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Lecture 9
Chemical and pharmaceutical enterprises as sources of environmental pollution

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THE ENVIRONMENTAL IMPACT OF PHARMACEUTICAL MANUFACTURING:

How does industry address its own waste?

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Introduction

Pharmaceutical products for humans or animals, as well as their related metabolites (degradation products) end up in the aquatic environment after use.

Recent investigations showed that low concentrations of pharmaceuticals are detectable in municipal waste water, surface water, groundwater and even drinking water.

Little is known about the effects and with that the risk, of long term exposure to low concentrations of pharmaceuticals for aquatic organisms.

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Introduction

Human exposure is but one part of the much larger issue of pharmaceuticals as environmental contaminants. Exposure is an extremely complex process, one that yields an effect only when a wide spectrum of processes happen to be suitably coordinated spatially and temporally so as to perturb the homeostasis mechanisms of an organism; this is embodied in the concept of the 4Ts:

1. **Toxicant;**
2. **Totality;**
3. **Tolerance;**
4. **trajectory.**

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World Wide Research

Recognising the problems highlighted above, Health Care Without Harm (HCWH) Europe conducted a survey to identify best practice and gather information about how pharmaceutical companies manage manufacturing waste throughout their supply chains.

The survey was sent to the top 50 pharmaceutical companies worldwide (according to Pharmaceutical Executive's annual ranking)18 and covered aspects such as waste and pollution management, environmental sustainability, governance, and transparency (page opposite).

Participating companies were evaluated according to their responses, as well as any publicly available information.

A traffic light system was used as an assessment tool with the following performance indicators:

Red – Low implementation/ no measures

Yellow – Average implementation of measures

Green – High implementation/ measures present

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World Wide Research

RESULTS

Five companies participated in the survey.

Three directly responded to the survey as drafted by HCWH Europe:

- AstraZeneca (AZ)
- GlaxoSmithKline (GSK)
- F. Hoffmann-La Roche (Roche)

Others compiled answers in their own format covering the areas of interest in the survey:

