Impact of waste pharmaceuticals: an environmental hazard or "greenwash"?

Do pharmaceutical products really present an environmental problem or is it just another case of "greenwash"? In this article, Colin Richman and Staffan Castensson aim to report the known issues, to identify what we do and do not yet know and to look at work taking place in Europe, with a focus on Sweden where considerable effort is being put into addressing the risk and acting on the evidence

What is meant by the environmental impact of pharmaceuticals? Medicines (including excipients and preservatives) are derived from many different sources, some natural and some synthetic. About 3,000 pharmaceuticals are licensed for human use in the UK.[1] Most drugs have some adaptation to resist biological degradation in the body and these same adaptations may lead to persistence in the environment when the drug is excreted via urine or faecal matter.

The presence of pharmaceutical micropollutants in various water environments has been extensively investigated within numerous studies for more than a decade. More than 170 references, relating to 181 compounds in samples from 23 countries, can be compiled to date.[2]

Pharmaceuticals, whether human or veterinary, will find their way into waste water plants or watercourses and potentially the ground water as the active pharmaceutical, metabolite or other transformation product. Some drugs have been found in drinking water, which is a warning sign that the current handling of pharmaceuticals may lead to future health and environmental problems.

Reports indicate that pharmaceutical micropollutants are detected at parts per trillion or parts per billion levels, far below their acute toxic levels. There is, however, positive evidence of an endocrine disruption effect on aquatic life with reports on the feminisation of male fish, notably the freshwater roach (*Rutilus rutilus*), causing intersex species or development of ova in the testes, where oestrogens (from HRT, oral contraceptive and endogenous human production) are present at the level of one part per billion.[3–5] It has been postulated that, as the UK takes one third of its water from rivers, water with these oestrogen levels have the potential to enter the drinking supply.[6] The effect of chronic exposure to these low levels of pollutants on humans remains unknown and arguments to apply the precautionary principle have been made as a reason for action into reducing the presence of pharmaceuticals in the environment.

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Sewage treatment plants are often the destination for unused drugs

For most chemical substances (eg, pesticides, agrochemicals and household chemicals) there is rigorous environmental hazard testing and guidance on disposal. The environmental safety of human medicines is defined by the EU Commission in directive 2004/27/EC (which amended directive 2001/83/EC). In a report of a European Parliament session, Erkki Liikanen, member of the European Commission responsible for enterprise was quoted as saying: "The possible effects of the use of medicinal products on the environment are important. The question needed to be addressed carefully as, at the end of the day, the availability of certain medicines was at stake. The compromise amendments, which require an environmental impact assessment and possible mitigating measures, but leave the criteria for granting the marketing authorisation untouched is to be seen as a well balanced solution."[7] The EU directive attempts to take into consideration two key elements — diminishing the risk to the environment while at the same time not restricting the availability of medicines.

For veterinary medicinal products a more straightforward approach is laid down in directive 2004/28/EC (which amended directive 2001/82/EC). This legislation forbids product authorisation when the environmental risk is unacceptable and the managing the risk is not possible.

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Drugs found in the environment

A Medline search for pharmaceuticals and the environment indicates that numerous studies have been carried out in this area. They include observational work, analytical methods for detecting pharmaceuticals in effluent water, the effects of low levels of pharmaceuticals on aquatic life, chemical changes to pharmaceuticals identified during sewage treatment processes and genetic responses to drugs present in water.

