



RESIDUES OF PHARMACEUTICALS IN THE ENVIRONMENT

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Introduction

Large volumes of pharmaceuticals are produced and sold each year, for both human and veterinary use. There are approximately 4000 Active Pharmaceutical Ingredients (APIs) authorised worldwide¹, but their production, use, and environmental fate are not systematically monitored. Human and veterinary consumption varies from one country to another. The proportion of medicines sold that are never consumed is estimated to be up to 50%. Of those medicines that are consumed, a substantial proportion is excreted, either unmetabolised or as an active metabolite. Unless removed from waste streams, these unused or excreted medicines find their way the environment. Some can be extremely persistent. The effect of trace-level pharmaceutical contaminants the environment is still poorly understood in comparison with pharmaceutical safety and efficacy.

This is not a generic issue. Each individual API and localised environment is an individual case, with its own root cause, its own hazards, exposure pathways and risks, and its own mitigation. Many environmental pharmaceutical residues are below concentrations that cause concern, but a significant minority are not. There is an increasing body of research highlighting specific risks with specific residues.

Research and regulation in this area often considers Pharmaceutical and Personal Care Products (PPCP) collectively, because the issues are shared with biologically active ingredients in cosmetics and toiletries. This paper only considers pharmaceuticals for human or veterinary use.

Regulatory framework – Environmental Risk Assessment

All medicines, whether human or veterinary, can only be sold if they have been given a Marketing Authorisation in the country of sale.

For veterinary medicines, each Marketing Authorisation requires an Environmental Risk Assessment (ERA). This process has been harmonised between the EU², USA and Japan, and also adopted by Canada, Australia and New Zealand. In the EU, an ERA has been taken into account within the Risk-Benefit analysis for new medicine approval since 1992. ERAs consider only the individual product, however, not the total tonnage of API in the environment. Risk management measures may be included in the marketing approval; for example, recommending that the animal's excrement is quarantined for a set number of days after treatment, or advising farms to apply for a discharge license from local water authorities. Such conditions are relatively rare, are advisory rather than mandatory, and monitoring of compliance is not included in pharmacovigilance schemes. There is no precedent, and no clear mechanism, for withdrawing a marketing approval on the basis of subsequent environmental monitoring data.

For human medicines³ the European requirement for an ERA was only clarified by guidelines issued in 2006, and the ERA is specifically excluded from the risk-benefit analysis when a new medicine is authorised. Many human medicines on the market therefore pre-date the mandatory requirement for an ERA.

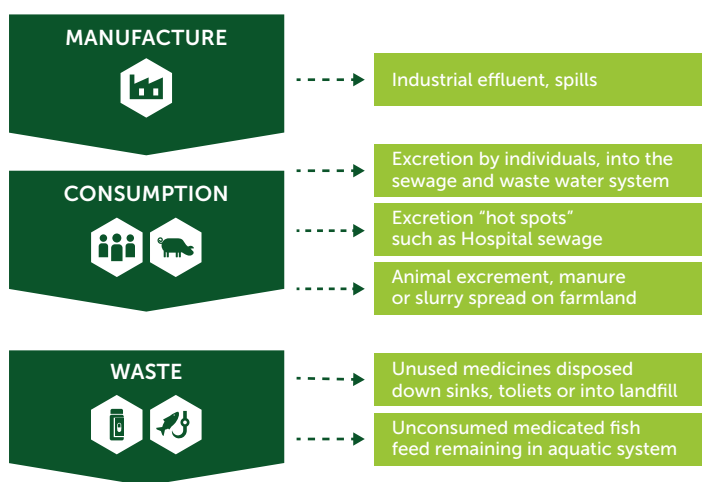
Both human and veterinary ERA procedures have an arbitrary cut-off concentration (e.g., in the case of human medicines, a predicted contamination in surface water at < 0.01 µg/L) below which any environmental impact is assumed to be negligible and no detailed ("Phase II") risk assessment is required.