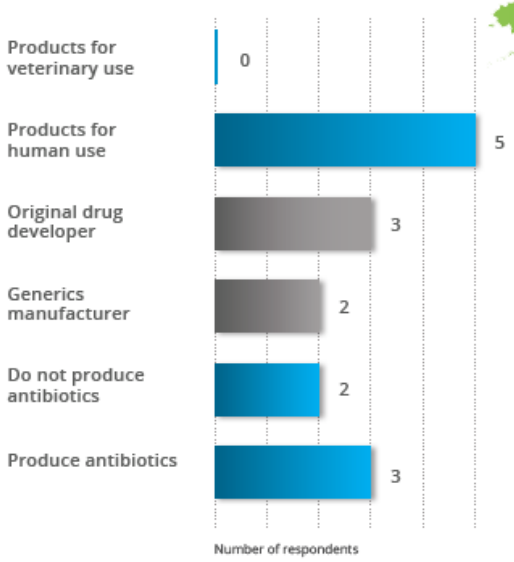
- Mylan
- Teva

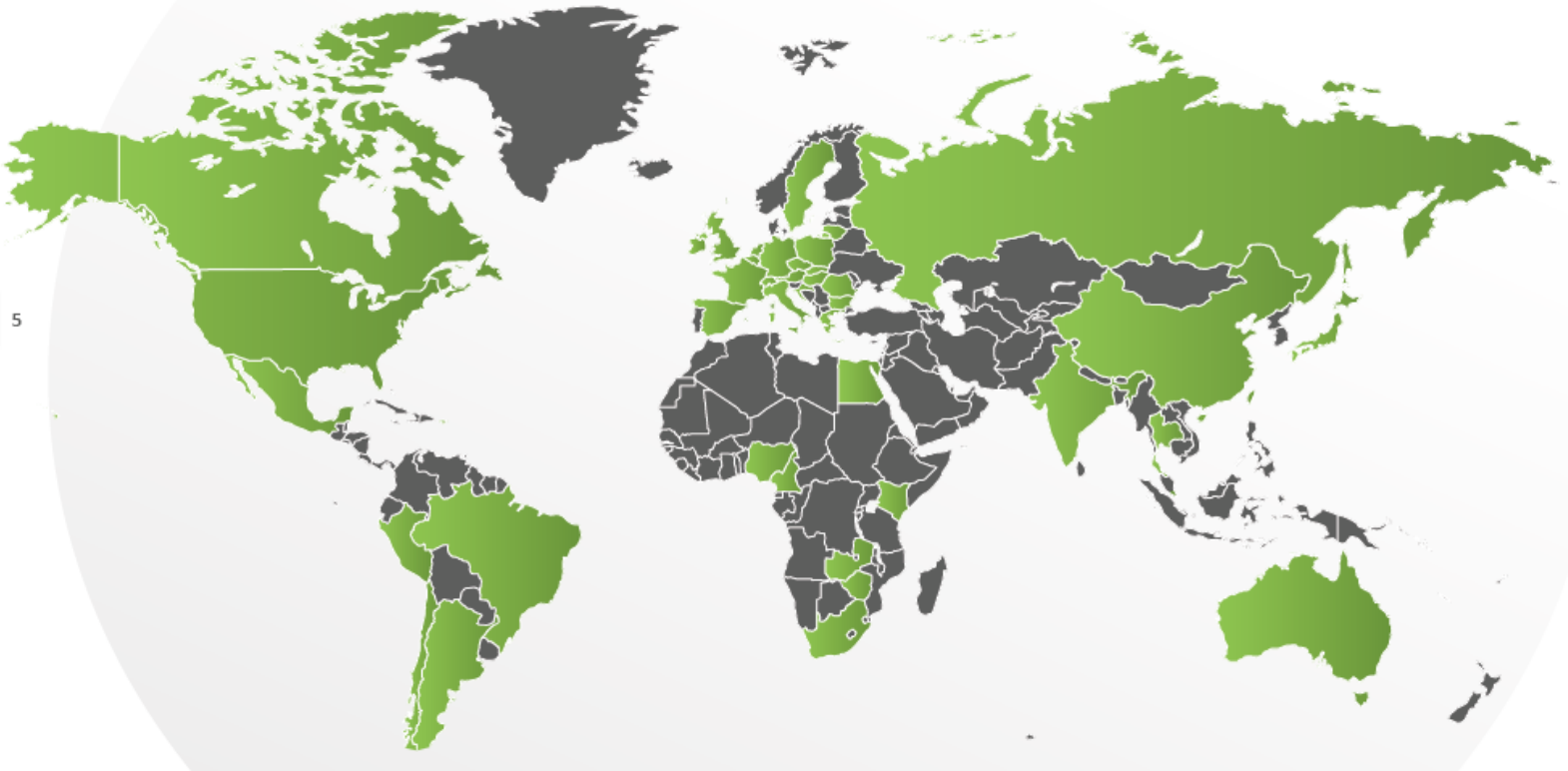
All the companies surveyed manufacture medicinal products for human use only, three develop original drugs, and three produce antibiotics.

All participating companies operate manufacturing sites in developed as well as emerging and developing countries (as defined by the IMF).[19] The UK, USA, Germany, Ireland, Canada, Australia, and Japan were the most frequently mentioned developed countries with manufacturing sites, whilst China, Brazil, India, Thailand, and Argentina were the most popular sites in emerging and developing countries.

LOCATION OF PARTICIPANTS' MANUFACTURING SITES

Argentina	China	Italy	Puerto Rico	Thailand
Australia	Czech Republic	Japan	Romania	UK
Austria	Egypt	Kenya	Russia	USA
Belgium	France	Lithuania	Singapore	Zambia
Brazil	Germany	Mexico	Slovakia	Zimbabwe
Bulgaria	Greece	The Netherlands	South Africa	
Cameroon	Hungary	Nigeria	Spain	
Canada	India	Peru	Sweden	
Chile	Ireland	Poland	Switzerland	





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Cite as: Daughton CG "The Environmental Life Cycle of Pharmaceuticals," illustration, US EPA, NERL, Las Vegas, NV, 2 December 2006; available: http://www.epa.gov/nerlesd1/bios/daughton/drug-lifecycle.pdf; published in: Daughton CG "Pharmaceuticals as Environmental Pollutants: the Ramifications for Human Exposure," In: International Encyclopedia of Public Health, Kris Heggenhougen and Stella Quah (Eds.), Vol. 5, San Diego: Academic Press; 2008, pp. 66-102.

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Common Pharmaceuticals Detected in Water (Surface and Groundwater)

I. Pharmaceutical compounds that reach water bodies, both surface water and groundwater, came from a number of different sources. The first of these is urban wastewater, which contains a high load of pharmaceuticals from human excrement, and also the inadequate disposal of expired or unused drugs due to the scarce control in their management.
II. Another major source of pharmaceuticals is agricultural and livestock waste, especially the latter, since in large farms for intensive livestock, animals are often fed with feed supplemented containing drugs and excreta are often used in agriculture as soil amendments, reaching groundwater by leaching.