Table 1 lists some pharmaceuticals that have been detected in the environment. All have been found in sewage outfall water, river water and river sediment and some have also been discovered at low levels in ground water or drinking water.[8]

Table 1: Drugs detected in water environments

Drug	Environment in which detected		
	Sewage outfall, river water and river sediment	Ground water	Drinking water
Acetylsalicylic acid	Yes	—	—
Atenolol	Yes	—	—
Betaxolol	Yes	—	—
Bezafibrate	Yes	Yes	Yes
Bisoprolol	Yes	—	—
Bleomycin	Yes	—	Yes
Caffeine	Yes	—	Yes
Carbamazepine	Yes	Yes	Yes
Chloramphenicol	Yes	—	—
Chlortetracycline	Yes	—	—
Cimetidine	Yes	—	—
Ciprofloxacin	Yes	—	—
Clarithromycin	Yes	—	—
Codeine	Yes	—	—
Cyclophosphamide	Yes	—	—
Dextropropoxyphene	Yes	—	—
Diazepam	Yes	Yes	Yes
Diclofenac	Yes	—	Yes
Digoxin	Yes	—	—
Diltiazem	Yes	—	—
Enalapril	Yes	—	—
Erythromycin	Yes	—	—
Estradiol	Yes	—	—
Estriol	Yes	—	—
Ethinylestradiol	Yes	—	Yes
Fenoterol	Yes	—	—
Fluoxetine	Yes	—	—
Furosemide	Yes	—	—
Gemfibrozil	Yes	Yes	—
Hydrochlorothiazide	Yes	—	—
Ibuprofen	Yes	—	—
Ifosfamide	Yes	—	—
Indometacin	Yes	—	—
Iomeprol	Yes	—	—
Iopamidol	Yes	Yes	—
Iopromide	Yes	Yes	—
Ivermectin (veterinary)	Yes	—	—
Ketoprofen	Yes	—	—
Metformin	Yes	—	—
Metoprolol	Yes	—	—
Naproxen	Yes	—	—
Norethisterone	Yes	—	Yes
Norfloxacin	Yes	—	—
Oxytetracycline	Yes	—	—
Paracetamol	Yes	—	—
Phenazone	Yes	—	—
Propranolol	Yes	—	—
Ranitidine	Yes	—	—
Roxithromycin	Yes	—	—
Salbutamol	Yes	—	—
Sotalol	Yes	Yes	—
Sulfamethoxazole	Yes	Yes	—
Sulfasalazine	Yes	—	—
Terbutaline	Yes	—	—
Testosterone	Yes	—	—
Tetracycline	Yes	—	—
Theophylline	Yes	—	—
Timolol	Yes	—	—
Trimethoprim	Yes	—	—
Tylosin (veterinary)	Yes	—	Yes
Warfarin	Yes	—	—

How do drugs enter the environment?

Opportunities for drugs to enter water systems or other environments are many. Among them are excretion of the pharmaceutical substance, release during the production of the drug and disposal of finished or unwanted medicines. The interaction with the environment can be seen in Figure 1.

Pharmaceutical waste

The disposal of waste is covered by European legislation. The relevant directives for management of pharmaceutical waste[10] are shown in Table 2.

Most medicines packaging that has not been in direct contact with the drug can be recycled via normal means. The preferred method of disposal of waste pharmaceutical products is incineration in a licensed facility. The risk of disposal in the sewerage system or in landfill is that the drug will ultimately reach the water cycle either by direct contamination or by leaching from landfill sites.

One method of preventing unregulated disposal is achieved by the pharmacy Essential Service for Disposal of Unwanted Medicines (Waste). However, audit has shown that 21 per cent of patients dispose of waste medicines in the dustbin with domestic rubbish and 10 per cent flush them down the toilet.[11] Medicines that are not required also present a waste issue. Reviews of patients who return medicines to pharmacies indicate that 60 per cent are aged 65 or older[12] and up to 20 per cent of all drugs are returned unopened.[13] Other research suggests that a small number of patients account for a high proportion of waste medicines,[14] highlighting the environmental importance of the patient medicines use review.