It is a recognised gap within European legislation that most chemicals must have a full life-cycle impact assessment under the REACH regulations (Registration, Evaluation and Authorisation of Chemicals), but medicines are exempt. Many medicines, in practice, have therefore undergone a less rigorous environmental impact assessment than other chemicals despite the fact that medicines are inherently biologically active.

Routes for pharmaceuticals to enter the environment

There are many potential pathways for pharmaceuticals to enter the environment (Figure 1). Most estimates put the consumption (excretion) route as the most significant⁴, but inappropriate disposal of pharmaceutical waste is also a major factor. In this context, inappropriate disposal includes wastage from poorly targeted medication of animals; for example, uneaten medicated fish feed from commercial aquaculture ponds.

Figure 1: Examples of routes for pharmaceuticals to contaminate the environment



Human effluent waste streams

Excretion, of either the pharmaceutical or its active metabolites, accounts for most emissions through this route. It also includes rinse-off of skin creams and lotions. Depending upon the pharmaceutical, the amount of unmetabolised drug excreted in urine can range from 5 – 80% of the administered dose. Hospital effluent is recognised as a particular problem as not only does it account for a significant proportion of many urban emissions it also provides a relatively concentrated source-point of contamination, and contains different classes of pharmaceuticals than those found amongst the general population. These may also be of higher acute toxicity than typical household pharmaceuticals, for example anti-cancer drugs.

In principle, pharmaceuticals can be removed by waste treatment. The effectiveness of waste treatment plants in removing pharmaceutical contaminants varies depending upon the individual molecule, and on the treatment technology. Techniques such as ozone or activated carbon have proven to be effective, but such technology needs to be highly targeted and locally optimised. They are still quite rare and expensive. Without optimised local treatment, significant contamination can remain in the post-treatment sewage sludge and in the cleaned water. In China, effluent from wastewater treatment plants has been found to be the primary route for contamination of major city rivers with antibiotics⁵.



Animal effluent and manure

Spreading of manure and slurry onto farmland accounts for a significant portion of pharmaceutical residues in agricultural soil, and hence in vegetables and run-off into surface water. Faeces and urine from pets is also a growing issue, with companion animal treatments being the only sector of the veterinary medicines market that is expanding. Composting will significantly reduce the amount of most pharmaceutical contamination in manure or sewage sludge⁶.

Inappropriate disposal of unused medicines

Medicines taken at home are generally poorly targeted, in terms of the amount supplied versus the amount consumed by the patient. There is widespread over-buying of over-the-counter medicines, with them supplied in standard sized packs which may not all be needed. Even with prescription medicines, many people do not finish the course. This may be through a patient's belief that the condition is cured, perceived or genuine adverse reactions, or a switch in treatment caused by a worsening of the condition. A 2005 UK poll⁷ showed that only about half of prescribed courses of medicines were finished by patients, with most of the unused excess being disposed down household drains. Disposal into landfill is a poor alternative, as it will eventually lead to leaching.

Some countries, such as EU Member States⁸, operate take-back schemes for unused medicines. These are highly variable in terms of their public uptake and effectiveness.

Fate of pharmaceuticals in the environment

Once in the environment, residues can partition between soil and water. Sorption coefficients for soils and sediments are highly dependent upon the individual molecule and also dependent on many other factors such as soil type, pH, and the presence of other contaminants and pollutants. The same is true of their rate

of degradation of pharmaceutical residues. A small but significant subset of molecules, such as ethinyl estradiol (the most common oral contraceptive), are sufficiently lipophilic to have potential to bioaccumulate in the food chain.

The overall load of residues in the environment is concentrated by droughts, as the water evaporates. Increase in water re-use as the planet's water supplies grow scarcer will inevitably concentrate the residue load, unless they can be removed by water treatment.

