_alpha.aspx?CdrID=44324). Because PK focuses on the active (plasma) concentrations of drugs, excretion is only of indirect interest to pharmacologists (sometimes measured solely for mass balance and to obtain a better idea of the portion of the API that might still be available within the body and to calculate half-lives). PharmEcokinetics is analogous to PK by also considering the fate of APIs in the environment (beginning at the point where an API or metabolite is excreted), with the primary difference being that its focus is decidedly not on plasma levels but rather on environmental levels, particularly wastewater, drinking water, and biosolids, as well as other locations (e.g., biota). The major aspects of PK that are of interest for PEK in environmental modeling are all of the pathways of excretion of the unchanged parent API (and bioactive metabolites and labile conjugates).

To date, the routes of excretion that are factored into environmental modeling are urinary and fecal, both long having been assumed to be the major contributors to ambient environmental residues. Although these generalizations are probably correct for APIs overall, the possibility has not been

ruled out that they might not apply to certain APIs. Although direct disposal of unused APIs is recognized as an additional source for entry to the environment, its significance is unknown and generally deemed to be inconsequential. Another route, which has been ignored essentially, is release of API residues from the skin, by bathing and washing (including laundering of clothing and bedding contaminated by dermal contact) and by direct transfer via surface contact.

Disposal has two distinct contributors: leftover unused medications (i.e., expired, unwanted, or unused for other reasons), and partially used medications that retain residual API (delivery devices such as transdermal or transmucosal delivery systems). Approaches to pollution prevention could differ for these two sources. Washing, bathing, and dermal transfer by direct contact have three contributors: residues remaining after the administration of dermal medications, APIs for local treatment (topical use) and systemic treatment (transdermal/transmucosal delivery); residues remaining on the skin after removal of transdermal systems (e.g., patches); and residues excreted via sweat, a route that has been discussed only briefly with respect to its possible role in environmental pollution [16,19].

Historically, consumers and other end users in the United States have disposed of leftover, unwanted medications by flushing them down sewer drains or by discarding them in the trash. For the vast majority of medications, the most prudent approach for addressing leftover medications is to avoid disposal to sewers. A number of countries (but not the United States) long have had programs where consumers can return leftover medications to pharmacies. In the last few years, various cities in the United States have begun implementing take-back collection programs, where consumers can return their unwanted medications [11]; in the United States, however, these types of collection programs can be complicated by the presence of controlled substances, which can be transferred only by the prescription holder to law enforcement (and their deputies) or agents of the Drug Enforcement Administration (DEA) or among DEA registrants [3].

Drug diversion (the use of licit drugs for purposes that differ from their original purpose; recreational use is one example) is an important public health and safety concern and occurs by various routes, such as burglaries of residences and pharmacies, breaches of the manufacturing, distribution, prescribing, and dispensing chains, and theft by family and friends (e.g., teen pharming) [20]. For medications that pose extraordinary and imminent hazards to humans (e.g., those subject to abuse or those having high acute toxicity), the possibility of unintentional poisonings or diversion for abuse must be minimized, because medications are a major cause of poisonings in the United States. The U.S. Poison Control Centers recorded over 1,330,000 cases of unintentional nonfatal poisonings by chemicals in 2003, 42.6% involving children aged 5 and younger. During 2001 to 2003, the U.S. Centers for Disease Control and Prevention estimated over 53,000 children aged 4 and younger (72% of which were aged 1–2) suffered unintentional poisoning from over-the-counter (OTC) and prescription medications [21]. Nearly 10% required special medical care. Over 75% occurred in homes. A survey of death certificate data indicates a considerable presence of drug-related mortality, specifically overdoses [22].

Imprudent storage and disposal (e.g., to trash) is possibly a major cause of unintended exposures of those for whom the medication was not prescribed or intended, especially children

[21]. Trade-offs therefore are required to best balance exposure of the environment (primarily via disposal to sewers) versus human exposure (e.g., via diversion from stored stockpiles of leftovers or from those medications disposed into the trash). It is widely accepted that a select number of medications still are disposed of best by flushing to sewers as soon as they are no longer needed. This limited list of medications includes those that remain unused as well as certain ones (such as transdermal patches) that retain appreciable residuals after being completely or partially used. A list of these medications is highlighted by the White House Office of the National Drug Control Policy as part of their drug disposal guidance for consumers [23] (http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf). This guidance, however, is in a state of flux and is subject to modification, especially because of the intricacies presented by the Controlled Substances Act [24] (http://www.deadiversion.usdoj.gov/fed_regs/rules/2009/fr0121.htm). Note that unanticipated adverse ecological consequences also have occurred from the veterinary use of drugs that have resulted in drug-contaminated waste; two noteworthy examples are pentobarbital and diclofenac, which have resulted in considerable adverse impacts on populations of raptors and vultures [3].

A major unanswered question, however, is what portions of environmental residues of APIs originate as a result of intended therapeutic use, disposal, and washing or bathing. The approach presented here is intended for assessing the significance of these alternative pathways. The API contributions from these pathways are important in order to gauge the possible efficacy of pollution prevention efforts for reducing environmental loads and to assess the hazard for humans. Evidence already exists that reducing the accumulation of drug waste has benefits with respect to health care, for which waste reduction is particularly attractive as a strategy, because it imposes no limits on the overall usage of medications and it does not adversely affect the quality of health care [17] and may even serve to improve it [16].

In calculating predicted environmental concentrations, a variety of assumptions are required for the many inputs for a model's variables [25–27]. Three factors for which practically no empirical data are available are: the portions of medications that are disposed to sewers; the portions of APIs discharged to sewers resulting from the use of medications designed for dermal use; and the contributions from oral or parenteral formulations that are washed from the skin as a result of excretion from eccrine and apocrine sweat.

With respect to disposal, the extensive examination of predicted environmental concentration calculations performed by Kostich and Lazorchak [25] had to assume that the following portions of medications are disposed to sewers: medicines prescribed for short-term therapy (15%), long-term therapy (5%), and topical medicines (33%). Unfortunately, there are no empirical data to validate these assumptions. These generalizations are likely much too high or too low when applied to many specific APIs.

Also with respect to disposal, another factor must be evaluated for delivery devices, especially transdermal systems, because the API residuals in used, high-content devices can be substantial (over 50% of the original API can remain); with patches, whose initial API content can exceed by 20-fold that which is eventually absorbed, more than 95% of the initial API content can remain in the used patch [28]. This means that for used patches, which are commonly disposed of by flushing, the

majority of the API from the used medication can be disposed of eventually via sewers. Also, although the portion of the API excreted via urine and feces is considered (as a major contributor), no consideration is given to the portion of the unchanged API that might be excreted via sweat (because such data are extremely rare for prescription and OTC drugs) or the portion remaining on the skin after dermal application. Finally, the need to assume single, average values for individual factors for all APIs in general does not accommodate for the extreme ranges that actually exist among individual APIs.

Once a prescription drug is dispensed to an end user or an OTC medication is purchased, there are at least seven factors that have received little attention in previous modeling efforts and that determine whether disposal or bathing become important factors with respect to the overall occurrence of APIs in the aquatic environment (Table 1). Figure 1 summarizes these factors and shows their interconnections.

In the determination of the significance of these secondary routes by which APIs can enter the environment, several key questions are prompted. For APIs with a presence in ambient waters, what individual portions or individual APIs originate from direct disposal of leftover, unwanted medications; release by bathing of residues remaining on the skin from dermally applied medications; and release by bathing of residues remaining on the skin from excretion via sweat? Another source, related to the last two factors, is laundering, because drugs present on the skin can be transferred to clothing and bedding. Note that the release of topically applied drugs from domestic animals is also a source of APIs in the environment [29].

From these data, rankings could be prepared eventually to show which drugs contribute the most and least mass of APIs to the environment via disposal and via washing, in terms of absolute amounts and relative to the amounts contributed directly via excretion. This would allow the development and better targeting of pollution prevention measures and better targeted environmental monitoring.

Regardless of what percentage of APIs in the environment might be contributed to sewers by disposal or bathing, these practices could lead to transient, episodic spikes in API concentrations. These momentary concentrations could be orders of magnitude greater than those being introduced continually via direct excretion [16]. Note, however, that for those APIs for which disposal and bathing contribute the largest portion of their presence in ambient waters, this still would not reveal the relative importance of disposal or bathing with respect to the potential for actual adverse impact to the environment.

For a given API, the total mass discharged to sewers as a result of disposal and washing or bathing (WM) could be calculated from the factors in Table 1 according to

$$WM = UR (\text{mass}) \times [(DP \times PDs) + (SMP + RD + TD)] \quad (1)$$

The relative significance (S_r) of the contribution from these alternative routes (versus direct excretion) for a particular API could be calculated by dividing the total mass contributed by disposal and washing or bathing by the total mass excreted unchanged in urine and feces

$$S_r = WM \times [(UR - WM) \times PMP]^{-1} \quad (2)$$

where UR is the usage rate, DP is the disposal potential

Table 1. Factors determining the significance of disposal and washing or bathing in the discharge of active pharmaceutical ingredients (APIs) via sewers^a

Factor	Term	Importance to contributing APIs	Relevant information
Usage rate	UR	Total mass or moles of API consumed per time period (mass/time). Disposal of little-used medications contributes insignificantly to the overall combined levels of APIs in the environment, regardless of the portion disposed. This contrasts with disposal of small portions of medications that are used in large quantities.	Usage includes prescribed and over-the-counter amounts that are: (1) purchased in-country (including gray and black markets), (2) distributed for free (e.g., physician samples, community programs for indigents, and charitable contributions from manufacturers), and (3) imported from other countries. One complication (discussed in the text) is that sales and disposal are not linked in time. Disposal always occurs from sales made in the past. This time lag also can vary, forcing gross simplifications for the purposes of modeling.
Disposal potential	DP	Portion of total API left over versus amount that was meant to be totally consumed as directed.	One complication is the portion of leftover drugs that are indefinitely stockpiled, never disposed of. Also requiring disposal are used delivery systems still containing residual APIs (see "Type of delivery system or container" below). The potential for a drug to be disposed of is probably partly a function of geographic locale and time of year (e.g., for seasonal medications).
Method of disposal	PDs	Portion of API disposed to sewers (flushed or poured down drains, such as in-sink garbage disposals) versus all other routes or fates (e.g., trash, burial, collection events, diversion, permanently stockpiled on site, or charitable contributions). Note that charitable contribution is a route generally relevant only in controlled health care settings (e.g., physician donation of unexpired samples).	How (and sometimes whether) a medication is disposed of is partly a function of the design of the medication's packaging. Some packaging (such as unit-packaged drugs) is more amenable to discarding to trash (because of the effort involved in removing from the package in order to flush), whereas other packaging is more likely to result in disposal to sewers (e.g., bulk-packaged tablets/capsules and liquids); excess medication that remains in delivery devices or delivery systems is also more prone to disposal via trash rather than sewers (see "Type of delivery or container" below), although some delivery systems (such as patches) that contain potent APIs (which can cause unintentional poisonings) or those subject to abuse still may require disposal via flushing. Charitable contributions (and drug sharing) merely postpone the eventual fate of APIs but might serve to reduce the need for new purchases.
Primary metabolic profile	PMP	Combined portions of systemic API excreted unchanged into urine and feces and portion of ingested dose not absorbed by the gut. Data come from pharmacokinetics studies. It is important to note, however, that excretion data can be highly variable for a given API and are often difficult to find in the published literature [131].	There are two extremes: (1) extensive metabolism, where little of the parent API (or glucuronides susceptible to hydrolysis) is excreted, and (2) extensive excretion in urine and feces, where the unchanged parent API is excreted, sometimes stoichiometrically; some drugs, such as neomycin, are absorbed poorly after oral or parenteral administration and therefore are excreted largely unchanged because of no opportunity for metabolism (even if the small absorbed portion is metabolized extensively). One complication is the excretion of glucuronides having the potential to later be hydrolyzed to products including the parent API; conjugates therefore often can be treated as the parent API. Excretion contributes primarily via urine and feces. For APIs that are metabolized extensively, alternative routes to sewers become comparatively more significant.
Secondary metabolic profile	SMP	Portion of systemic API excreted unchanged via sweat (and other minor routes such as vomitus).	When excreted via sweat, APIs tend to be excreted unchanged. The relative contributions from sweat compared with urinary or fecal excretion are unknown and comparatively much smaller but measurable for many drugs. The end result is that this portion is washed from the skin or transferred by bodily contact to other surfaces (including people).
Route of delivery (bioavailability)	RD	Portion of API remaining on the skin after topical application, whether the medication is designed for topical use, where little API is actually absorbed dermally, and the majority remains on the skin. Medications designed for external use efficiently introduce APIs to sewage via bathing or washing (as well as laundering), as if they were disposed directly. These pharmaceuticals serve essentially as inputs tantamount to unintended disposal.	Medications designed for topical use, such as gels, creams, lotions, sprays, tinctures, ointments, plasters, shampoos, foams, powders, and soaps, or for transdermal delivery (where only a fraction is actually absorbed across the skin and a portion is retained on the surface of the skin) are efficiently discharged to sewers as a result of their intended use, via bathing or washing. These medications contribute APIs to sewage as if they were disposed directly. Transdermal patches also leave residual on the skin, residue that will later be washed away as if it had been applied topically.

Table 1. Continued

Factor	Term	Importance to contributing APIs	Relevant information
Type of delivery system or container	TD	Portion of dose remaining in the delivery system and discharged to sewers. Delivery systems and containers often can have large amounts of residual APIs (some of which remains inaccessible because of the design of the system's device or containers). These residues can then serve as used medications that then require disposal.	Drugs administered via delivery devices (e.g., transdermal patches or vaginal rings) can retain very large portions of their total APIs after use is completed because only fractions of their contents are actually delivered systemically (e.g., as little as 15% or less). Containers (e.g., injection vials) and injection or infusion devices also can contain residues. When disposed of after use, these can contribute substantial quantities of APIs. These used devices need to be factored in with their unused new counterparts as contributors during disposal. Although most new or used devices are not disposed to sewers, some must still be flushed according to the U.S. Office of National Drug Control Policy guidelines (one example being fentanyl patches) ^b . Important to note is that the very drugs that are subject to waste minimization via charitable donations (as set up by various states) are the same ones that would otherwise most likely be disposed into the trash—not the sewer—simply because of the time and effort required in removing each dose from its packaging. It is most likely that the drugs currently disallowed for donations play larger roles in disposal via the sewer.