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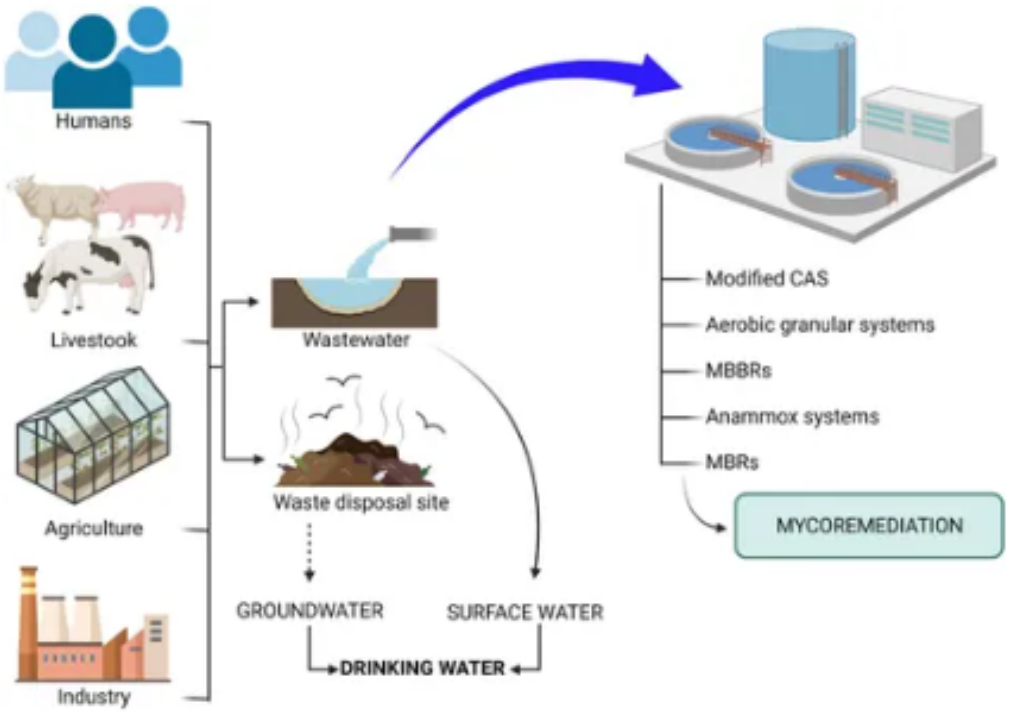
Common Pharmaceuticals Detected in Water (Surface and Groundwater)



Pharmaceuticals route to a body of water and bioremediation technologies. (⟶): Direct contamination. (⇢): Contamination through different steps. The monitoring suggests that contamination accumulates in surface water and groundwater.