Some drugs have an inherent waste problem because of the quantity of residue remaining after use (Table 3). The residual drug

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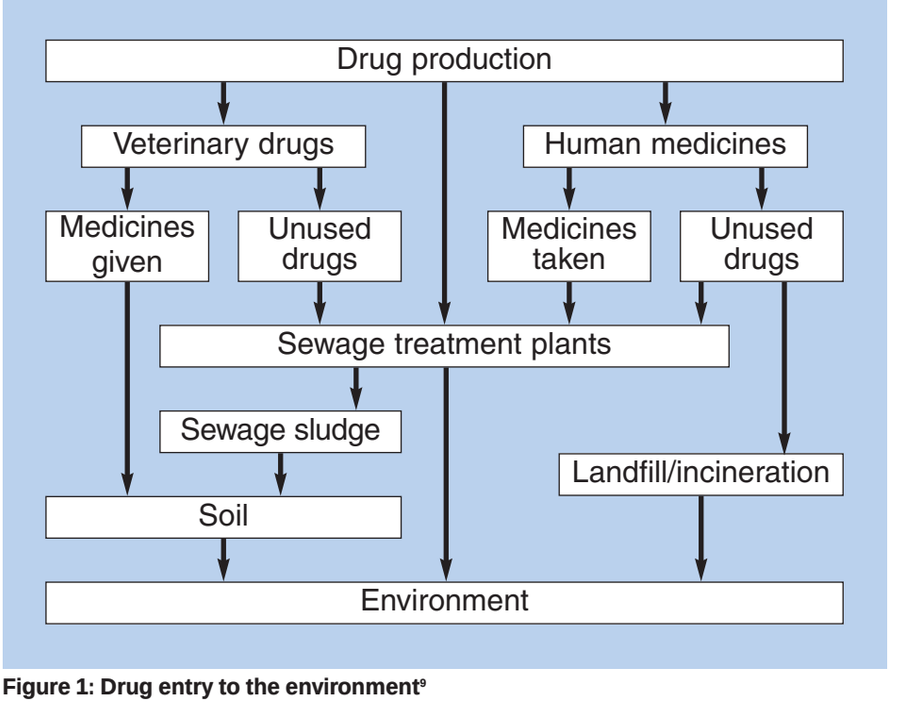

Figure 1: Drug entry to the environment[9]

Table 2: European directives on pharmaceutical waste

Area	Directive title	Directive number
Specific waste	Packaging and packaging waste	94/62/EC
Waste framework	Directive on waste	75/442/EEC
	Directive on hazardous waste	91/689/EEC
Shipment, import and export	Supervision and control of transfrontier shipment of waste	259/93
Treatment and disposal facilities	Incineration of waste	2000/76/EC
	Landfill of waste	99/31/EC

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may exist because of achieving a suitable diffusion gradient, eg, transdermal patches or a short expiry to ensure microbial stability, eg, eye and ear drops.

Currently the best solutions to environmentally managing pharmaceutical waste are preventing the generation of waste (by minimising wastage and overprescribing) and incinerating the waste that is generated. Incineration is regulated by European legislation (2000/76/EC)[15], which sets out limits for emissions of substances such as dioxins, heavy metals, dust, acidic gases and nitrogen oxides in newer plants. Limitations to incineration are the availability of plants and the potential for atmospheric pollution from the incinerated materials.

Table 3: Pharmaceutical dosage forms with significant residues after normal use (Swedish products 2006)[10]

Dosage form	Reason for residual drug*	Residual drug (%)
Eye drops	Design; dose; shelf life	0–91
Eye drops, prolonged release	Design; dose; shelf life	50–72
Implant	Design; dose	8–27
Inhalation gas	Design; dose	–
Inhalation powder	Design; dose	20–83
Intrauterine delivery system (veterinary)	Design; dose	51
Medicated chewing-gum	Design; dose	10–30
Medicated plaster	Design; dose	42–81
Nasal spray	Design; dose	2–29
Transdermal patch	Design; dose	28–98
Vaginal delivery system	Design; dose	28–88

**Key: dose = ensuring correct dose is achieved; shelf life = shelf life after first opening or following reconstitution*

Table 4: Volume of most prescribed medicines in England by defined daily dose (DDD)