^aThe factors in this table can be used in the following two equations (described in the text): WM (API mass discharged to sewers from disposal and washing) = UR (mass) \times [(DP \times PDs) + (SMP + RD + TD)] and Sr (relative overall significance of secondary routes) = $WM \times [(UR - WM) \times PMP]^{-1}$.

^b[23] (http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf).

(portion of API leftover), PDs are the methods of disposal (portion disposed to sewers), PMP is the primary metabolic profile (portion excreted in urine or feces), SMP is the secondary metabolic profile (portion excreted by other routes such as sweat), RD is the route of delivery (portion remaining on skin after dermal application), and TD is the type of delivery system or container (portion of dose remaining in device).

As the portion of an API in sewage resulting from the alternative disposal routes increases (as WM increases or as the portion used as intended decreases), Sr increases. As the portion resulting from disposal decreases, Sr approaches zero. In the absence of values for UR , however, Sr cannot be evaluated fully.

One factor regarding the correlation of disposal with intended usage needs to be emphasized, because it would complicate efforts at modeling. Sales are not linked in time to disposal. Disposal always occurs from sales made in the past. This time lag also can vary, forcing gross simplifications for the purposes of modeling. The significance of the time lag between dispensing and when leftovers will be disposed of diminishes as the time period examined increases. In other words, the correlation over time between sales figures and if or when the drug is disposed of will improve as the time period examined increases (perhaps extending out to the shelf life of the drug). The consistency of correlation between sales and disposal over time is a function of the consistency in sales. For a medication whose usage (as reflected by sales) remains constant over time, the rate of disposal during a given time period probably will correlate best with the sales during that same time period even though the disposal results from sales during a prior time period. With this complication in mind, special circumstances become evident when disposal could become the primary source of an API in the environment. For example, the environmental contributions from disposal might be greater than those from intended usage if the sales for a

medication dropped precipitously, for example, if the drug lost market share quickly or if it was recalled by the U.S. Food and Drug Administration. Likewise, the relative contributions from disposal would be less if a medication experienced a rapid increase in sales, for example, an antiviral or antimicrobial drug dispensed during epidemics.

Clearly, to model the contributory origins of APIs present in the environment requires far more empirical data than currently exists. The empirical data necessary for many of the factors in Table 1 are not available. What is currently known regarding these previously unexplored factors is discussed in the remainder of the present study.

Sweat as a route of excretion

Although most unmetabolized, parent APIs are excreted via feces and urine, often overlooked is that measurable quantities of many APIs or their metabolites can be excreted via sweat. Excretion via sweat has been known at least since the 1950s, with one of the very early studies being published by Thaysen and Schwartz [30]. Although the initial studies (up until the 1990s) focused on therapeutic drugs, interest has since shifted to illicit drugs, where sweat has become a matrix for monitoring illicit drug usage. Most of this literature therefore deals with what is known as sweat-patch testing as a means of noninvasive monitoring; see overviews by Rouen et al. [31] ([http://notes.med.unsw.edu.au/ndarcweb.nsf/resources/TR_18/\\$file/TR.120.PDF](http://notes.med.unsw.edu.au/ndarcweb.nsf/resources/TR_18/$file/TR.120.PDF)) and Fortner [32]. Upon oral ingestion (or any other means of drug delivery), excretion of the original dose via sweat can continue for anywhere from a day to weeks. Excretion can begin in less than an hour and varies from drug to drug. Excreted residues then can be collected on absorbent patches affixed to the skin. The concentration in sweat might vary depending on the sweating rate, with the rate for some APIs remaining the same and others increasing with increasing rate of sweating [33].

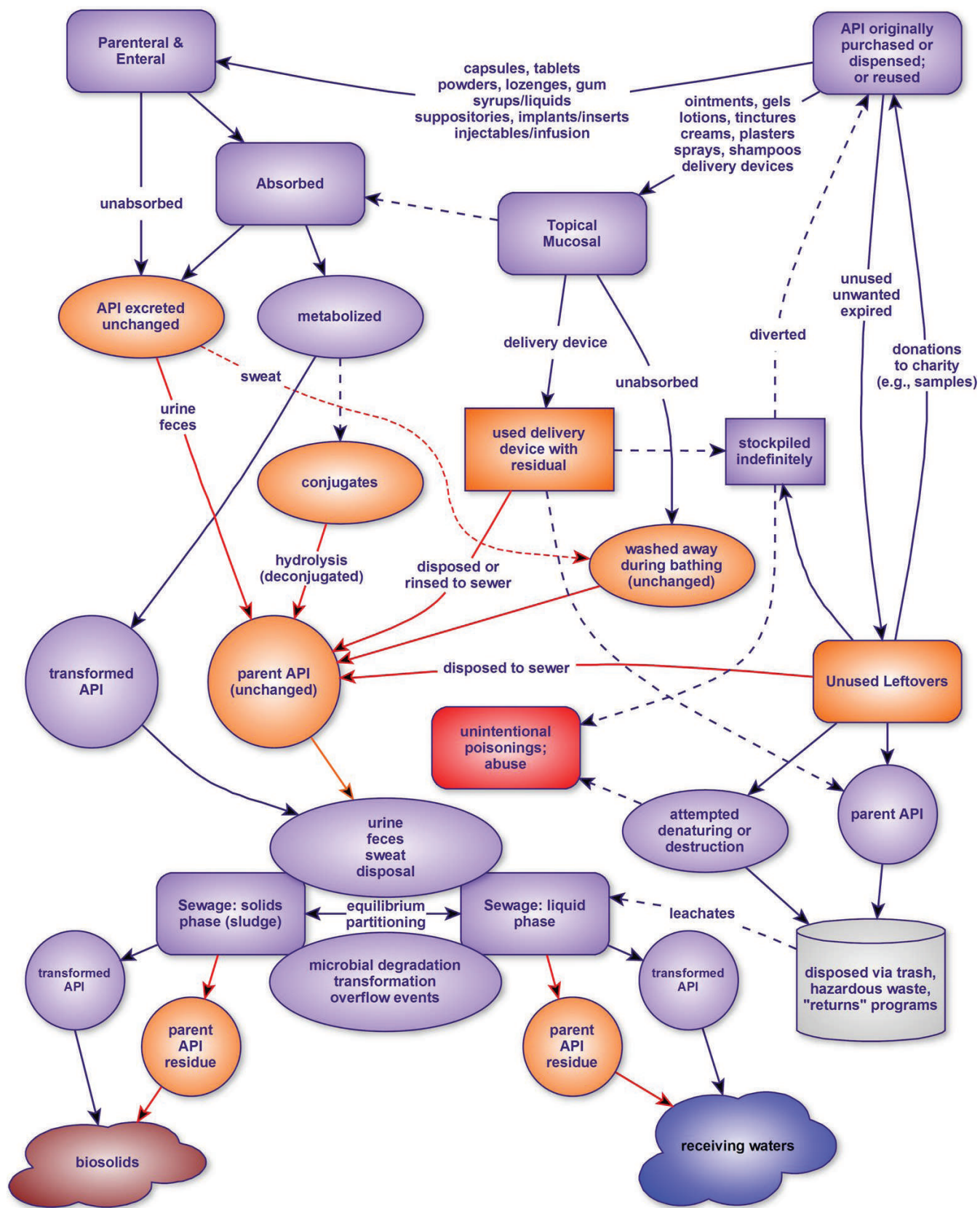


Fig. 1. PharmEokinetics of active pharmaceutical ingredients (APIs).

Sweat contributes to two pathways for transporting APIs to the immediate and surrounding environments: direct exposure of others and contamination of surrounding objects via dermal contact (e.g., drugs released in sweat through the rows of pores located along fingerprint ridges are known to be deposited in fingerprints) [34] and release of APIs directly to sewers, via bathing and other hygiene activities.

Insensible sweat (passive diffusion through the skin) is produced at a rate of 300 to 700 ml/d per individual (at a rate of up to 100 g/m²/h in air temperatures below 31°C). With rigorous exercise, sensible sweat production (primarily from eccrine glands and secondarily from apocrine glands) can increase to 2 to 4 L/h for short periods or 1 L/h for prolonged periods. Eccrine sweat glands are distributed widely across the body, whereas the apocrine glands have very limited distribution; apocrine glands excrete via the hair follicles. As the largest organ of the body (and comprising 10% of body mass), the average skin surface area is very roughly 2 m² [35]. Drugs become incorporated with sweat via passive diffusion through cellular membranes driven by the concentration gradient established by the free drug in plasma and fat depots. Because sweat is normally very slightly acidic (pH <6.5) and blood is slightly alkaline, those drugs that are primarily nonionized in plasma experience a negative concentration gradient across the skin (because they become ionized in the accumulating sweat). Therefore, excretion and accumulation in sweat favor those APIs that are neutral at around pH 7.4. See overviews by Tobin [36] and Fortner [32]. Excretion via sweat also seems to discriminate against polar metabolites. One extreme example is cocaine, which is excreted extensively in urine as ecgonine methyl ester and its hydrolytic product, benzoylecgonine. But in sweat, cocaine is excreted extensively in its unchanged parent form [37].

Although the concentrations of APIs in the aqueous natural environment are generally very low [7,38], usually less than 1 µg/L, it is not known what the relative contributions might be among urine or fecal excretion, disposal, or bathing. The extent and magnitude of excretion via sweat and its significance with respect to contributing APIs to sewage are clearly largely dependent on the amount (and type) of sweat that is generated per day (which can vary widely depending on the individual, the level of activity, the level of hydration, the temperature and humidity, the level of stress, the content and distribution across the skin surface of apocrine and eccrine sweat glands, and the health and skin condition of the individual), the pH of the sweat, the plasma concentration and p*K*_a of the API, and the bathing frequency, among other factors.

Despite the use of sweat-patch testing for illicit drugs, the published quantitative data on excretion of commercial drugs via sweat is rather limited. Most of the major studies are summarized in Table 2; note that in this discussion sweat from eccrine and apocrine sources is not distinguished. The data on excretion via sweat are not obtained generally for the PK studies performed on a drug for registration purposes. Instead, these data are obtained during independent research studies. The excretion data provided by PK studies perhaps could be used, however, as an indirect indicator of the possible extent of excretion via sweat (e.g., by examining mass balance discrepancies of the percentage of an API not accounted for by excretion via urine and feces), but these studies are done generally under comfortable conditions where excretion via sweating would be minimized. If the excreted API is removed

continually (e.g., via bathing or periodic recontact with clothing), then the amount reabsorbed would be minimized. Also note that only recently it has become possible to determine accurately the actual concentration of xenobiotics in sweat as determined with sweat-patch testing. Appenzeller et al. [39] normalized the quantities collected on patches to the content of sodium ion. Without normalization, excretion rates can be estimated only roughly by making assumptions regarding sweat volume production rate and collection efficiency.

Significance of excretion via sweat as a contributor to environmental residues

By performing some rough calculations, a general estimate of the relative contribution of APIs from sweat versus fecal or urine excretion can be obtained. The total amount of many APIs excreted via sweat may comprise very roughly up to 2% of the total oral (or parenteral) dose. For those APIs that are the most extensively metabolized (e.g., when the percentage of the parent API excreted unchanged and not in conjugated forms is less than 2%), the contribution from sweat could prove to be an important factor.

The following serve as examples. With the ratio of the sweat-patch area and body surface area, Pichini et al. [35] derived a crude estimate of the total amount of 3,4-methylenedioxymethamphetamine excreted via sweat 24 h after a 100-mg oral dose. The mean total mass excreted via sweat was estimated as 0.6 mg, with an upper range of 1.5 mg (because of large interindividual variability). This amounts to at least 0.6% (with an upper range of 1.5%) of the total excreted (assuming 3,4-methylenedioxymethamphetamine is excreted extensively unchanged).

After daily doses of 1,500 mg of ciprofloxacin, assuming a conservative rate of sweat production of 1 L/d and assuming sweat concentrations ranging from 2 to 23 µg/ml [40], the total daily excretion of ciprofloxacin in sweat would range from 2 mg/d (2 µg/ml × 1,000 ml/d) to 23 mg/d. Assuming that ciprofloxacin is excreted extensively unchanged, the fraction excreted via sweat would be roughly 0.1 to 1.5% of the total available.

For drugs that are excreted extensively unchanged, the portions contributed by sweat are measurable but, as seen from these examples, not very significant (e.g., roughly less than 2%). For these drugs, the importance of excretion via sweat would more likely be dispersion to the immediate environment via dermal contact. For drugs that are metabolized extensively, however, the contribution to excreted APIs via sweat could be considerable and probably should be considered in predictive fate models.

Consider another example applied to a drug (fentanyl) that is metabolized more extensively (less than 8% excreted unchanged in the urine). In this case, the majority of the dose that is excreted might be excreted via sweat rather than urine. Schneider et al. [41] calculated the amount of fentanyl excreted via sweat as ranging from 19 to 150 µg/d, which translates to 3 to 25% of the total daily dose (600 µg). Relative to the amount imputed to be excreted in the urine (8%), the relative amount contributed by sweat would have ranged from 40 to 300%. As for many drugs, measurable quantities also are excreted via the hair (through apocrine sweat), but this is harder to quantify on a per-body basis. So for a drug that is not excreted extensively in the urine or feces unchanged, the portion excreted via sweat could be comparatively significant.