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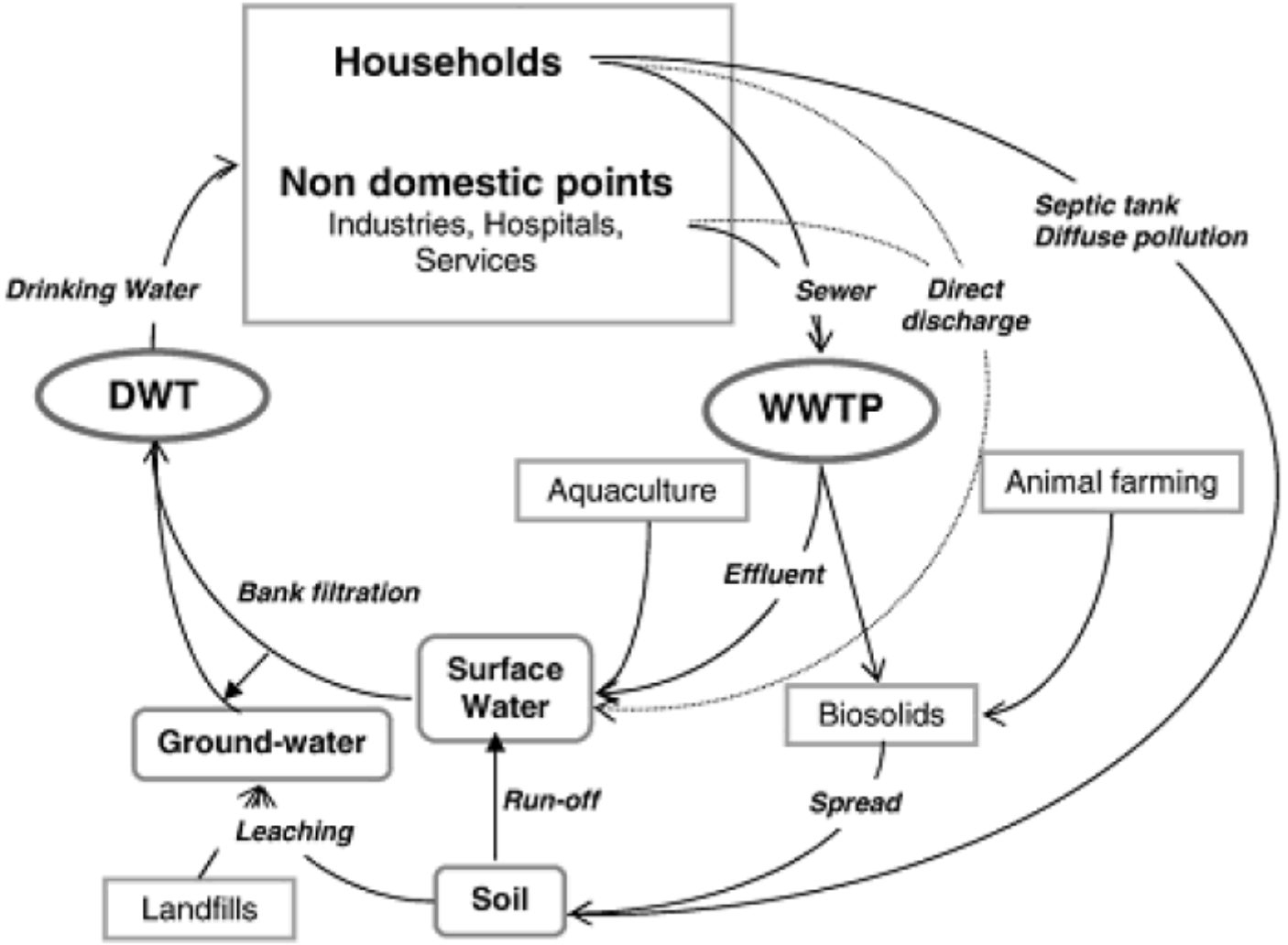

Fig. 1 Origin and routes of pharmaceutical products (after Petrovic *et al.* 2003).

*the wastewater treatment plants (WWTPs)
deadweight (DWT)

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Classification

We sometimes loosely (but incorrectly) refer to drugs, medicines, medications, or pharmaceuticals as being the substances that contaminant the environment.

The actual environmental contaminants, however, are the *active pharmaceutical ingredients* – **APIs.**

These terms are all often used interchangeably

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APIs

Active pharmaceutical ingredients (**APIs**) are the active chemical substances used in the manufacture of medicines. **APIs** are synthesized through a number of standard processes, which include key filtration steps that produce the active ingredients of the drug.

Table 2 Functions determining human exposure

Key function determining exposure	*Types of data needed*
Identities, quantities, and geographic distribution of APIs	Numbers, types, quantities, and geographic usage patterns of human and veterinary pharmaceuticals
ADME	Absorption, distribution (in the body), metabolism, and excretion. Pharmacokinetics of each human and veterinary drug and how these metabolic processes contribute to drug excretion (together with bioactive metabolites) from humans and animals
Major source of unchanged APIs: unwanted, leftover drugs	Direct disposal of unwanted, unused pharmaceuticals to sewerage and trash maximizes the quantities of various drugs that can gain entry to the environment or that can then become diverted
Environmental transport	Partitioning of the excreted chemicals to environmental compartments that then serve as reservoirs for recycling back to humans (including recreational and drinking waters [municipal, wells, and bottled], sewage sludge, plants, and animal food sources)
Environmental fate	Structural transformation, including excreted bioactive metabolites (or radiological decay products), those formed in the environment from degradation or natural transformation processes (hydrolysis, photolysis) (the numbers of transformation products can greatly add to the scope of these chemicals in the environment, as some pharmaceuticals yield a plethora of products [carbamazepine is one example], or those formed during waste or water treatment, such as disinfection byproducts (e.g., quinones from the chlorination of water containing acetaminophen)
Exposure routes	Eventual unintended, unexpected human contact with environmental residues in various compartments (via oral ingestion, inhalation, or dermal contact, such as via potable and recreational waters)

API, active pharmaceutical ingredient.