Table 1: Examples of residues frequently detected in the environment⁹

Class	Examples
Antibiotics	Macrolides, sulphonamides, tetracyclines, fluoroquinolones, aminoglycosides
Non-Steroidal Anti Inflammatory Drugs (NSAIDs)	Acetylsalicylic acid, ibuprofen, diclofenac, mefenamic acid
Anticonvulsants	Carbamazepine, primidone
Beta-blockers	Metoprolol, propranolol, betaxolol, bisoprolol, nadolol
Beta-agonists	Salbutamol
Opioids	Dextropropoxyphene
X-ray contrast agents	iopromide, iopamidol, iohexol, diatrizoate
Hormones	17 α -ethinyl estradiol, mestranol, 19-norethisterone



Effect of pharmaceuticals in the environment

There has been some concern about the human health effects of medicine residues in drinking water¹⁰, but in general the direct risk to human health is assumed to be negligible.

The same cannot be said for chronic environmental impacts. Medicinal products are designed to be biologically active, and in many cases designed to be persistent. Environmental impacts are relatively poorly understood¹¹. There have been many individual studies and research projects, either on specific effects of selected single substances or combined effects of multiple residues. But there is no systematic study or assessment, and research priorities tend to be driven by the scope of funded projects or by known localised pollution.

For each API and environmental interaction it is critical to appreciate the different end-points to be measured. Conventional toxic end-points are relatively straightforward to understand, although it can be difficult to predict which species might be vulnerable. The toxic effect on non-target species in the environment may be unpredictably different to the therapeutic mode of action in the target species; aquatic insects, for example, may have different receptors than humans. The starkest example of this was the catastrophic impact on Indian subcontinent vultures¹². The population decline of over 90% in the 1990s was retrospectively linked to renal failure after vultures fed on the carcasses of livestock which had been treated with the anti-inflammatory drug diclofenac. Yet, in studies on other species, diclofenac had given no cause for concern. In a more recent study on direct effect on aquatic species¹³, diclofenac was ranked as one of the least toxic drugs.

APIs where concern has been raised over the acute toxic effect of residues on fish and invertebrates are as varied as dextropropoxyphene (opioid), sertraline (antidepressant), thioridazine (antipsychotic) and diphenhydramine (antihistamine)¹⁴.

Many end-points, however, relate to impacts on animal behaviour; these are more unpredictable, chronic, are not covered by the standard PBT approach (Persistence, Bioaccumulation, aquatic Toxicity) to environmental pollutants and may never have been imagined in the original Environmental Risk Assessment. For example, oxazepam residue concentrations within the range found in Swedish rivers have been found to alter the feeding behaviour of fish¹⁵. There are huge number of potential end-points. Examples of known cause for concern are shown in Table 2, but it seems certain that there are many more as yet unknown.

Table 2: Examples of effects of pharmaceutical residues

Pharmaceutical or Class	End-point
Cytotoxic cancer treatments	Genotoxicity and/or teratogenicity in any eukaryote cell-based organism i.e. any animal, bacteria or plant
Diclofenac	Renal failure in predator birds
Contraceptive hormones	Endocrine disruption; changes to fish reproductive behaviour
Antibiotics	Increase in antibiotic resistant bacteria
Anti-depressants	Premature spawning in shellfish
Diphenylamines	Disruption of biofilms (nutrient coatings on stream rocks, waste outlet pipes, ships' hulls etc.)
Ivermectin	Impact on dung fauna

A single pharmaceutical contaminant is rarely present in isolation, and so the effect of mixtures of residues must be considered. As well as medicines, this must also consider other contaminants present such as pesticides and biocides, or the active ingredients



of personal care and cosmetic products. For contaminants with the same mode of action, it is a reasonable assumption that concentrations can be added; this is a particular concern with cytotoxic anti-cancer drugs. But for those with different modes of action, the general assumption that only one of the competing modes of action will be significant does not always hold true. Mixture effects are poorly understood although – fortunately – there is little evidence of synergistic effects.

There is also potential for interaction with other chemicals in the environment; for example ranitidine (an anti-ulcer treatment) reacts with the chloramine disinfectants used in drinking water plants to form carcinogenic nitrosamines.