Table 2. Overview of active pharmaceutical ingredients (APIs) measured in sweat

API or class (Chemical Abstracts Service Registry No., freebase)	Concentration (on basis of volume of sweat) or mass collected on sweat patch or wipe	Reference
β -Lactam antibiotics	Mean maximum concentrations: benzylpenicillin (axilla, 2.6 $\mu\text{g/ml}$); ceftazidime (axilla, 28.4 $\mu\text{g/ml}$; forearm, 11 $\mu\text{g/ml}$); ceftriaxone (axilla, 8.9 $\mu\text{g/ml}$; forearm, 2.5 $\mu\text{g/ml}$); cefuroxime (axilla, 7.8 $\mu\text{g/ml}$); phenoxymethylpenicillin (axilla, 0.4 $\mu\text{g/ml}$)	[46]
Aminopyrine (58-15-1) and antipyrine (60-80-0)	Extensively excreted via sweat; up to 14 $\mu\text{g/ml}$ after single 1-g oral doses	[132]
Amitriptyline (50-48-6)	Extensive excretion in sweat after acute poisoning (0.78–0.2 mg/L)	[133]
Amphetamine (300-62-9)	Median (range) after low and high doses: 15.5 (6.5–40.5) and 53.8 (34.0–83.4) ng per patch	[134]
Carbamazepine (298-46-4)	Present in sweat	[33]
Clomipramine (303-49-1)	Extensive excretion in sweat after acute poisoning (3.267 mg/L)	[133]
Ciprofloxacin (85721-33-1)	Extensive excretion in sweat after acute poisoning (0.28 mg/L)	[133]
Cocaine (50-36-2)	2.2–5.5 $\mu\text{g/ml}$ (during 7-d course of 750 mg/d oral dose)	[40]
	33–3,579 ng per patch per 30 min (from heat-induced sweating)	[135]
	43–3,799 ng per wipe	[136]
	ng/ml: cocaine (378), benzoylecgonine (78.7), ecgonine methyl ester (74)	[37]
Codeine (76-57-3)	Up to 315 ng/patch (140 ng/L) during 1 week after nasal doses of 50–126 mg	[137]
	11–1,123 ng per patch per 30 min (from heat-induced sweating)	[135]
	0–225 ng per patch per week	[138]
	2–127 ng per patch per day (after 90-mg oral dose)	[139]
Clomipramine (303-49-1)	Extensive excretion in sweat after acute poisoning: 0.28 mg/L	[133]
Clozapine (5786-21-0)	49–5,609 ng per patch in sweat after oral dosing of 200–700 mg/d	[140]
Diazepam (439-14-5)	0.1–6 ng per patch total after one dose (first detected 2–4 h after dose; also detected was nordiazepam but not oxazepam)	[141]
	Extensive excretion in sweat after acute poisoning	[133]
Doxorubicin (23214-92-8)	Observed	[47,48]
Fentanyl (437-38-7)	Concentrations in sweat varied from 0.17 to 1.02 ng/ μl	[41]
Fluconazole (86386-73-4)	High concentrations in sweat, all above the serum concentrations	[142]
Griseofulvin (126-07-8)	200–300 ng/ml independent of sweat volume; after 0.5-g oral doses at 12-h intervals	[143]
Itraconazole (84625-61-6)	Mostly excreted through sebaceous glands; moderately excreted by the sweat glands	[144]
Loratadine (79794-75-5)	Detectable on skin 40 min after ingesting a 10-mg oral dose	[44]
MDMA (“ecstasy”) (3,4-methylenedioxy-methamphetamine) (42542-10-9)	Mean, 542 ng per patch per day; range, 42.4–1,326 ng per patch per day accumulated after a single 100-mg oral dose (first observed 1.5 h after dose)	[35]
Methadone (76-99-3)	Presence correlated with urine	[145]
	Detected in sweat of heroin addicts undergoing treatment	[146]
Methamphetamine HCl (51-57-0)	Median (range) after low and high doses: 63.0 (16.8–175) and 307 (199–607) ng per patch	[134]
	Constant rate of 1.4 $\mu\text{g/ml}$ after oral dose of 10 mg	[147]
Methotrexate (59-05-2)	Mean 725 ng/ml (mean maximal concentration 1.7 $\mu\text{g/ml}$)	[50]
Opiates	Median concentrations (ng/ml): heroin (10.5), 6-acetylmorphine (13.6), morphine (15.9), and codeine (13.0)	[148]
Phenobarbital (50-06-6) (phenobarbitone)	0.5–33 ng per patch per day (first observed 3 h after 100-mg oral dose)	[139]
	Concentration in sweat found to increase with increasing sweat flow	[33]
Phenytoin (57-41-0)	Concentration in sweat was independent of sweat flow	[33]
Sulfonamides	One of the very early studies documenting that drugs are excreted via sweat; sulfapyridine, sulfathiazole, sulfadiazine, and <i>p</i> -aminohippurate ranged up into the tens of $\mu\text{g/ml}$	[30]
Tetrahydrocannabinol (1323-34-8)	0.9–3.11 ng per patch per day	[149]
	Below detection limit after daily ingestion of 14.8 mg	[150]

With the data of Schneider et al. [41], a series of calculations were made using a different approach. The minimum mass of fentanyl excreted per day via sweat could be calculated from the minimum amount found on a sweat patch (5.7 ng) and with 1.5 m² as the body skin surface area. The maximum mass of fentanyl excreted per day via sweat could be calculated from the maximum amount found on a patch (88 ng) and with 2.0 m² as the body skin surface area. By calculation of the number of patches that could hypothetically cover the body (total area in square millimeters divided by 1,480 mm² per patch) and with the fraction of a day during which sweat was collected (0.42 d = 611 mins), the range of fentanyl mass excreted via sweat would have been 17 to 284 $\mu\text{g/d}$ per body. Because the presumed daily dose was 600 μg , the percentage of the dose excreted via sweat could have ranged from 2.8 to 47%. It must be noted, however, that the

heterogeneity of sweat excretion (as well as the concentrations of the APIs in different microenvironments of sweat) could vary greatly. Therefore, all extrapolations of total amounts of API excreted are subject to considerable error. Insufficient data exist regarding API excretion to fully understand total-body excretion via sweat.

Assuming that only 8% of a fentanyl dose is excreted unchanged via urine each day (which in this example is 48 μg), the range of mass excreted via sweat would have been equivalent to that excreted from the following number of daily doses delivered via patch (in terms of relative contributions of fentanyl to sewage): 17/48 to 284/48 = 0.35 to 5.9. Of course, there are many variables, including actual skin area over which sweating occurs, uniformity of sweating over the body, uniformity of sweating rate (which could be seen as varying over a 15-fold range), uniformity of excretion via

sweat, uniformity of rate of fentanyl absorption (which determines plasma concentration), etc. But from these crude calculations, the contribution of fentanyl to sewers via washing of sweat from the body could be equivalent to 30 to 600% of the mass originating from urine, in agreement with the estimates provided by Schneider et al. [41].

With respect to medications, appropriate exposure results from use by those for whom the API was intended and for whom the API was deemed safe, and inappropriate exposure results from use by those for whom the API was not intended (or for whom the API is contraindicated or for whom the exposure was unwelcome). Inappropriate exposure to APIs via interpersonal dermal transfer (or hand–mouth contact) might prove to be a more important source of exposure than exposure via drinking water. A comparative yardstick might be that the occurrence of APIs in sweat can reach concentrations at least three orders of magnitude higher than those eventually occurring from recycling of residues from the environment via drinking water. Drinking water concentrations are generally much less than 1 $\mu\text{g/L}$ [42] versus concentrations in sweat, which are roughly 1 $\mu\text{g/ml}$ and higher. The very limited numbers of oral or parenteral APIs that eventually make their way into finished drinking water [42] must survive a series of steps that successively reduce their concentrations, including absorption and metabolism, sewage treatment, dilution in receiving water, environmental transformation, sorption to sediments, and final polishing to produce finished drinking water. A broader spectrum of APIs at much higher concentrations therefore could occur in sweat, including those that otherwise are metabolized extensively.

Although direct exposure to APIs via contact with the sweat of others has unknown significance, the APIs excreted from the skin of those taking medications (including those undergoing chemotherapy) have the potential to be released fully from the entire body in public spas and swimming pools. This is a scenario where inappropriate or unwanted dermal contact could occur to concentrations higher than those in waters from the ambient environment (e.g., >1 ppb, $\mu\text{g/L}$). For those undergoing polypharmacy, the release of multiple APIs likely would occur.

The use of recently developed ambient surface sampling/direct desorption mass spectrometry techniques (such as Desorption Electrospray Ionization [DESI], Desorption Atmospheric Pressure Chemical Ionization [DART], and Direct Analysis in Real Time [DAPCI] or single-particle aerosol mass spectrometry) for very fast in vivo surface analysis of tissues could prove to be very useful for a broad survey of the prevalence of APIs excreted to the surface of skin and items commonly touched by the public. These techniques excel at rapid identification of chemicals sorbed to complex solid substrates. The abilities of these techniques to readily detect drugs and metabolites on the skin have been demonstrated by Martin et al. [43], Takats et al. [44], and Williams et al. [45]. Application of this type of technique could be used to quickly reveal the extent and magnitude of drug excretion via skin and indirect contamination by APIs by dermal transfer.

A final note is warranted regarding the significance of excretion via sweat. Much has been published regarding the growing prevalence of antibiotic resistance, especially among human pathogens. Excretion of antibiotics via sweat has been proposed as a possible major means of quickly promoting and spreading resistance. The comparatively higher and sustained concentrations on skin can serve to expose dermal bacteria,

which then can be transferred readily to other locations or people. This has been demonstrated by Høiby et al. [40,46], who documented the excretion onto the skin of floxacin and β -lactam antibiotics where bacteria would come into ready contact. This could be an overlooked cause of transmission of multiresistance among bacteria in hospitals and other care facilities that routinely administer antibiotics.

Chemotherapeutics in sweat

Excretion of chemotherapeutics via sweat is well established, but its overall significance as a secondary exposure route for others is not. That chemotherapeutics are excreted via sweat is reflected by its becoming recognized as a primary cause of a variety of adverse cutaneous effects during chemotherapy (e.g., doxorubicin), including hand-foot syndrome (hand-foot skin reaction) [47,48] and hyperpigmentation and alterations to nails. The specific formulation can enhance the excretion of the API via sweat.

But with respect to unanticipated exposure, this route of excretion holds the potential for promoting subsequent incidental exposures for others and poses higher risks than for other drugs because of the extreme cytotoxicity and mutagenicity of oncolytics. Excretion via sweat undoubtedly also plays a role in the development of hypersensitivity to certain other drugs because it ensures skin contact with drugs not intended for dermal application.

Early studies indirectly measured the excretion of chemotherapeutics via sweat by mutagenicity assays. For example, a 1988 study showed that sweat collected from patients treated with cyclophosphamide and other antineoplastics showed greater mutagenicity than controls 8 h after treatment [49]. A mean concentration of methotrexate in sweat was measured as 725 ng/ml (mean maximal concentration of 1.7 $\mu\text{g/ml}$), calculated as translating into excretion of 300 μg per day through sweat [50]. Other studies provide strong indirect evidence that sweat conveys chemotherapeutics outside the body. These studies have focused on studies of occupational exposure [51], where bedding becomes contaminated and serves as a route of exposure for health care workers and especially those working outside hospitals, such as home care providers [52]; workers in laundry facilities were noted as having the potential for higher exposures to antineoplastics than oncology nurses during the handling of bed sheets.

Chemotherapeutics and pulmonary exposure

Occupational exposure to antineoplastic agents has been well documented, especially direct exposure from the compounding, preparation, administration, and disposal of these highly toxic chemicals. Of the many routes of exposure, however, the excretion of residues via sweat (and breathing) of patients has been less understood. Several chemotherapeutics have appreciable vapor pressures. These include carmustine, cyclophosphamide, ifosfamide, thiotepa, and mustargen [53]. Others have much lower vapor pressures: doxorubicin, cisplatin, etoposide, 5-fluorouracil, and mitomycin. Kiffmeyer et al. [54] determined that the vapor pressures of five antineoplastics (carmustine, cisplatin, cyclophosphamide, etoposide, and fluorouracil) and one antimicrobial drug (fosfomycin) were all low but with carmustine having a vapor pressure one order of magnitude higher. Nevertheless, cyclophosphamide still was detected in the gas phase in 7 out of 15 locations, at levels ranging from 45 ng/m^3 to 13 $\mu\text{g/m}^3$. Inhalation of excreted cytotoxics also could be enhanced for

those who work in laundry facilities that clean bedding and clothes from patients [52], although Fransman et al. [55] did not detect vaporization of antineoplastics from bedding at a laundry facility.

These data also indicate the theoretical potential for pulmonary exposure to the expired breath from those undergoing treatment. Fransman [56] (<http://igitur-archive.library.uu.nl/dissertations/2006-1003-200854/full.pdf#page=131>) notes that exposure to people or animals associating with those undergoing treatment with antineoplastic drugs has not been investigated. Unintended exposure in these settings could prove important with the increasing usage of antineoplastics in outpatient and veterinary clinics and because more intimate and chronic interpersonal contact can occur in the household.

Dermal application

The continuing trend toward the dermal application of drugs will increase the probability of drugs being introduced to the environment as a result of release via bathing of concentrated residues remaining on the skin and discarding the used delivery device (e.g., patches), which often contains very high levels of residues (sometimes considerably greater amounts than would have been needed orally). It also could increase the unintended risk of exposure to others by direct dermal–dermal contact and transfer and from indirect exposure via contact with contaminated objects.

A wide array of drugs are available in topical form [57,58] (<http://www.empr.com/dermatological-disorders/category/28/0/>). See Table 3 for those that are employed commonly. The concentrations of APIs in these topical preparations range from a fraction of a percent to 5% or more, by weight. They include potent steroids, antibiotics, pesticides (e.g., lindane and malathion), immunomodulators (e.g., pimecrolimus), a psychotropic (doxepin), and cytotoxics (e.g., fluorouracil). Some of these drugs have no routine oral use (because of toxicity or facile metabolism), such as tolnaftate, ciclopirox, flurandrenolide, and imiquimod. For these drugs, bathing (and disposal) is most likely to account for the vast majority of any residues that might be detected in the environment. For others that also have equivalent oral uses but are metabolized extensively (little excretion of unchanged API), bathing still could be a major contributor of residues to sewage.

Those APIs with equivalent dermal and oral uses, which are excreted extensively unchanged, are highlighted in Table 3. This group comprises the only topical APIs where washing and bathing could be competing with excretion from oral or parenteral use in terms of contribution to the environment and therefore where bathing would be a less important source. The APIs in this group (highlighted by footnotes in Table 3) are acyclovir, doxepin, fluorouracil, metronidazole, neomycin, nystatin, polymyxin, sulfadiazine, tobramycin, and tretinoin. All of the remaining APIs in Table 3 (those not highlighted), if detected in the environment, could have origins primarily from dermal application. These latter APIs could be ranked according to overall usage rates (e.g., total mass sold) and potency to guide the selection of those to include in targeted monitoring in order to gauge their potential frequency and extent of occurrence in the environment. In terms of accounting for bathing as a source term in fate models, another source of APIs on the skin to account for is the residue remaining after the removal of a transdermal device such as a patch.