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Routes of Entry to the Environment for APIs

APIs are released to the environment by two primary routes:

sewerage:

- excretion (as a function of pharmacokinetics)
- bathing (topically applied drugs and residues excreted via sweat)
- disposal to drains

trash:

- discarding unwanted new medications
- as well as used delivery devices or containers with residuals

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Sewage Treatment & Natural Attenuation

- Efficiency of API removal is highly variable – ranging from nearly complete to almost nil as a function of the API.
- Concentrations in treated sewage often range from 1-100 ng/L.
- "Removal" does not necessarily equate with "destruction" or with elimination of toxicity.
  - Parent (unchanged) APIs can partition to solid sludge.
  - Bioactive transformation products can be created.
  - API conjugates serve as hidden reservoirs of parent API.

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Effects on Aquatic Organisms: Cause for Concern

- "Pseudo-persistence"
  - Continuous, multigenerational exposure
- Endocrine disruption (sub-ppb/ppt levels)
  - alterations to sexual differentiation
    - feminization; intersex
  - reproduction and growth impairments
    - Canadian lake study – EE2
    - subtle, behavioral effects - antidepressants
- More questions than answers

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The Potential for Human Health Effects

- Human exposure to APIs recycled from the environment via potable water is limited
- Extremely low concentrations (< 10 ng/L)
- Many APIs in source waters are removed by treatment
- Toxicological research restricted to *in vitro* studies and very limited epidemiological data.
- Concern focused primarily on vulnerable windows of exposure (e.g., fetal exposure) or to contraindicated APIs.
- Therapeutic levels are irrelevant (different mechanisms of action at ultra-low levels)

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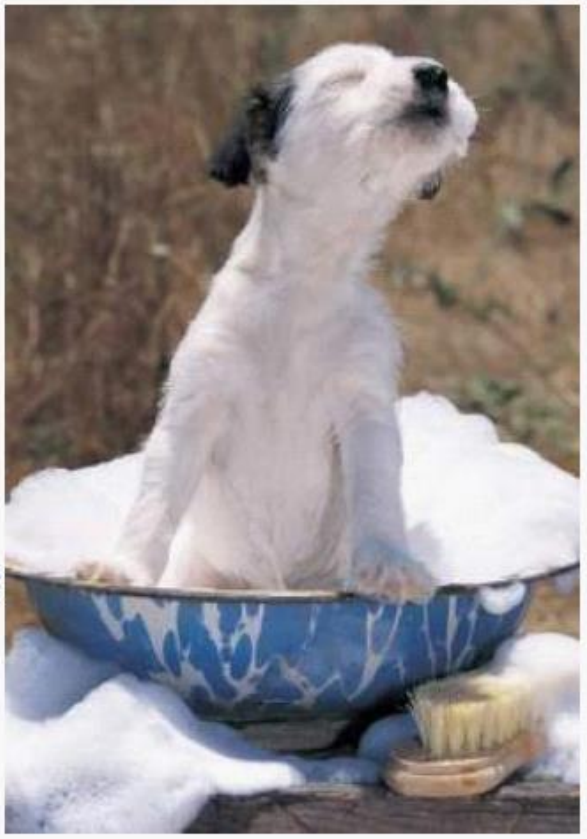
Significance of Disposal versus Excretion and Bathing

- **Excretion**: continual low-level contributions of wide spectrum of APIs from multitudes of people
- **Bathing**: releases fewer types of APIs (medications applied directly to the skin and excreted via sweat) but at higher levels
- **Disposal:** acute but transient and episodic contributions from fewer people
  - Disposal is the only route that is most directly amenable to pollution prevention or source control measures
  - Proper disposal is greatly complicated by the conflict between the need to protect public safety and the need to minimize aquatic (and terrestrial) exposure



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Major Unknown

- **What fractions of drug residues occurring in the ambient environment result from discarding leftover drugs?**
  - No studies provided objective data from well-defined populations to support any type of conclusion
  - Data are needed on the types, quantities, and frequencies with which drugs accumulate and are disposed of as household waste

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Summary of API Masses Disposed to Sewerage: Categorized by Therapeutic Class