The risk of Antimicrobial Resistance (AMR)

Antibiotic resistance is one of today's global challenges. With the lack of commercial incentive to develop new antibiotics there is a limited and increasingly stale armoury with which to fight disease. Bacterial resistance to any of this armoury is a major public health risk. The World Health Organisation has designated "critically important" antibiotics, which should be ringfenced for last resort human use when other antibiotics are ineffective.

Of the 100,000 + tonnes of antibiotics used globally, 50% is released in active form into the environment¹⁶, mainly by excretion in urine. More antibiotics are sold for veterinary than for human use. Approximately 80% of the antibiotics sold in the United States are for meat and poultry production and many are given at sub-therapeutic doses for growth promotion, a use that is banned in the European Union. It has recently been discovered that the environmental concentrations needed to trigger resistance are much lower than previously thought¹⁷, and that long term tipping-points may have already been reached.

Marketing Authorisations for veterinary antibiotics include consideration of the Minimal Inhibitory Concentration (MIC). This is the concentration which could trigger the mutation of a resistant gene. Such mutations would play out over a timescale of hours-to-weeks, and put exposed individuals such as farmworkers at immediate risk of antibiotic-resistant infections. This risk is generally well-managed in developed countries although poor husbandry, such as recycling antibiotic-treated milk to feed calves, can still lead to MICs being exceeded.

Antibiotic-resistant genes, however, are already present to a small degree in the bacterial population. The subtler risk, which has more recently been appreciated, is that small concentrations of antibiotics in the environment could give these genes a tiny selective advantage. This would gradually increase their proportion in the population over a timescale of years-to-decades. The minimum concentration of certain antibiotics needed to impose this genetic "fitness cost" and instigate a gradual population change has been modelled as less than 1 ng/L: well below the concentration already found in many environmental monitoring surveys, and below the level assumed as not requiring a Phase II Environmental Risk Assessment for new Marketing Authorisations. To make the situation worst, this selectivity pressure has been found to be accentuated by other pollutants such as trace metals.

The data gap: usage statistics, waste statistics and residues monitoring

There are significant knowledge gaps in the tonnage of medicines sold, the tonnage excreted or incorrectly disposed, and the resulting residues in the environment. There is a lack of mechanism or strategies to fill some of these data gaps.

Usage statistics

Some pan-national data are collected on the overall sales of medicines, although not in a coordinated and systematic manner. For example, the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) scheme has a mandate to “develop a harmonised approach for the collection and reporting of data based on national sales figures combined with estimations of usage in at least major groups of species (poultry, pigs, veal, other ruminants, pets and fish)”, but remains voluntary, only applies to antibiotics, and has only recently introduced the Defined Daily Dose standardisation of consumption metrics analogous to that used in human medicine.

Residue limits and monitoring data

There are very few regulatory limits set for pharmaceutical residues, and few systematic monitoring schemes in either the statutory or private sector. The Water Framework Directive¹⁸ provides an EU legislative framework, in principle, for monitoring pharmaceuticals in water but the current list of priority pollutants (mandatory for testing) does not include any medicines. No EU limits are set for medicines in water, although in some countries there are national permitted limits set for specific medicines and voluntary monitoring is undertaken by some water companies or administrative regions. The European Commission has requested more data on residues of three specific medicines - diclofenac, 17 β -oestradiol and 17 α -ethinyl estradiol - by placing them on a “watch list”¹⁹. The Sewage Sludge Directive²⁰ sets limits for heavy metals in sewage reapplied to farmland, but not for medicine residues. There is no EU legislation on soil contamination.

Some countries, such as France, operate national monitoring schemes on a discretionary basis but others, such as the UK, undertake no monitoring.