Among those topical or transdermal medications with no oral equivalents and that also have minimal excretion (of the absorbed dose), those sharing common mechanisms or modes of action (and for which dose addition therefore might be an important exposure consideration) could prove to be the most important with respect to environmental hazard. The corticosteroids, for example, all affect the hypothalamus–pituitary–adrenal axis, especially those that are not approved for oral or parenteral use. Many of the antibiotics could promote selection for antibiotic resistance on the surface of skin because their localized concentrations can be extremely high [40,46].

Comparing the mass of the API residue remaining in a used delivery device or the residue remaining on the skin with the mass that would be excreted if the API had been taken orally (or endogenously produced, such as certain hormones) can provide insight as to the relative significance of the pathways. For example, one recently introduced formulation is a metered-dose transdermal spray of estradiol (EvaMist®, Vivus) where each metered dose (containing 1.7% estradiol) delivers 1.53 mg of 17 β -estradiol. An estradiol gel (Estrogel®, Solvay Pharmaceuticals) contains 0.06% estradiol, and a 1.25-g dose of the formulated gel contains 750 μ g. The various reference ranges for urinary excretion of endogenous estradiol (assuming no deconjugation, which can be substantial [59]) range from 10 to 100 μ g/d (depending on the woman's age and health) or up to 30 mg/d (during pregnancy) [60]. Assuming a dermal estradiol absorption efficiency of 17% (24-h absorption reported for Estrogel [61]), one dose of the spray or gel could leave on the skin 1.3 or 0.6 mg of estradiol, roughly the endogenous amount excreted daily by 6 to 130 women who are not pregnant.

Another example is testosterone. A high-content gel form of testosterone (Androgel®, 1% testosterone) has a maximum daily dermal dose of 100 mg of testosterone. Approximately 10% is systemically absorbed. Assuming that the remainder (90 mg) is washed eventually from the skin and assuming that the combined urinary excretion of free and conjugated endogenous testosterone from adult males ranges up to 0.3 mg/d (calculated from Al-Dujaili [62] and Timón Andrada et al. [63]), the daily use of testosterone gel could contribute a mass of testosterone equivalent to that excreted naturally from 300 (90/0.3) males.

An example of a dermal drug that also has oral formulations is ketoconazole. Once absorbed, only a fraction of a percent is excreted unchanged, meaning that, except for the unabsorbed oral dose, bathing (and disposal) also could be the major source of this API in the environment. To assess the significance of dermal drugs as a contributory route to the environment, the following data would need to be compiled for each: fraction of dermal API not absorbed across the dermis (or residue left on skin after removal of a transdermal device), fraction of oral form not absorbed from the gut, and fraction of API excreted unchanged (as well as in easily hydrolyzable conjugates).

Pollution reduction

Possible approaches that might help to reduce the introduction of dermal APIs to sewers prior to bathing include removal of as much of the product from the skin as possible with an absorbent wipe such as toilet paper or cotton balls and then disposing in the trash; for preparations that have dried on the skin (such as gels), adding an oil (such as olive oil or hand

Table 3. Active pharmaceutical ingredients (APIs) commonly used in topical medications^a

Steroids
Alclometasone dipropionate ^b 0.05%; cream, ointment
Amcinonide 0.1%; cream, ointment, lotion
Betamethasone dipropionate ^d 0.05%; ointment, cream, lotion, gel
Betamethasone valerate ^d 0.12%; foam, lotion, cream
Clobetasol propionate 0.05%; foam, lotion, cream, ointment, gel, shampoo, spray
Clocortolone pivalate 0.1%; cream
Desonide 0.05%; foam, ointment, lotion, gel, powder, aerosol
Desoximetasone ^b 0.25%; cream, ointment, gel
Diflorasone diacetate 0.05%; cream, ointment
Fluocinonide acetate 0.025%; cream, oil (also vitreal implant)
Fluocinonide 0.05%; cream, ointment, gel, solution
Flurandrenolide 4 µg/cm ² ; tape
Flurandrenolide 0.05%; ointment, cream, lotion
Fluticasone propionate ^e 0.05%; cream, lotion, ointment, spray
Halcinonide 0.1%; cream, ointment, solution
Halobetasol propionate 0.05%; cream, ointment
Hydrocortisone acetate ^e 2.5% (with pramoxine HCl 1%); lotion, cream, ointment
Hydrocortisone butyrate ^e 0.1%; cream, ointment
Hydrocortisone (cortisol) ^e 1%, iodoquinol 1%; cream
Hydrocortisone valerate ^e 0.2%; cream, ointment
Mometasone furoate ^b 0.1%; cream, ointment, lotion, spray
Prednicarbate 0.1%; cream, ointment
Triamcinolone acetonide ^e 0.2%; cream, lotion, ointment, aerosol
Acne
Adapalene 0.1%, 0.3%; gel
Clindamycin phosphate ^d 1.2%; gel, cream, foam, lotion, pads
Erythromycin ^{d,f} 5%; gel, solution, ointment, swabs
Sulfacetamide, sodium 10%; lotion, ointment, cream, foam, gel, wash, pads
Tazarotene 0.1%; gel, cream
Tretinoin 0.1%; alcohol, gel, cream, solution ^e
Skin/eye infections
Acyclovir 5%; cream, ointment, solution ^e
Bacitracin zinc 500 units; ointment
Butenafine HCl ^b 1%; cream
Chloroxine 2%; shampoo
Ciclopirox ^{b,g} 1%; shampoo, cream, lotion, gel
Ciclopirox ^b 8%; topical solution (nail lacquer)
Clotrimazole ^e 1%; cream, lotion, solution
Docosanol 10%; cream
Econazole nitrate 1%; cream
Ketoconazole ^e 2%; gel, shampoo, foam, cream
Miconazole nitrate 2%; powder, spray, cream, suppositories
Mupirocin 2%; ointment, cream
Naftifine HCl ^b 1%; cream, gel
Neomycin 3.5 mg (with bacitracin zinc 500 units/g, polymyxin B sulfate 10,000 units/g); ointment ^e
Nystatin 100,000 units/g; powder ^e
Oxiconazole nitrate 1%; cream, lotion
Penciclovir 1%; cream
Polymyxin B sulfate 10,000 units/g (with bacitracin zinc 500 units/g or neomycin sulfate 0.35%); ointment, powder, cream ^e
Retapamulin 1%; ointment
Sertaconazole nitrate 2%; cream
Sulconazole nitrate 1%; cream, solution
Sulfadiazine, silver 1%; cream ^e
Terbinafine HCl ^f 1%; cream, solution
Tobramycin 0.3%; ointment, solution ^e
Tolnaftate 1%; cream, powder, solution, aerosol
Psoriasis
Calcipotriene ^b 0.005%; ointment, solution, cream
Salicylic acid 6%; shampoo
Warts
Imiquimod ^b 5%; cream
Podofilox ^b 0.5%; gel, solution
Salicylic acid 40%; plaster

Table 3. Continued

Scabies/lice
Crotamiton 10%; cream, lotion
Lindane ^b 1%; lotion, shampoo
Malathion ^b 0.5%; lotion
Permethrin 5%; cream
Pyrethrins 0.33%, piperonyl butoxide 4%; gel, shampoo, lotion
Pyrethrum extract 0.33%, piperonyl butoxide 4%; oil
Rosacea
Azelaic acid ^b 20%; cream, gel
Metronidazole 1%; lotion, cream, gel ^e
Local anesthetics
Benzocaine, butamben, dibucaine, lidocaine, pramoxine, tetracaine; cream, ointment, gel, lotion
Miscellaneous
Doxepin HCl 5%; cream ^e
Fluorouracil 5%; solution, cream ^e
Nitroglycerin ^c 2%; ointment, solution, patch
Pimecrolimus ^b 1%; cream
Tacrolimus ^d 0.03%; ointment

^a This listing [57] (<http://www.empr.com/dermatological-disorders/category/28/0/>) excludes those medications that are specially formulated as transdermal systems (e.g., patches). Note that only the highest concentration in use is listed, which may not apply to all of the formulations. The APIs used in multiple categories are listed only under the category that uses the highest concentration. Usage and excretion data from [151] (<http://dailymed.nlm.nih.gov/dailymed/about.cfm>), [152] (<http://www.rxlist.com>), and [153] (<http://www.druglib.com>). Unless otherwise noted, all APIs are approved only for external use (topical, dermatologic, or ophthalmic), having no common off-label oral or parenteral use.

^b The API is used only externally, but a small portion is known to be systemically absorbed and excreted.

^c The API also has oral or parenteral use but is extensively metabolized and therefore little is excreted unchanged.

^d The API also has oral or parenteral use, and a small portion (<10%) is excreted unchanged.

^e The API also has oral or parenteral use and is extensively excreted unchanged or as active metabolites.

^f Erythromycin readily undergoes internal dehydration to inactive anhydroerythromycin (erythromycin-H₂O) [154], which is detected routinely in the environment [155].

^g Approximately 10% of ciclopirox dermal dose is excreted unchanged over 10 h [153] (<http://www.druglib.com>).

cream) to the wipe might enhance removal; development of hand dispensers for topical drugs that minimize overapplication (too large a quantity or applied over too large an area), which is difficult to avoid with many topical formulations; development of hand dispensers that permit more accurate dispensing to the target site with minimal wastage or overspreading; and formulations that improve transdermal flux (which also would allow lower applied doses). Overviews of current and future transdermal systems and technologies are provided by Wilkosz and Bogner [28] and Tanner and Marks [64].

APIs commonly used in topical medications

The APIs commonly used in topical medications (excluding drugs delivered by transdermal systems) are listed in Table 3. Except where noted, these are the APIs for which the potential is highest that dermal application (as opposed to excretion) is a source for environmental residues. Some of these APIs also are used in oral and parenteral medications. Annotated in Table 3 is a rough categorization of the portion of an API that can be excreted unchanged. Those remaining APIs in Table 3 that cannot be excreted extensively, if detected in the environment, would have a higher possibility of having originated from

bathing (as opposed to excretion via urine or feces). Of this subgroup of topical APIs, data from environmental monitoring exist only for a select few; these data are compiled in Table 4.

Although the existing data show these APIs present in waters at sub- $\mu\text{g/L}$ concentrations (except for crothamiton), those that belong to the same therapeutic class (such as the corticosteroids or antibiotics) have the potential for combined action via concentration (or dose) addition. Little is known regarding the environmental occurrence of the corticosteroids, because the first papers appeared only recently [65–67]. Note that clotrimazole is included on the List of Chemicals for Priority Action by the Convention by the OSPAR Commission for the Protection of the Marine Environment of the North-East Atlantic [68] http://www.ospar.org/documents/dbase/decrecs/agreements/04-12e_List%20of%20Chemicals%20for%20Priority%20action.doc). Also note that both clotrimazole and terbinafine were identified using a quantitative structure–activity relationship approach as among the top 10 chemical substances targeted for further screening [69] (<http://publications.environment-agency.gov.uk/pdf/SP6012-06-TR-e-p.pdf>).

Biopharmaceutics Drug Disposition Classification System

The Biopharmaceutics Classification System (BCS), developed by Amidon et al. [70], is a system for classifying APIs according to bioavailability. The BCS essentially categorizes APIs that are administered orally according to the four combinations of permeability and solubility, because absorption largely depends on solubilization of an API across the intestine. Wu and Benet [71] transformed this system into the Biopharmaceutics Drug Disposition Classification System (BDDCS), which categorizes APIs for oral administration according to the four combinations of solubility and metabolism. Categories 1 and 2 of the BDDCS are subject to a wide array of metabolic pathways leading to extensive excretion of metabolites, whereas categories 3 and 4 primarily are metabolized poorly and therefore are eliminated unchanged in the urine and bile. A wide spectrum of other variables, such as food intake and its composition, also affect excretion [72]. Wu and Benet [71] state that very few APIs undergo intermediate metabolism (e.g., 50%). They are either extensively metabolized or largely excreted unchanged.

Categories 1 and 2 of the BDDCS are of interest with respect to understanding the significance of APIs that are administered topically as a primary source for the API in the environment. The environmental presence of those topical APIs that do not have an oral or parenteral equivalent will be clearly a direct function of the extent of their intended usage, which then leads to introduction to sewage via bathing. But for those topical drugs that also have oral or parenteral uses, the significance of the topical use will be a function of whether oral and parenteral use is accompanied by extensive metabolism and therefore little excretion of the unchanged parent API. Therefore, APIs in categories 1 and 2 of the BDDCS will contribute little unchanged parent API to the environment via excretion by urine and feces. The dermal use of these APIs could be responsible for the largest portion of the parent APIs in the environment. Because a trend is emerging for new molecular entities to be highly permeable, poorly soluble, extensively metabolized compounds (BDDCS class 2) [72], this means that, for those new molecular entities designed for dermal and oral or parenteral use, bathing and washing could

play increasingly important roles with respect to release of APIs to the environment. This also means that disposal to sewers would have the potential also to grow in importance as a source, if newer drugs will be extensively metabolized. Note that of the dermal APIs listed in Table 4 and that also have oral use, four are listed in categories 3 and 4 by Wu and Benet [71]: acyclovir, neomycin, nystatin, and erythromycin. The primary source for APIs in the environment from these classes will probably continue to be direct excretion.

Interpersonal dermal transfer

Considerable residues of APIs on skin (from dermal excretion, from topical application, and remaining after removal of transdermal systems) have the potential for being transferred directly to other persons or to surfaces with which others come into contact. Just as with exposure to APIs via drinking water, for most people this would constitute unexpected, unwelcomed exposure [42].

Although direct dermal–dermal contact obviously increases the probability of interpersonal passive transfer, the possibility also exists for indirect human exposure during daily routine activities via dermal contact with surfaces previously contaminated with APIs from dermal products that remain on the hands of those who have personally applied topical drugs. One noteworthy example is hormonal preparations, such as testosterone, progesterone, and estradiol, those that are applied dermally as preparations containing very high concentrations (percent levels) by rubbing onto the skin with fingers or the hand. Even after hand-washing, substantial residues can remain, resulting in physiologically significant exposures for others. Indirect transfer might be possible by contamination of inanimate objects (e.g., door handles, telephones, keyboards, plumbing fixtures, clothing, currency, etc.) followed with contact by others. The APIs from all types of medications applied by hand or from devices that are touched (e.g., new and used medicinal patches) clearly have the potential for widespread dispersion by these means.