Most prescribed by DDD	BNF name	Total volume of active drug substance (kg)
1.	Simvastatin	32,967
2.	Ramipril	3,475
3.	Aspirin	1,147
4.	Atorvastatin	10,625
5.	Folic acid	357
6.	Bendroflumethiazide	1,967
7.	Amlodipine	3,502
8.	Salbutamol	484
9.	Omeprazole	8,851
10.	Lisinopril	4,076
11.	Atenolol	29,919
12.	Furosemide	15,172
13.	Levothyroxine	53
14.	Lansoprazole	9,636
15.	Metformin	573,837
16.	Diclofenac sodium	28,572
17.	Fluticasone propionate	161
18.	Ferrous sulphate	52,094
19.	Paracetamol	769,498
20.	Citalopram	5,020

Data source: Data PPD — based on top 20 DDDs reported for England January to December 2007 converted to kg. data excludes non-prescription sales

Annual volumes of prescribed medicines

Table 4 shows the top 20 drugs by defined daily dose calculated back to weight of drug substance prescribed in the period January to December 2007. This measure is illustrative as drug potency will affect the total weight of drug substance and the figure excludes any non-prescription supplies of medicines or hospital prescribing. However, it clearly indicates that the weights of active substance that may reach water systems are not insignificant.

Environmental rating of pharmaceuticals

According to environmental risk assessment guidelines from the European Medicines Agency,[16] vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Similarly, vaccines and herbal medicinal products are also exempted due to the nature of their constituents.

The Swedish Association of Pharmaceutical Industries (the Swedish equivalent of the Association of the British Pharmaceutical Industry) began to conduct environmental risk assessments of pharmaceuticals in 2005; these assessments aim to include all medicinal products on the Swedish market by 2010. The method adopted to show the environmental impact of drugs identifies both the environmental risk and the environmental hazard. This model is published (with English translation) at www.fass.se/environment and is summarised in the Panel.

The Swedish model for the environmental classification of pharmaceuticals

The information in the Swedish model for the environmental classification of pharmaceuticals is presented at three levels:

- Level 1: Patient information
- Level 2: Prescriber information
- Level 3: Specialist information

Level 1: Patient information Level 1 provides a simple aquatic environmental risk description, based on a risk quotient reflecting acute toxic risk to the aquatic environment. The risk quotient is calculated as the ratio between predicted environmental concentration of the substance (PEC) and the highest concentration of the substance that does not have a harmful effect to the environment — the predicted no effect concentration (PNEC).[17–19] The PEC may be calculated from market volume data (sales or prescription data) against the area of distribution.

Risks are defined as follows:

- PEC/PNEC less than 0.1: Use of the medicine has been considered to result in insignificant environmental risk
- PEC/PNEC 0.1–1: Use of the medicine has been considered to result in low environmental risk
- PEC/PNEC 1–10: Use of the medicine has been considered to result in moderate environmental risk
- PEC/PNEC greater than 10: Use of the medicine has been considered to result in high environmental risk

If there are insufficient data to calculate the PEC/PNEC, either of the following will be used depending on the weight of evidence:

- Risk of environmental impact cannot be excluded, since no ecotoxicity data are available
- Risk of environmental impact cannot be excluded; however some ecotoxicity data are available

Where the PEC/PNEC is less than 1 but the medicine is flagged as potentially PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative), the risk description will be replaced with:

- Hazardous environmental properties.

Level 2: Prescriber information Level 2 repeats the environmental risk information given in Level 1, but also includes additional information about the environmental persistence (resistance to degradation) and bioaccumulation of the drug. The intrinsic environmental characteristics of a substance are expressed in the following terms (bullets indicate preferred term):

- Persistence — ability to resist degradation in the aquatic environment:
  - The medicine is degraded in the environment
  - The medicine is slowly degraded in the environment
  - The medicine is potentially persistent
  - The potential for persistence cannot be excluded due to lack of data
- Bioaccumulation — accumulation in adipose tissue of aquatic organisms:
  - No significant bioaccumulation potential
  - Potential to bioaccumulate in aquatic organisms
  - The potential for bioaccumulation cannot be excluded due to lack of data

If the drug fulfils the criteria for PBT and/or vPvB the following description should be added:

- According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance

Level 3: Specialist information Level 3 provides in-depth specialist environmental information. Those with further interest in this area and the science supporting the work are recommended to visit www.fass.se/LIF/produktfakta/fakta_lakare_artikel.jsp?articleID=76074 [English translation].