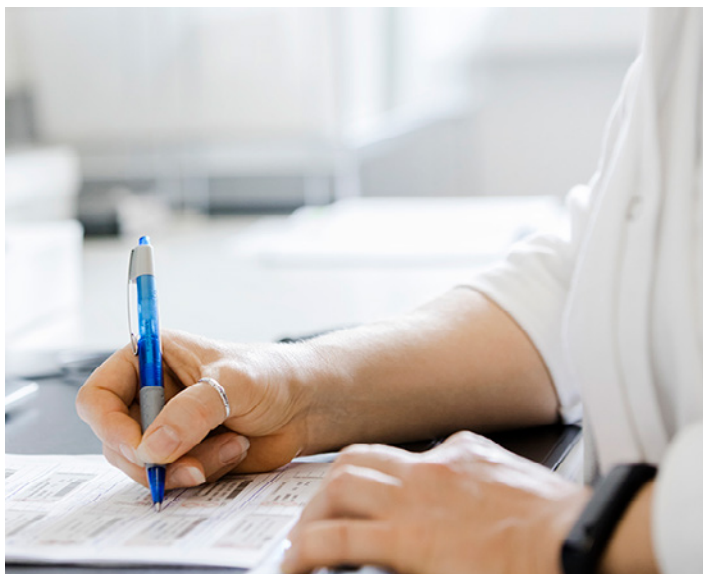
There have been many academic research studies and individual case studies, and a wealth of uncoordinated data in the scientific literature. A 2013 meta-analysis²¹ of published global monitoring data in river waters concluded that, in a significant number of world regions, the concentrations of many pharmaceutical contaminants are above the level believed to cause chronic effects.

Demands upon analytical test methods

There are so many potential contaminants, it is difficult to decide on analytical priorities. A number of risk ranking approaches have been proposed, notably the classification system used by the Stockholm International Water Institute. The US Environmental Protection Agency has a priority list of pharmaceuticals in water. Prioritisation must take into account the intrinsic toxicological properties of the drug, the persistence and bioaccumulation, and location-specific factors such as vectors for contamination and local populations or environments at risk. There will be different priority lists for different local areas.

Pharmaceuticals are a very chemically-diverse group of compounds and metabolites, so multi-residue detection methods to cover them all are technically challenging. The number of sample preparation approaches is also diverse, with different sample extraction and purification procedures needed for waste water, surface water, soil, sludge, sewage, sediment, landfill leachate, incinerator smoke stacks, ash and plants. A typical approach, such as that used in US EPA Method 1694²², is to segment the target list of pharmaceuticals into subclasses with a different extraction method for each subclass. Incremental improvements²³ now mean that EPA 1694 can cover around 70 different pharmaceutical active residues, encompassing classes of extremely different chemistries. Measurement of the concentration(s) in the purified extract is extremely demanding; not only are concentrations low, but there is a requirement for quantitative accuracy. This is because numerical results are subsequently used for exposure assessments, which can be sensitive to a small absolute error in the measured value at such relatively low concentrations. Most modern test methods are based upon LC-MSMS, sometimes in conjunction with GC-MSMS, in order to provide a high sensitivity and selectivity for a wide scope of chemical classes within a single multi-residue test method. If possible, LC-MSMS methods should use isotopic internal standards to reduce the quantitative uncertainty.





Conclusions

The use of human and veterinary medicines inevitably leads to residues in the environment. It is increasingly apparent that the low concentrations already present are causing adverse environmental effects. These can be incredibly varied, depending on the pharmaceutical, and some effects are very subtle and long-term. There is a large body of evidence from individual research projects and studies. Compared to other bioactive residues, such as pesticides, there is a lack of systematic environmental risk-assessment, regulation, risk-control and monitoring. This varies between different countries, and even between different administrative regions of the same country. High profile environmental risks, particularly endocrine disruption effects and the prevalence of antibiotic resistance, are driving the control of pharmaceutical residues up the regulatory agenda.



About the author

John Points is an independent consultant, offering advice on chemical risks and testing strategies to industry, regulators and laboratories in the food and pharmaceuticals sectors.

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- ¹⁸ Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy
- ¹⁹ Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy
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