The propensity for topical medications to be dispersed beyond their application sites was demonstrated over 20 years ago with the use of tetracycline. When topically applied, tetracycline was demonstrated to not remain in its original location but rather to be transferred to other parts of the body. The degree and pattern of transfer was a function of the original site of application, the individual patient, and especially the vehicle in which the tetracycline was prepared (i.e., ointment, cream, lotion, or tincture) [73]. This demonstrated the ease with which dermal applications could be transferred.

Several cases have been reported of incidental, passive dermal transfer from parents to children. For example, androgenic steroids such as testosterone (cream) [74–77] and 4-androstenediol [74] topically applied to adults have resulted in profound physiological changes in children (substantial virilization of boys and girls) after interpersonal dermal contact. The vehicle in which the testosterone is delivered could play a role in the potential for transfer, because an alcoholic gel preparation seemed to prevent even purposeful interpersonal transfer [78]; the same was noted for a gel form of estradiol [79]. But appreciable transfer resulting from a different gel formulation of testosterone was evident in another study, probably from much longer chronic contact [80]. One hour after dermal application of estradiol, purposeful interpersonal skin contact (for 15 min) resulted in measurable

Table 4. Topical active pharmaceutical ingredients (APIs) poorly excreted but identified during environmental monitoring^a

API (Chemical Abstracts Service Registry No.)	Sewage influent (ng/L)	Sewage effluent (ng/L)	Surface water (ng/L)	Biosolids (ng/kg dry wt)	Reference
Betamethasone (378-44-9) (plus dexamethasone; the two could not be distinguished)	15	7	0.02–0.31		[66] [65]
Clindamycin (18323-44-9)		1,000 30	Up to 24	1,540	[156] [157] [158] [67]
Clotrimazole (23593-75-1)	80–120		Up to 22 6–34		[159] [160] [66]
Cortisone (53-06-5)	10–33 174	229	0.06–4.2		[65] [66]
Cortisol (hydrocortisone) (50-23-7)	4.6–86 53	0.13–0.58 63	0.08–3.4		[65] [66] [65]
Crotamiton (483-63-6)	7.6–120 370	0.25–1.9 38	Up to 504 6.67 (groundwater)		[161] [162]
Docosanol (661-19-8)	1,610	245–968 580–979	269–504 Reported in river sediments (but source might be natural)		[163] [164] [165]
Fluocinolone acetonide (67-73-2)	0.3	11	Up to 9		[66] [160]
Miconazole (22916-47-8)		Up to 9 Not detected	Up to 9 Not detected		[166] [157]
Salicylic acid (69-72-7)		25–47	Up to 2,100 370	96,000–253,000	[167] [168] [66]
Triamcinolone acetonide (76-25-5)	40	Up to 2,100 3			

^a The APIs from Table 3 for which the potential is highest for dermal application (as opposed to excretion) as a source for environmental residues; all of the scabies/lice APIs have been excluded because of their large nontherapeutic usages in pest control.

systemic uptake by a naive recipient, largely because the majority of the initially applied dose remained on the skin surface for extended periods [81].

The ease with which dermally applied drugs can be transferred by contact and their sustained persistence on the skin even after repeated washing are shown by the contamination that can be introduced to laboratory analyses. After application of 5% progesterone cream by fingers to the body, simply transferring a sample with a pipet introduced considerable background levels of progesterone, even after the fifth hand-washing. Contamination could even occur when using gloves, simply by pulling the gloves from their storage box by gripping a finger tip [82]. The same problem also has been noted for a technician who had been using topical testosterone (in gel form) and performing tests for testosterone. Contamination on the fingers led to very high errant test results [83]; the authors noted that it was not possible to remove all traces from the fingers. Also worth noting is that because residues of those drugs that are applied topically (usually in large quantities) can remain on the skin and because many APIs are excreted through the skin, unique challenges are posed for environmental monitoring. Stringent quality control measures must be implemented to guard against contamination during sampling, monitoring, and sample preparation; a comprehensive system of blanks is particularly important.

Residuals remaining in used delivery systems

Although the topic of drug disposal primarily concerns leftover medications, completely used and partially used medications (especially nonoral delivery systems or devices) also serve as a source of APIs during disposal, because the

remaining residuals in their leftover contents can represent a substantial portion of the amount present in new, unused devices. Leftover residuals in delivery devices is an issue only recently suggested as a source term needing further evaluation [3,84]. This aspect has not been accounted for in source terms for fate models and would be quite difficult to accommodate in a realistic manner, because the residual quantities would vary immensely depending on the type of device, its duration of use, and patient compliance.

These used devices themselves also can serve as a considerable acute hazard, because they are responsible for documented morbidity and mortality due to poisonings from unintended exposure and abuse. As a prime example, consider the list of APIs used most commonly in patch delivery devices designed to administer sustained dermal doses (Table 5). This table also shows the mass content per device, a rough estimate of the number of lethal oral doses in an unused device, and a rough estimate of the equivalent number of oral doses required to contribute the same mass of API if the unused device were flushed to the sewer. A major variable in determining the residual quantity is the conditions under which the device is used. Failure to clean or dry the skin prior to application, for example, impedes permeation of the dermal layer.

Of the drugs listed, fentanyl patches (either new or used) have an API content sufficient for roughly up to 10 lethal oral doses in adults. Clonidine, nicotine, and possibly lidocaine patches have roughly sufficient API for multiple lethal doses in children or pets. These patches clearly require special care to ensure fast, secure, and safe disposal. These instances are not reflective of the much higher possible incidence of morbidity from exposures to other APIs or lower doses.

Table 5. Active pharmaceutical ingredients (APIs) commonly used in delivery devices for administering sustained dermal doses^a

API device (purpose) [trade name]	Chemical Abstracts Service Registry No. (freebase)	Mass/device	Daily oral dose (if applicable); unless otherwise noted
Fentanyl-transdermal patch (pain) —UNUSED [Duragesic]	437-38-7	1.25–10 mg per patch	200 µg/d up to 1,200 µg/d oral
Fentanyl transdermal patch (pain)—USED		Reported to retain 28–84% of original fentanyl content [85]	As above
Clonidine transdermal patch [Catapres-TTS]	4205-90-7	2.5–7.5 mg per patch per week	0.1–0.3 mg/d oral
Methylphenidate transdermal system [Daytrana]	113-45-1	27–82 mg per patch	2.5–10 mg/d oral; max 90 mg/d
Selegiline transdermal system (depression) [Emsam]	14611-51-9	20–40 mg per patch	10 mg/d oral
Rotigotine transdermal system (Parkinson's) [Neupro]	99755-59-6	4.5–13.5 mg per patch	Not used orally; high clearance and a relatively short duration of effect
Rivastigmin patch (Exelon) reversible cholinesterase inhibitor (Alzheimer's; Parkinsons) [Exelon]	123441-03-2	9–18 mg per patch	1.5–6.0 mg twice a day
Oxybutynin transdermal (antispasmodic, anticholinergic) [Oxytrol]	5633-20-5	36 mg per patch	5–15 mg/d oral
Ethinylestradiol (EE2) with norelgestromin (NGMN) patch (contraception) [Ortho-Evra]	57-63-6 53016-31-2	6.00 mg NGMN 0.75 mg EE2 per patch (per week)	250 µg NGMN/day (1.75 mg/week) 35 µg EE2 per day (0.245 mg/week) Female hypogonadism: 0.02–0.05 mg EE2 1–3 times daily for first 2 weeks of cycle. Inoperable progressing prostatic cancer: from three 0.05 mg to four 0.5 mg daily for palliation. Inoperable progressing breast cancer: two 0.5 mg three times daily.
17β-Estradiol (E2) transdermal system [Estraderm; Menostar; Esclim; Alora; Vivelle; Climara]	50-28-2	0.39–1.56 mg per patch	Replacement therapy oral doses ~1–2 mg/d (up to 30 mg/d for breast cancer) ^d
17β-Estradiol metered-dose transdermal spray (EvaMist)		Each metered dose (1.7%) contains 1.53 mg E2 (1–3 doses per day)	Replacement therapy oral doses ~1–2 mg/d (up to 30 mg/d for breast cancer)
E2/levonorgestrel transdermal system [Climara Pro]	797-63-7	4.4 mg E2 and 1.39 mg levonorgestrel	E2: ~1–2 mg/d Levonorgestrel: 0.1 mg/d
E2/norethindrone acetate (NETA) transdermal system [Combipatch]	51-98-9	0.62–0.51 mg E2 2.7–4.8 mg NETA per patch	0.5 mg of Norethindrone
Testosterone transdermal system [Androderm]	58-22-0	12–24 mg per patch	50–400 mg (testosterone enanthate, IM) once or twice per month
Diclofenac epolamine topical patch (pain) [Flector]	119623-66-4	180 mg per patch	100–200 mg/d oral of diclofenac HCl
Nicotine [Nicotrol; Nicoderm CQ]	54-11-5	7–21 mg per patch	NA
Scopolamine patch (nausea) [Transderm SCOP]	51-34-3	1.5 mg per patch	Oral dose 0.4 mg every 4–8 h as needed
Flurandrenolide topical tape (corticosteroid)	1524-88-5	4 mg/cm ²	NA
Nitroglycerin (angina) [Minitran; Nitro-Dur]	55-63-0	20–160 mg per patch	~3 × 0.6 mg sublingual
Lidocaine [lignocaine] patch (5%) [Lidoderm]	137-58-6	700 mg per patch 46 mg per mucoadhesive patch	NA
Lidocaine/tetracaine [Synera]	94-24-6	70 mg each per patch	NA
Salicylic acid (warts) [Duofilm; Duoplant]	69-72-7	17% flexible collodion	NA

^a Unless noted otherwise, data from [152] (<http://www.rxlist.com>), [153] (<http://www.druglib.com>), and [172].

^b Extensive metabolism was assumed to equate with 10% of dose excreted unchanged.

^c (mass contained in device) × [(dose in mass per day) × (fraction of API excreted unchanged)]⁻¹; calculated to provide the minimum and maximum possible.

^d [172].

^e [175] (<http://www.spfiles.com/pinitrodur.pdf>).

Table 5. Extended

Lethal dose	Equivalent lethal oral doses per device	Excretion efficiency ^b	Equivalent oral daily doses contributing API to environment if device is disposed to sewers (range) ^c
~1 mg [85]	1–10 (for 70-kg person)	>90% transformed to N-dealkylated and hydroxylated inactive metabolites	1.25 mg/(1.2 × 0.1) = 10 10 mg/(0.2 × 0.1) = 500
As above	<9 (for 70-kg person)	As above	(1.25 × 0.28)/(1.2 × 0.1) = 3 (10 × 0.84)/(0.2 × 0.1) = 420
Highly toxic with ingestion by child of 0.01–0.04 mg/kg [169]	~10–30 (20-kg child)	40–60% excreted unchanged	2.5 mg/(0.3 × 0.6) = 14 7.5 mg/(0.1 × 0.4) = 188
Unknown (children) 2–5 g (adults)	0	Only small quantities (<1%) of unchanged methylphenidate appear in the urine; most of dose is excreted in urine as ritalinic acid (60–86%), the remainder comprising minor metabolites	27 mg/(90 × 0.01) = 30 82 mg/(2.5 × 0.01) = 3,280
>140 mg [170]	0	Extensively metabolized	20 mg/(10 × 0.1) = 20 40 mg/(10 × 0.1) = 40
>0.1 mg/ml plasma concentration	0	Extensively metabolized	Unlimited
		Extensively metabolized; no parent drug detectable	9 mg/(6 × 0.01) = 150 18 mg/(1.5 × 0.01) = 1,200
		Extensively metabolized; <0.1% excreted unchanged in urine	36 mg/(15 × 0.01) = 240 36 mg/(5 × 0.01) = 720
		EE2: very low but can undergo extensive deconjugation	EE2: 0.75 mg/(0.035 × 0.1) = 214
		NGMN: extensively metabolized, but also to active metabolites [171] (http://www.orthoevra.com/shared/pi/OrthoEvraPI.pdf)	NGMN: 6 mg/(0.250 × 0.1) = 240
		10% of oral dose excreted unchanged in urine [173] but can undergo extensive deconjugation; urinary excretion of endogenous estradiol ranges 5–100 µg/d (women), 2–25 µg/d (men), but up to 30 mg/d (pregnant women) [60]	0.39 mg/(2 × 0.1) = 2 1.56 mg/(2 × 0.1) = 8
		As above	1.53 mg/(2 × 0.1) = 8
		Levonorgestrel partly excreted unchanged in urine	E2: 4.4 mg/(2 × 0.1) = 22 4.4 mg/(1 × 0.1) = 44 Levonorgestrel: 1.39 mg/(0.1 × 0.5) = 28
		<5% excreted unchanged, but extensively conjugated	NETA: 2.7 mg/(0.5 × 0.05) = 108 4.8 mg/(0.5 × 0.05) = 192
	0	Testosterone not usually administered orally (excretion of free and conjugated testosterone from adult males ranges up to 0.3 mg/d calculated from data in [62,63]) About 90% given intramuscularly excreted as urine conjugates and about 6% excreted unchanged in feces	Equivalent oral daily dose = 2.5–5 mg/d (assuming no metabolism) 12 mg/(400 × 0.1) = <1 24 mg/(50 × 0.1) = 5
	0	Little excreted unchanged in urine	180 mg/(200 × 0.1) = 9 180 mg/(100 × 0.1) = 18
30–60 mg [174]	<1 (toxic for children)	10–30% excreted unchanged in urine	21 mg/(30 × 0.3) = 2
>2–4 mg	<1	<10% excreted unchanged in urine	1.5 mg/(0.4 × 0.1) = 38
>200–1,200 mg ^e	<1	Extensively metabolized	Unlimited 20 mg/(3 × 0.1) = 67 160 mg/(0.6 × 0.1) = 2,667
Severe effects >15 mg/kg [176]	>2 (20-kg child)	Lidocaine, <10% excreted unchanged, but several less-potent metabolites are also excreted; tetracaine, unknown but undergoes rapid hydrolysis	NA
		As above	NA NA

By use of the daily doses and excretion efficiencies for the oral versions, the quantity of an API released to sewers from disposal of a device can be compared with the API released from oral doses. Several devices, if disposed to sewers unused, would contribute the equivalent of thousands of oral doses (after accounting for pharmacokinetic data for excretion of the unchanged API): methylphenidate (equivalent to 3,280 oral doses), rivastigmine (1,200), and nitroglycerin (2,667). Others would contribute the equivalent of hundreds of oral doses: clonidine (188), ethynylestradiol (214), oxybutynin (720), norethindrone (192), and norelgestromin (240). The residual content of used patches was available only for fentanyl, where a used patch would still be equivalent to hundreds of oral doses (420) [85]. Some patches would serve as unique contributors to the environment because oral equivalents of their APIs do not exist; these include rotigotine, flurandrenolide, and lidocaine.