Table 5. Risk assessments of selected higher risk pharmaceuticals

Drug	Risk assessment	Data quality
Allopurinol	Moderate	Good
Amoxicillin	Moderate	Good
Estradiol	High /moderate	Incomplete or differing results
Ethinylestradiol	High	Incomplete
Ketoconazole	Moderate	Good
Norethisterone	Moderate	Incomplete
Propranolol	Moderate	Good
Raloxifene	Moderate	Good
Sertraline	Moderate	Good

Table 6: Environmental hazard ratings for selected drugs

Substance	Persistence	Bioaccumulation
Beclometasone	Slowly degraded	Potential to bioaccumulate
Citalopram	Slowly degraded	Potential to bioaccumulate
Desogestrel	Slowly degraded	Potential to bioaccumulate
Escitalopram	Slowly degraded	Potential to bioaccumulate
Etonogestrel	Slowly degraded	Potential to bioaccumulate
Mirtazapine	Slowly degraded	Potential to bioaccumulate
Mometasone	Slowly degraded	Potential to bioaccumulate
Paroxetine	Slowly degraded	No significant risk

When comparing the environmental impact of two substances, consideration must be given to both the risk quotient and additional environmental characteristics such as bioaccumulation and persistence as well as PBT/vPvB (persistent, biochemical and toxic/very persistent and very bioaccumulating) criteria. A review of the environmental rating using the Swedish model was performed in March 2007 (Staffan Castensson, unpublished data). Of 233 drug substances assessed at that time, nine were classified as having a high or moderate environmental risk (risk quotient >1, see Table 5). Seven drugs were classified as low risk and 93 insignificant. Thirteen drugs had more than one risk assessment term or lacked data depending on product. For 114 drugs data were lacking.

The March 2007 study also reviewed persistence and bioaccumulation characteristics.

Since this study the Swedish model has developed further and added the assessment term "potentially persistent". The biological degradation of the 233 drugs was classified: 122 degraded slowly; nine degraded; 85 lacked data; and 17 had more than one risk assessment term or lacked data depending on product. The bioaccumulation of the drug substances was also classified: 22 were identified as having the potential to bioaccumulate; 122 had no significant bioaccumulation potential; 74 lacked data; and 15 had more than one risk assessment term or lacked data depending on product. Table 6 lists some drugs with high environmental hazard ratings.

Suggested actions for the UK

Environmental concerns are widespread throughout the population although there appears to be a low awareness of the presence of pharmaceuticals in the water cycle.

The following are areas that could be considered for the pharmacy profession to provide a lead:

- Agree a risk rating for pharmaceuticals in the environment
- Encourage environmental data to be published as part of licensing requirements and for the data to be available through summaries of product characteristics (SPCs)
- Inform prescribers about the environmental impact of different formulations of medicines
- Raise profile of the environmental impact of medicines to the public and politicians
- Use risk rating in publications such as British National Formulary, SPCs and local formularies
- Lobby the EMEA and the Medicines and Healthcare products Regulatory Agency to put in place a system to make non-confidential environmental information on pharmaceuticals easily available and accessible
- Decrease inappropriate prescribing through medicines use reviews and local prescribing policies
- Encourage full use of pharmacy waste disposal schemes to minimise inappropriate waste disposal
- Encourage collaboration between the pharmaceutical and water industries to improve knowledge in supporting identification, risk assessment and effective removal of pharmaceuticals

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Further reading

(All internet links cited in this article can be accessed from www.rx-info.co.uk)

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