ATC Code	ATC Main Group	Quantity (mg) disposed	#of APIs	% of Total
A	Alimentary Tract	18,685,271	56	34.6
N	Nervous System	16,510,963	95	30.6
C	Cardiovascular System	6,331,976	71	11.7
J	Anti-infectives	5,608,735	45	10.4
M	Musculoskeletal System	3,851,949	21	7.1
R	Respiratory System	984,780	16	1.8
B	Blood	721,450	9	1.3
V	Various	622,800	1	1.2
P	Antiparasitics	236,269	2	0.44
L	Antineoplastics	186,013	14	0.34
G	GU System & Sex Hormones	146,440	23	0.27
H	Hormonal Preparations	50,601	10	0.09
S	Sensory Organs	4,375	1	0.008
D	Dermatologicals	3,420	3	0.006
TOTAL		53,945,042	367	

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Drug Disposal: Major Unknowns

- Unknown: what types or quantities of APIs enter the environment via disposal.
- More importantly, it is not known what percentage of each API's environmental loading is contributed by disposal.
- Disposal could be significant for certain APIs and insignificant for others.
- This means that conscientious control of disposal may not lead to any detectable change in the environmental occurrence of many (or most) APIs.

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Drug Disposal: Major Unknowns

- Significance of antibiotic residues in environment with respect to evolution of pathogen resistance
- Portion of human poisonings resulting from accidental ingestion and abuse of diverted drugs that are stored or disposed imprudently
- Prevention of diversion and human poisonings may be the more important driver for prudent disposal.

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Drug Disposal: Major Objectives

- An emphasis regarding disposal needs to be on protecting humans, pets, and wildlife from unintended acute exposures as a result of imprudent storage, stockpiling, or disposal of unwanted medications.
- Critical that guidance for disposal of drugs not jeopardize protection of human (or ecological) health.
- The ultimate objective, however, needs to be on reducing or eliminating the incidence of unwanted medications to begin with.

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Ultimate Objective: No Leftover Drugs

long-term focus should not be how to properly dispose of drugs, but rather ***how to minimize, and ultimately eliminate the creation of drug waste***

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Reducing Leftover Drugs

- **Actions can be directed at improvements to any part of the life cycle of medications**, such as those spanning the vast, complex chain beginning with design/discovery, manufacturing, packaging, and advertising, and proceeding to prescribing (as also modified by practices of healthcare insurers) and dispensing, and ending with whether the medications are eventually consumed or used by the consumer.

- **Actions can be directed** not just at prudent alternatives for disposal, but **also (and more significantly) to reducing the contributions from excretion and bathing.**

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Actions to reduce APIs in the environment and protect human health & safety

- Unit dosing
- Trial scripts
- Reduce polypharmacy
- Samples and donations
- Increased monitoring of patient
- Implement practice of concordance
- Personalized medicine (e.g., lower doses)
- Reduce incentives for excessive purchasing
- Low-quantity packaging of OTC medications
- Lower doses via non-racemic or deuterated APIs
- Prescribers to account for possible environmental impact
- Widespread implementation of sustainable take-back programs

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Stewardship and Pollution Prevention

Disposal control vs. Usage control:

two basic approaches for reducing the entry of APIs to the environment

- **Disposal control**: prudent and environmentally sound engineered practices for disposal of unwanted medications.
- **Usage control**: prudent healthcare practices to minimize or optimize prescribing and dispensing of medications by eliminating unnecessary or imprudent customs.
- Significantly, **usage control perhaps has greater potential for reducing overall entry of APIs to the environment.** It can eliminate the need for disposal PLUS also minimize the residues that would otherwise be released by excretion and bathing.

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Collateral Benefits to Pollution Prevention & Usage Control

In addition to reducing environmental contamination by APIs, prudent stewardship actions aimed at ensuring prudent, efficacious usage of medications might also:

- **lessen healthcare costs** (via more effective treatment, reduced purchase costs, fewer prescribing/dispensing errors)

- **improve therapeutic endpoints and healthcare outcomes** (via better patient adherence/compliance)

- **reduce morbidity and mortality** caused by poisonings of infants, children, adults, pets, and sometimes wildlife by unused stored drugs or by drugs improperly disposed in trash.

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Concussion: PharmEcovigilance

Conventional pharmacovigilance expanded beyond conventional focus on adverse drug reactions (ADRs) to encompass environmental concerns

Unify the parallel but interconnected needs for protecting both human and ecological health

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THANK YOU FOR ATTENTION!