The residual APIs in transdermal therapeutic systems (or other drug delivery devices designed for external extended release) can represent a substantial portion of the amount present in new or unused devices. It can also be considerable when compared with oral daily doses. This pertains especially to APIs formulated for transdermal or transmucosal devices. For transdermal patches, as an example, the residual is a function of how efficiently the API is absorbed across the skin and how long the patch is left in place. This adds an important but highly variable dimension to calculating the significance of disposal compared with excretion. The amount of API that is retained on the skin surface from transdermal delivery devices also can be appreciable, because interdermal transfer of clinically significant amounts from these particularly concentrated areas can then occur between individuals as a result of bodily contact. This has been documented, for example, for estradiol [81], where the authors noted that "clinically significant transfer of topical bioactive drugs can occur."

A major concern regarding these devices (as with all APIs reformulated for low-dose extended release) is the purposeful circumvention of the design in order to acquire a high-dose immediate-release drug that can be taken via a direct route (such as by mouth, nose, or intravenous); this is an approach used by drug abusers. Indeed, design of devices to accommodate new delivery forms of APIs already in therapeutic use can lead to diversion and abuse because of their high content of the API [86]. Some APIs pose extreme risks and are tightly controlled under formal restricted-access programs, which impose restrictions on various aspects of prescribing, dispensing, or patient usage in order to reduce the risk of diversion, abuse, and imprudent use [87]. These risks largely fall into three major categories: potential for abuse (e.g., buprenorphine), severe adverse drug reactions (e.g., clozapine), and teratogenicity (e.g., thalidomide or isotretinoin). The latter are two examples of those for which inadvertent exposure must be minimized.

The first transdermal therapeutic system was a transdermal patch (incorporating scopolamine for motion sickness) approved by the U.S. Food and Drug Administration in 1979. This was followed by the development of the nicotine patch. An overview of transdermal systems is provided in [88]; the number of therapeutic classes being formulated for dermal transfer continually expands, now including such drugs as psychotropics. Most drugs administered by patch pose four main hazards: potential for abuse of used patches, which can contain acutely toxic residual doses when administered by

alternative routes (e.g., oral ingestion); potential for accidental poisoning by used (as well as new) patches, which can be ingested accidentally by infants, toddlers, and pets; when disposed to sewers, used patches can contribute a mass of API equivalent to that resulting from excretion from multiple doses of oral formulations; and residues remaining on the skin after a patch is removed can be substantial, contributing to API release to sewers during bathing or to transfer to others by interdermal contact.

Delivery devices that usually are not disposed of by flushing also can pose eventual exposure hazards, especially if disposed to trash that is landfilled [89]. As one example, Geurts et al. [90] calculated that the ethynylestradiol (EE2) remaining in used vaginal contraceptive rings is roughly 85% of the initial amount, corresponding to roughly 2.4 mg of EE2. This EE2 is then available for accumulation in landfill leachate; the same concern would apply to EE2 implants once removed by a physician. Ethynylestradiol is an extremely potent endocrine disruptor in the aquatic environment, having profound effects in fish populations at concentrations in the low parts-per-trillion range [91].

The acute risks posed by used delivery systems containing substantial API residues have been demonstrated amply. Unintentional poisonings and abuse are not uncommon. After 3 d of use, fentanyl patches have been reported to retain 28 to 84% of their original fentanyl content, more than sufficient for a lethal oral dose if the patch were applied dermally on an opioid-naïve person or ingested, for example, by an infant [85]. Note that a new 2.5-mg fentanyl patch contains the equivalent of approximately twelve 200- μ g fentanyl lozenges (which are available in formulations of 200 to 1,600 μ g in 200- μ g increments). The residue in a used 2.5-mg patch might be equivalent to four to ten 200- μ g lozenges.

Patches are indeed a known cause of fatal poisonings [92] after intentional ingestion by adults [93] and by children [94,95], injection of API extracted from patches [96], and misuse and abuse of patches by misapplication and inappropriate application in numerous different ways [97]. Used nicotine patches have been ingested and applied dermally by children [98]. Used patches may be more likely than new medications to be accessed by children because they can be forgotten once removed.

A continuing trend toward designing new and existing APIs in dermal delivery systems could serve to reduce the ameliorative role that metabolism would play normally in reducing the load of APIs in the environment; the API content of dermal delivery systems is also often much larger than that required for oral doses. This trend could increase the significance of used and unused leftover medications as a source of APIs in the environment, particularly for those APIs that otherwise would be metabolized extensively if consumed orally or parenterally. The unused portion of APIs in delivery devices clearly serves as a reservoir of APIs that may require additional attention with regard to disposal. Although flushing might be currently the best alternative for quickly ensuring that used patches are not accessible to others, there are situations where flushing nonsoluble materials is problematic, such as with septic systems. Because of their very high potential for abuse or accidental poisonings, used fentanyl patches pose exceptional challenges, because even patches on decedents are known to be diverted and reused [99] and have led to overdose and death [100]. Except for patches, most devices have very low potential for disposal via flushing

(inhalers and venipuncture and other injection devices), so their API residues are not prone to immediately entering sewage. One way to reduce the significance of residual APIs remaining in transdermal and topical (e.g., cream and gel) applications is to improve the efficiency of dermal permeation or absorption (via reformulation); this also would allow the use of less API per application, thereby reducing the remainder yet further.

With respect to veterinary practice, the use of medicated feeds can contain substantial concentrations of drugs such as hormonal growth promoters and antibiotics. Unused feed and feed incompletely consumed (e.g., in aquaculture, where large portions sink before being consumed) can contribute residues to the environment [101] or be eaten by nontarget animals.

Residuals and the hazards of attempted medication destruction

The desire for methods that consumers can use to render unwanted, leftover medications unusable (prior to disposal) has led to recommendations to alter the physical form of the medication. One example is the SMARxT disposal campaign, which advises: "Pour medication into a sealable plastic bag. If medication is a solid (pill, liquid capsule, etc.), crush it or add water to dissolve it" or "add kitty litter, sawdust, coffee grounds" [102] (<http://www.smarxtdisposal.net>). But guidance aimed at altering or destroying medications poses acute hazards for people and pets and also possibly facilitates the entry of APIs to the environment.

Practices that attempt to render medications unusable by physical alteration not only do not prevent diversion to drug abusers—who can easily reclaim the APIs—they also pose additional risks. The need for new approaches for safe and environmentally prudent drug disposal has been discussed [8]. The magnitude of leftover medications has been documented in a number of publications, a recent one being De Bolle et al. [103].

A form of medication alteration long used in medical care is a common practice known as dose-form modification, used especially in long-term care facilities where patients often refuse oral medication or have difficulty swallowing (dysphagia) [104]. Health care professionals often resort to dose-form modification to encourage these patients into compliance. This commonly involves crushing pills or opening capsules and transferring to a more easily administered format (e.g., mixing in sweetened food). Dose-form modification is controversial because it has the potential to radically alter the pharmacokinetics of medications that are specially formulated to release APIs gradually (e.g., special-release medication forms such as extended release and delayed release formulations). Physical modification can reduce greatly the time required for an API to reach a maximum plasma concentration, and this concentration can often exceed the threshold for adverse effects, because all of the API is released at once instead of over an extended time (e.g., a 12- or 24-h dose delivered all at once). It is widely recognized by drug abusers that pill crushing can lead to greatly enhanced biological activity [105].

After the tablets are crushed, the extended release design is defeated, making immediately bioavailable the tablets' entire contents of APIs. Those opiate medications containing APIs that are extremely potent can contain up to several lethal doses per pill for those who are opioid-naïve, especially children. Although documented reports of harm to patients by health care professionals are few (most likely because professional health care workers are aware of those medications, such as

cytotoxics and teratogens, that pose the greatest hazard if modified), the potential clearly exists. Some tablets are specially coated not to modify the absorption or release characteristics but rather to prevent dermal contact or pulmonary exposure when handling. Breaking this coating poses an acute hazard to anyone in close proximity; residues then can disperse to the surrounding environment. Examples include cytotoxics (e.g., methotrexate or tamoxifen), steroids, prostaglandin analogs, and other hormones. An updated compilation of medications that should not be crushed, not just for therapeutic reasons but also for safety concerns, is available at the Institute for Safe Medication Practices Web site [106] (<http://www.ismp.org/tools/donotcrush.pdf>). An example of the cautions issued on this Web site include the one for finasteride (Propecia® and Proscar®, Merck) and dutasteride (Avodart®, GlaxoSmithKline): "drug may cause fetal abnormalities; women who are, or may become, pregnant, should not handle capsules; all woman should use caution in handling capsules, especially leaking capsules." Oxymorphone (Opana ER®, Endo), oxycodone (OxyContin®, Purdue Pharma), and tramadol (Ultram ER®, Ortho-McNeil Pharmaceutical) users are warned, "tablet disruption can lead to rapid release and absorption of a potentially fatal dose of" oxymorphone, oxycodone, or tramadol. The Web site offers advice about handling hydroxyurea (Droxia® and Hydrea®, Bristol-Myers Squibb) capsules, "exposure to powder may cause serious skin toxicities," and lenalidomide (Revlimid®, Celgene) capsules, calling it a "teratogenic analog of thalidomide."

Although some of the dangers in the practice of physical drug destruction pertain solely to the administration of health care, some are also pertinent to the relatively recent recommended practice of crushing leftover, unwanted medications in order to facilitate their disposal, such as these instructions on the SmartRx Web site [102] (<http://www.smarxtdisposal.net>): "Pour medication into a sealable plastic bag. If medication is a solid (pill, liquid capsule, etc.), crush it or add water to dissolve it." The intent of this recommendation is to render the medication useless to others so that disposal via trash does not lead to subsequent diversion by others. The consumer, lacking the knowledge of a health care professional, would probably not be aware of those medications that would pose acute risks from mechanical alteration, such as by crushing or opening capsules. The average consumer really has no way to know which pills are safe to mechanically destroy and which are dangerous without carefully reading manufacturers' instructions. Many drugs possibly could be crushed safely (with the proper equipment), but because many should not be altered, comprehensive guidance for disposal would become complicated, as it has always been with respect to the ultimate route of disposal, where certain select medications (e.g., those with extreme toxicity or potential for abuse) still should be flushed into sewers to prevent unintended poisonings [23,107]). Any additional handling of medications, beyond what is needed for therapeutic use, poses added risks for those in proximity and for the environment.

Crushing tablets or opening capsules by the consumer also should be discouraged for a variety of other reasons in addition to the immediate hazard to the person disposing of the medication in this manner. Some of these medications are formulated expressly to resist crushing. Mechanical destruction of medications can be time consuming and difficult. Some

tablets can be extremely difficult to crush because of coatings or other properties designed purposefully to prevent alteration (making them physically impenetrable), and capsules can resist disassembly. Frustration could cause the consumer to rush the process or use excessive force and, as a result, disperse or spill dust, particles, or entire pills into the air, on the floor, countertop, or other surfaces or containers that might come into contact with food or beverages; sudden crushing of capsules could expel liquid contents. The dispersed API (or misplaced pills) could then come in contact with pets, infants, toddlers, and other unsuspecting people, where dermal, oral, and pulmonary exposures could occur.

Few consumers even have a mortar and pestle, much less a device specially designed to crush pills, such as those sometimes used in health care. They therefore will resort to any number of other improvised approaches, all of which require manual strength and dexterity and greatly increase the chances of local area contamination via spillage or dispersal: hammers, knives, pill splitters, spoon bottoms, nested spoons, rolling pins, etc. If a dedicated crushing device is used, then it also might serve double duty for subsequent food preparation (e.g., a mortar and pestle used for spices) or eating (e.g., a spoon or cutting board). Yet another exposure pathway is then created. Consumers are often creative and also might resort to other methods such as food blenders; we have even handled an inquiry from a consumer who had planned to bake their medications in an oven, a practice that could result in pulmonary exposure to highly toxic chemicals. Once the hazards are understood, for consumers still wishing to crush pills, perhaps the best economical approach would be to use a heavy-duty commercial device specially designed for the purpose of crushing [108] (<http://www.abinn.com>) and where the crushed medications are collected directly into a plastic bag, thereby preventing accidental dispersal. For health care workers who want to dispose of larger quantities by crushing, electric automated crushers are available with automatic containment.

Furthermore, encouraging the consumer to mechanically destroy or to make unpalatable medications disposed via trash, "Mix drugs with an undesirable substance, such as cat litter or used coffee grounds . . ." [23] (http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf) may provide only an illusion of preventing reuse and diversion. Addicts and those who abuse drugs are known to be extremely persistent and clever at reclaiming drugs from all sorts of dirty matrices [105]. Any additional step or manipulation recommended for disposal of leftover medications incurs additional risk that medication can fall unnoticed onto floors or countertops. Mixing with other substances (such as cat litter) prior to trash disposal is also not without controversy in the pharmacy community [109]; mixing with used cat litter also poses a risk of exposure to pathogen-laden dust.

The continuing need to flush or destroy those medications (both new and partially used) that are prone to diversion and abuse could be avoided possibly with advancements in formulation technologies for these drugs. There are a number of approaches under development; several, for example, are specifically designed to deter abuse of oral-use opiates [110]. Some examples include: formulations that resist crushing and dissolving to obtain an injectable form, where the API is released very slowly and dissolving does not yield an injectable form (the oxycodone formulation Remoxy[®], Pain Therapeutics is an example); formulations having additives that cause

unpleasant side effects if taken orally at supratherapeutic doses or if administered by a nontherapeutic route such as by injection or nasally (an example is the oxycodone formulation Acurox[®], Acura Pharmaceuticals); and an approach that uses an opioid antagonist (such as naltrexone) in an indigestible form that cannot be absorbed if taken orally as designed but that is readily released if the medication is crushed (an example is the Embeda[®] [Alpharma] formulation of morphine).

The literature often mentions the use in Britain of drug destruction kits, usually referred to as DOOP kits, sometimes called controlled drug destruction (or denaturing) kits. Although DOOP stands for Destruction of Old Pharmaceuticals, the process employed has nothing to do with actual destruction or denaturing of the API's chemical structure but rather refers to the physical form of the medication. The process involves physically destroying the medication (e.g., crushing pills or emptying capsules) and mixing with a liquid that solidifies and serves to merely encapsulate the APIs. The point of emphasis here is that this approach would not, as its name implies, provide a means for consumers to destroy APIs.

The chemical destruction of APIs has been investigated as an alternative approach to incineration and for dealing with small quantities of waste drugs, especially the highly toxic antineoplastics [111,112] (http://72.32.87.20/lib/downloads/waste/Non-Incineration_Technologies.pdf). These approaches generally have involved the use of concentrated acids and oxidants, such as permanganate, sodium hypochlorite, hydrogen peroxide (also with iron, Fenton's reagent), sulfuric acid, nitric acid, and hydrochloric acid. They also usually involve heating and are quite hazardous. Different methods seem to be required for different APIs. One universal approach for all APIs has never been proposed. Often proposed as a means of on-site destruction of APIs at drug collection events (with the intent of permitting the return of controlled substances), chemical destruction is not yet feasible for widespread implementation because of the hazardous nature of the procedures, the fact that the complete destruction of all APIs cannot be assured (a Drug Enforcement Administration requirement for controlled substances), and the unknowns with regard to the possible generation of hazardous by-products (especially those that are volatile) as a result of multiple APIs undergoing many reactions simultaneously. Greener, less hazardous destruction methods are just beginning to be developed. These use comparatively less hazardous reagents and generate much less hazardous waste. One example is the use of an iron-tetraamidomacrocyclic ligand (Fe-TAML) in conjunction with hydrogen peroxide, which has proved highly effective at destroying a variety of APIs, such as estrogens [113]. Another might be the use of electrolysis [114].

Certain drugs should not be handled unnecessarily or altered by consumers, especially those that are considered hazardous. In an occupational setting, hazardous drugs should be handled only when proper containment of dusts, particles, and vapors is sufficient. Crushing tablets or opening capsules containing hazardous drugs should be avoided, even by compounding pharmacists and other health care professionals; this points to the heightened hazards that pill alteration could pose to untrained and ill-equipped consumers. Overviews of hazardous drugs and guidelines for their proper and safe handling are available [115–117] (<http://www.cdc.gov/niosh/docs/2004-165/pdfs/2004-165.pdf>). A subset of these pose risks with respect to dermal or pulmonary exposure (via particulates, dusts, or powders); although for health care

workers, dermal contact with these drugs (from patients or other sources) is a primary route of exposure, possibly via subsequent hand-to-mouth contact [117].

In the United States, unintentional poisoning by medications is a leading cause of injury in children (ages 18–35 months). The types of medications commonly involved with poisonings are summarized by Meyer et al. [118]. These are among the medications for which mechanical alteration would pose the highest risk as a result of inadvertent dispersal of particles or whole doses. Those drugs commonly involved in non-life-threatening poisonings include: antibiotics, β_2 -agonists and sympathomimetics (e.g., phenylephrine and ephedrine), and nonsteroidal anti-inflammatories (e.g., mefenamic acid and phenylbutazone). Those involved with a high potential for adverse effects include: antihistamines (H_1 and H_2 receptor antagonists), β -blockers, calcium channel blockers (e.g., dihydropyridines such as nifedipine), phenylalkylamines such as verapamil, benzothiazepines (e.g., diltiazem), digoxin, isoniazid, sulfonyleureas, and tricyclic antidepressants. Those with the potential for life-threatening effects from even small doses (such as the equivalent of a single, nondelayed release tablet) include: calcium channel blockers, chloroquine/hydroxychloroquine, clonidine, clozapine/olanzapine, flecainide, imidazolines, loxapine, opioids, phenothiazines (thioridazine and chlorpromazine), quinine, sulfonyleureas, theophylline, and tricyclic antidepressants (amitriptyline, imipramine, and desipramine); also see Bar-Oz et al. [119]. Still others are noted for delayed effects that might not be immediately noticed: diphenoxylate and atropine, hypoglycemic agents, monoamine oxidase inhibitors, and acetaminophen (larger quantities).

Some caveats are also important regarding the guidance issued by manufacturers and others [23,107] on the disposal of certain hazardous medications by the consumer. The manufacturer's instructions themselves can cause confusion. One example is the disposal of fentanyl formulated in transmucosal delivery systems such as oral (buccal) lozenges or handles (lollipops). The residue that remains on the handle itself (which should not be flushed) or in partially used lozenges varies greatly but can be hazardous. Disposal instructions call for dissolving the residue of partially or completely used doses by holding under running hot water. An opiate-naive person possibly could absorb a toxicologically significant dose of fentanyl through the skin (especially if open wounds were present) if partially used lozenges or handles were held with exposed fingers during this process.

A final concern regarding destruction prior to disposal via the trash is if someone were poisoned by accidental or purposeful ingestion of crushed pills reclaimed from the trash or from spillage, then it would not be as simple and fast to identify the responsible medication as it would be if the intact medication (with identifying information) were available.

Disposal

The wastage caused by unused, leftover medications was recognized as early as the 1970s with some evaluations of the types and quantities of medications returned by the public [120,121]. The processes developed over the last three decades for handling drug waste generated by consumers has varied greatly among countries [3,10,11]. In the United States, despite federal guidelines [23] (http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf), confusion and debate surround what

constitutes the best approaches for disposal [24,122] (<http://blog.epa.gov/blog/2008/12/08/qotw-prescription-drug-disposal>).

The overall significance of disposal of medications with respect to its contribution of individual APIs (and APIs in general) is an unresolved question [15]. The information needed to make this type of assessment has not been available. Here, we refer to the relative significance of disposal (versus excretion) as the relative environmental footprint (REF) of a disposed drug. As used here, the REF does not refer to the impact in the environment of the API but rather to the potential importance of disposal. The REF for disposal is a simplified form of the more comprehensive relative significance (S_r) factor discussed earlier.

Similar to S_r , a disposed drug's relative environmental footprint (REF_d) is a function of two factors: the fraction of overall API mass (or moles) disposed via sewers, and the fraction of API that is excreted unchanged (or washed from the skin). The REF_d for a particular API is defined as the contribution of an API to sewage by disposal relative to that released from intended usage (such as via excretion). This can be calculated on the basis of either mass or moles of API as

$$\frac{[\text{fraction disposed}]}{[\text{fraction excreted}]} = REF_d \quad (3)$$

Here are some hypothetical examples. Assuming that 10% of an API is excreted and 5% is disposed of, then disposal of one dose would be equivalent to consuming 0.5 doses with respect to the introduction of the API to sewage. Similarly, assuming that 80% of an API is excreted and 5% is disposed of, then disposal of one dose would be equivalent to consuming 0.06 doses. With 1% excreted and 5% disposed of, disposal would be equivalent to consuming five doses. And with 0.01% excreted and 95% disposed of (e.g., the remaining residue retained in the container or dispenser), disposal would be equivalent to consuming 9,500 doses. The latter example might emulate the case for an API that was used almost exclusively in topical preparations (and with nominal systemic absorption), which then would be washed from the skin during bathing. So the possible range for REF_d values can range from near zero (where disposal is a nonfactor in contributing an API to the environment) to extremely high (where disposal is a major factor).

Although REF_d provides the relative potential contributions by disposal among APIs, in order to gain an understanding of the actual magnitude of API release via disposal, the REF_d must be multiplied by the actual number of doses sold or dispensed (during a defined period of time).

When multiplied by the number of doses (ND), the REF_d for a particular API yields the hypothetical number of consumed doses that would be required to release the equivalent amount of API actually contributed by disposal

$$REF_d \times \frac{ND}{\text{time}} = \text{equivalent doses contributed by disposal during a defined time period} \quad (4)$$

The number of doses must be calculated on the basis of the same units as REF_d (either mass or moles). Note that when ranking drugs according to REF_d equivalent doses, the relative ranking could change depending on whether REF_d is calculated on the basis of mass or moles; low-molecular-weight APIs would yield larger numbers of doses when REF_d is expressed in terms of moles, and high-molecular-weight APIs would yield more doses when REF_d is expressed in terms of mass.

A ranking of REF_d values for various APIs would not be necessarily in the same order as the ranked actual contributions. For example, disposal of a high REF_d API for an infrequently prescribed medication might contribute less API than a medication whose REF_d is comparatively very low but that is prescribed frequently.

The variance in the REF_d for a given API will be affected most by the rate of disposal, which could vary wildly as a function of many variables [8]. The rate of disposal might be affected most by the type of drug or its therapeutic class, some of which have much greater rates of noncompliance than others. The REF_d could allow intercomparisons of drugs to determine the relative importance of disposal with respect to contributing to the occurrence of their respective APIs in sewage. By conversion of the number of doses to daily doses in terms of mass or moles, a direct relationship with potency can be obtained. If human potency were assumed to correlate with the potential for ecological effects, then REF_d could be used to reveal which APIs are being disposed of in amounts having the greatest potential for ecological effects.

The REF_d can be understood best by considering some extreme examples. A drug that is disposed of in relatively large quantities nonetheless can have a comparatively low REF_d if its overall use is comparatively larger or if it is excreted largely unchanged (extensively excreted). A drug that is disposed of in relatively small quantities can have a comparatively higher REF_d if its overall use is comparatively smaller or if it is extensively metabolized (leaving little to be excreted unchanged). For an extensively excreted API, both disposal and excretion contribute equally to the environmental loading of the API (each pill disposed contributes to the environmental load the same as if the pill were ingested). For externally applied APIs that are poorly absorbed, the significance of disposal is a direct function of the portion disposed of versus the portion absorbed after its designed use (each dose disposed of contributes to the environmental load the same as if the dose were applied externally as intended but not absorbed).

The two extreme scenarios that maximize and minimize the significance of disposal are, respectively: disposal of a large fraction of an API that otherwise would be metabolized extensively and disposal of a small fraction of a drug that otherwise would be excreted largely unchanged (or of topical drugs that are absorbed poorly). The former is exacerbated when the API is purchased in large quantities, and the latter is attenuated yet further when the API is purchased in small quantities.

Five generalizations can be made: Disposal of APIs that otherwise would be metabolized extensively will tend to be responsible for larger percentages of the API in the environment. Disposal of APIs that otherwise would be excreted extensively unchanged will tend to be responsible for smaller percentages of the API in the environment. Models that use the default assumption of extensive excretion (no metabolic conversion) for APIs that actually undergo extensive metabolism will underestimate greatly contributions from disposal. For APIs applied dermally or by delivery devices, the significance of disposal is a direct function of the portion disposed of versus the portion absorbed after intended usage. The REF_d is maximized when 100% is disposed of or 100% is metabolized (none excreted unchanged).

Three major questions could be addressed with this approach. For those APIs that are most frequently detected by environmental monitoring (and in the highest concentra-

tions), do they also have high REF_d values? These might have higher contributions from disposal. For those APIs that are monitored for but rarely detected, are they also among the ones with lower REF_d values and that are extensively metabolized? These might have little contribution from disposal. Are there APIs with high REF_d s that have never been monitored for? If so, these might be likely targets for monitoring. If detected at critical concentrations, then these are also the drugs that might be likely targets for stringent controls on disposal.

Dermal excretion, dermal application, disposal, and lack of absorption from the gut may well explain the presence in sewage of those APIs that otherwise are metabolized extensively; note, however, that this does not take into consideration the extensive conjugation that many drugs undergo, which can be followed by bacterial deconjugation to return the parent drug [59].

In fact, alternative sources of API pollutants that have attracted little attention (such as dermal application, excretion via sweat, and disposal to sewers) already may have served to confuse the conclusions reached by some regarding the presence of certain APIs in the environment. For example, Jjemba [123] reported a possible negative correlation (based on a very small data set) between the efficiency of excretion of an API in its unmetabolized, parent form and its occurrence in the environment, "the drugs that have a low proportion of the parent compound excreted also display a higher concentration in the aquatic environment". Noted was the widespread occurrence of poorly excreted APIs (e.g., acetylsalicylic acid [aspirin], ibuprofen, acetaminophen [paracetamol], and carbamazepine) and some moderately excreted APIs (e.g., sulfamethoxazole, diclofenac, primidone, and ranitidine). All but three of these, however, are available OTC and are purchased in large quantities, which makes them prone to expiration and subsequent disposal. Ibuprofen, acetaminophen, and diclofenac have been reported as among the unused drugs most frequently returned to pharmacies by consumers [124]. Because drugs returned to take-back events currently represent such a small percentage of those that are otherwise disposed to sewers and trash, this poses the possibility that perhaps even larger quantities of these drugs are disposed to sewers. Indeed, in Ruhoy's study of medication disposal inventories assembled from a coroner's office [125] (<http://environment.unlv.edu/abstractsGrad/ruhoy.html>), acetaminophen and ibuprofen were the first and ninth most abundant medications disposed of over a 1-year period (I.S. Ruhoy, unpublished data). Both are extensively conjugated or oxidized with little unchanged API excreted. The negative correlation noted by Jjemba [123] might be simply the result of not considering all of the possible sources.

Another example is the fifth most abundant API disposed of in the inventory of coroner data conducted by Ruhoy (unpublished data), i.e., carisoprodol. Extensive metabolism yields at least three active metabolites (one of which is meprobamate); only traces of carisoprodol appear in the urine [126]. Despite being extensively metabolized, carisoprodol has been reported in several recent monitoring studies. It was even reported at a concentration of 129 ng/L in recycled water [127]. It was the only API identified in recycled water (at up to 217 ng/L) and also reported in secondary effluent [128] (<http://www.valleywater.org/website/media/pdf/Streamflow%20AugmentationDraft%20IS%20MND.pdf>). It also has been identified tentatively in runoff from fields irrigated with

Table 6. Unknowns/variables in calculating relative environmental footprint of a disposed drug

Total consumption	No ready source of data on total quantity of an active pharmaceutical ingredient (API) consumed (on the basis of either locale or population). Must be derived from sales figures and by making assumptions of average cost per dose and average mass per dose. When local coroner data is used [15], this can be derived from the dispensed amounts (but then it must also be known whether the medication was for short-term treatment or long-term maintenance). Multiple medications sharing the same API further complicate calculations.
Fraction disposed	Even though coroner data specify the route of disposal and even if the fraction disposed were known for the larger population, assumptions still would be required as to what portion was disposed of via sewage versus trash or take-backs (or stockpiled indefinitely). One complication (discussed in the text) is that sales and disposal are not linked in time. Disposal always occurs from sales made in the past. This time lag also can vary, forcing gross simplifications for the purposes of modeling.
Fraction excreted unchanged	Pharmacokinetic data are generally available for nearly all APIs ^a , but there are three major caveats: (1) these data are acquired usually from healthy volunteers, and absorption, metabolism, and excretion could differ widely for patients in diseased states or because of gender, ethnicity, age, body weight, diet, and other factors; (2) the metabolism of many drugs yields conjugates, which can be hydrolyzed during sewage treatment or once in the environment, yielding the parent API; and (3) for drugs administered with a delivery device (e.g., patches), the amount of API remaining in the used or partially used device is unknown, and this residue comprises large amounts of fully unmetabolized parent API.

^a[152] (<http://www.rxlist.com>), [153] (<http://www.druglib.com>), and [172].

treated wastewater or effluent-dominated stream water [129]. Note, however, that some conditions can cause the excretion of unchanged carisoprodol (as with many other APIs); these include concurrent administration of APIs that inhibit microsomal oxidases, certain polymorphisms in microsomal oxidases, and stress, which reduces absorption from the gut. Nonetheless, carisoprodol is an example of an API for which disposal might be playing a dominant role in its environmental occurrence.

Disposal of problematic medications

The continuing need in the United States to dispose of certain medications by flushing to sewers and actively avoiding disposal in the trash [23,107], at least until sustainable take-back or collection programs are developed, poses a dilemma in balancing the protection of human health and safety with protection of the environment [16]. These are the highly hazardous medications or those subject to abuse that could be diverted or accidentally acquired if they were disposed in the trash. The potential significance of disposal by flushing can be evaluated by examining the pharmacokinetics of this subgroup of medications to determine the fraction of the API that is excreted unchanged. But two other factors also are required to determine the relative significance of disposal among APIs: the total amount of drug purchased and the fraction eventually disposed of (Table 6).

In the absence of data for these two factors, a preliminary idea can be formulated as to which drugs that currently require flushing are contributing the highest percentage of APIs to the environment. An expanded list of drugs (but still not comprehensive) where disposal via flushing is recommended [107] is shown in Table 7. These are annotated with information regarding whether they are extensively metabolized or excreted unchanged.

If the efficiency with which an API is excreted unchanged is high, then contributions by disposal would have comparatively less impact (unless an inordinate percentage of the drug is disposed of versus actually being used, for example, if a medication experiences inordinate noncompliance among patients). However, if the excretion efficiency is very low (extensive metabolism), then disposal might play an important contributory role. These would be the drugs that could be targeted for alternative approaches for safe disposal should their APIs prove hazardous for the environment.

The subgroup of drugs (those where sewer disposal is still recommended) for which disposal has the potential to play a dominant role in contributing to environmental residues is annotated in Table 7. Note, however, that this assessment ignores the possible contributions from hydrolyzable conjugates or bioactive metabolites excreted in urine or feces. From this assessment, the limited subgroup for which disposal might play only a minor role as a source of APIs in the environment includes: entecavir (Baraclude[®], Bristol-Myers Squibb); oxymorphone (Opana[®]/Opana ER[®], Endo Pharmaceuticals); buprenorphine (Suboxone[®] and Subutex[®], Reckitt Benckiser); gatifloxacin (Tequin[®], Bristol-Myers Squibb); telbivudine (Tyzeka[®], Novartis Pharma Stein AG); and stavudine (Zerit[®], Bristol-Myers Squibb).

These are the medications whose continued flushing most likely would contribute the least to environmental loadings for the APIs that they contain. Until suitable disposal alternatives are available, consideration could be given to continue advising the flushing of these drugs in order to ensure that they do not contribute to poisonings or abuse. Human safety concerns (from unsecured disposal, such as in trash) might clearly outweigh the probably negligible risks for the environment (from disposal to sewers).

This approach, however, only conveys the potential role that disposal could play. Two other factors required in determining the significance of disposal are the fraction of total drug purchased that is disposed of eventually and the overall usage rate of the medication (Table 6). Unfortunately, disposal data are very rare. Disposal data were collated from the records collected and maintained by the Clark County Coroner (Las Vegas, NV, USA) using the approach described by Ruhoy and Daughton [3]. These data are located in the last column of Table 7. By cross-check of the two sets of data (i.e., the potential for disposal significance, based on PK data, versus actual disposal data), the following drugs are the ones that are disposed of in the largest quantities (in Clark County Nevada over a particular 1-year period) and that also have the potential for contributing the larger portions of APIs to the environment: morphine sulfate extended release (Avinza[®], Ligand Pharmaceuticals); meperidine (Demerol[®], Sanofi-Synthelabo); methadone (Dolophine[®], Roxane Laboratories); oxycodone (OxyContin[®], Purdue Pharma and Percocet[®], Endo Pharmaceuticals); and atazanavir (Reyataz[®], Bristol-Myers Squibb); morphine is excreted largely as conjugates, and

Table 7. Drugs that should be disposed by flushing^a

Drug tradename (API)	Chemical Abstracts Service Registry No. (freebase)	Excretion efficiency ^b	API disposed (mg) ^c
Actiq (oral transmucosal fentanyl citrate) ^d	990-73-8	>90% transformed to N-dealkylated and hydroxylated inactive metabolites	0
AndroGel (1% testosterone gel) ^d	58-22-0	Testosterone not usually administered orally Excretion of free and conjugated endogenous testosterone from adult males ranges up to 0.3 mg/d calculated from data in [62,63] ~ 90% given intramuscularly excreted in urine as conjugates, and about 6% excreted unchanged in feces	4,430 total (16 × 5-mg patches = 80 mg; 3 × 75-g 1% pumps = 2,250 mg; 42 × 5-g 1% packets = 2,100 mg)
Avinza (morphine sulfate extended-release) ^d	64-31-3	Approximately 10% of morphine dose excreted unchanged in the urine; 7–10% excreted in feces; most excreted as conjugates but also excreted as the major metabolite of codeine and heroin	103,000
Baraclude (entecavir)	142217-69-4	Predominantly eliminated in urine as unchanged API (62–73% of dose)	0
Daytrana (methylphenidate) ^d	113-45-1	Only small quantities (<1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as ritalinic acid (60–86%), the remainder being accounted for by minor metabolites	0
Demerol (meperidine) ^d	57-42-1	Negligible excretion unchanged [177] (http://www.sanofi-aventis.ca/products/en/demerol.pdf)	81,000
Diastat AcuDial (diazepam rectal gel) ^d	439-14-5	Well absorbed following rectal administration (equivalent of 90% of oral dose); extensively metabolized to conjugates	0
Dilaudid/Dilaudid-HP (hydromorphone) ^d	466-99-9	Extensively metabolized (>95%)	5,870
Dolophine (methadone) ^d	76-99-3	Extensively metabolized	53,480
Duragesic (new and used) (fentanyl) ^d	437-38-7	See Actiq	2.9 total; (3 × 25-µg patches; 38 × 75-µg patches)
EstroGel (estradiol gel; 0.06%) [a 1.25-g dose contains 750 µg; a new 93-g dispensing pump contains 55 mg; a fully used pump will retain about 10% residual] ^d	50-28-2	10% of oral dose excreted unchanged in urine [173] but can undergo extensive deconjugation; urinary excretion of endogenous estradiol ranges 5–100 µg/d (women), 2–25 µg/d (men), but up to 30 mg/d (pregnant women) [60]; replacement therapy oral doses <1 mg/d	Amount washed from skin and hands (after application/absorption); dermal absorption efficiency is approximately 17% per day [61]
Fentora (fentanyl buccal tablets) ^d	437-38-7	See Actiq	0
Ionsys (transdermal fentanyl) ^d	See Actiq	See Actiq	0
Opana/Opana ER (oxycodone)	76-41-5	Poorly absorbed; 50% excreted unchanged in urine	0
OxyContin (oxycodone) ^d	76-42-6	4% excreted unchanged	271,636
Percocet (oxycodone) ^d	See Actiq	See Actiq	0
Reyataz (atazanavir) ^d	198904-31-3	7% unchanged in urine	14,000
Suboxone (buprenorphine/naloxone)	52485-79-7	Great variability in excretion of buprenorphine; mainly excreted in feces; conjugates excreted in urine	0
Subutex (buprenorphine)	See Actiq	See Actiq	0
Tequin (gatifloxacin)	112811-59-3	70% unchanged in urine	12,500
Tyzeka (telbivudine)	3424-98-4	Extensively excreted unchanged	0
Videx/Videx EC (didanosine) ^d	69655-05-6	Extensively metabolized	0
Xyrem (sodium oxybate) ^d	502-85-2	<5% excreted unchanged in urine	0
Zerit (stavudine)	3056-17-5	16–62% unchanged in urine	2,120

^aDisposal by flushing recommended by U.S. Office of National Drug Control Policy [23] (http://www.whitehousedrugpolicy.gov/publications/pdf/prescrip_disposal.pdf) or manufacturers.

^bNote, however, that this assessment ignores the possible contributions from hydrolyzable conjugates or bioactive metabolites. Also note that elimination data for APIs is derived from testing on healthy humans. The actual percentages of clearance of unchanged API could be lower (but probably higher) in diseased patients or from those with certain metabolic polymorphisms.

^cData acquired from a single county (Clark County, NV, USA) over the course of 12 months [15].

^dDrugs for which disposal may play a more dominant role in contributing to environmental residues; unless otherwise noted, pharmacokinetic data compiled from [152] (<http://www.rxlist.com>), [153] (<http://www.druglib.com>), and [172].

therefore disposal's contribution might not be appreciable. These are the medications for which alternative disposal practices (other than flushing) might be beneficial for the environment. Note that in 2008 the manufacturer relabeled Reyataz and Baraclude and no longer recommends flushing [130].

Note that fentanyl, although not in the coroner's inventory in substantial quantities, also would be among the drugs where disposal to sewage could prove to be an important source, because it is metabolized extensively. Also note that for drugs administered via a delivery device (e.g., patches or lollipops) or dermally there always will be additional wastage (residue remaining in the device). These residues, which can be substantial for patches or partially used lozenges, essentially serve as another contributor analogous to disposal.

For those drugs in Table 7 that were not recovered in the coroner's inventory (buprenorphine, diazepam, didanosine, entecavir, methylphenidate, oxymorphone, sodium oxybate, and telbivudine), this could indicate that these drugs are sold in very small quantities or that patient compliance tends to be very high—either scenario not promoting leftovers. For these drugs, guidance to dispose by flushing may be inconsequential with respect to environmental impact resulting from excreted residues. It is important to emphasize that these assessments are based on only one study of actual disposal practice and need to be corroborated by further studies (e.g., using data collected from coroners' offices in other locales).

CONCLUSION

It has been long assumed that the active ingredients from human pharmaceuticals (APIs) enter the environment as trace pollutants primarily as a result of their excretion via urine and feces. Urine conveys portions of the APIs that escape metabolism and conjugates that are susceptible to later hydrolysis (returning the parent form of the API) and other metabolites (some of which can be highly bioactive). The feces convey metabolites excreted via the bile as well as those portions of APIs that are not absorbed from oral medications.

For the first time, several alternative routes for the entry into the environment by way of sewage have been shown to possibly be important for certain APIs (or therapeutic classes) having particular pharmacokinetic parameters or usage characteristics. These routes include release of APIs from skin during bathing and washing (those applied topically or transdermally as well as those excreted to the skin via sweat); disposal of unused, leftover medications; and disposal of used and partially used medical devices, especially transdermal delivery systems. The published literature relevant to these alternative routes has been compiled for the first time, and examples of drugs for which these routes are possibly important are presented.

Routes other than drinking water and foods by which humans can be directly and inappropriately exposed to chronic and acute doses of APIs also are discussed. These include direct interpersonal dermal transfer; indirect exposure via contact with items touched or used by those who are medicated (e.g., door knobs, telephones, clothing, or spas); accidental exposure (such as ingestion by infants, toddlers, or pets) and inappropriate reuse (or abuse) of used or partially used transdermal devices; and unintended exposure to dust, particulates, and scattered pills or capsules that consumers unwisely attempt to destroy (such as by crushing, a recommendation made by some organizations wanting to keep

abused drugs from being diverted) before disposal in the trash. Some of these routes are documented as leading to morbidity or mortality. All of these routes are interconnected in the life cycle of APIs in the environment (Fig. 1).

The unifying concept of PEK was introduced as the umbrella under which the interrelationships can be understood. Some of the vulnerabilities in the life cycle of an API present opportunities for pollution prevention, an example being more efficient and better targeted delivery of transdermal APIs; proper education of patients by prescribers and pharmacists regarding the application of topical products also might help to reduce overusage. Current recommendations regarding the disposal of certain highly abused drugs by flushing into sewers may not contribute substantially to APIs in sewers; until disposal alternatives are made available more prudent than domestic trash, a rationale is presented for the continuation of disposing these particular medications to sewers. Predictive models that assume extensive excretion for APIs that actually undergo extensive metabolism will underestimate greatly the significance of disposal.

There are many variables that determine the overall significance of these secondary transport and exposure routes. Although none of these routes has been factored realistically into published exposure, transport, or fate models (other than in a general way, using generic assumptions), the present study should facilitate the collection of the needed data to make models more accurate and useful, especially for basing decisions involved with pollution prevention or source control.

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