Environmental risk management for pharmaceutical compounds

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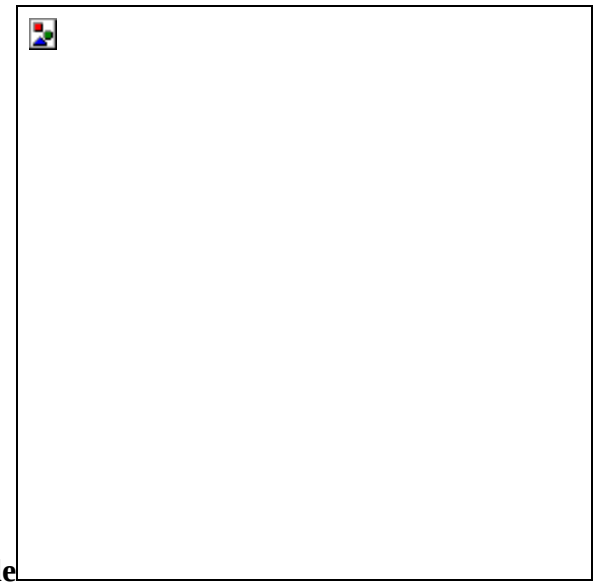
Introduction

Pharmaceuticals are a highly variable group of organic compounds with the potential to cause harm to aquatic ecosystems and human health. Thousands of tones of pharmacologically active substances are used annually but surprisingly little is known about their ultimate fate in the environment (Jones et al., 2001). The data collected to date, rarely provide information on the processes that determine their environmental fate and although they receive considerable pharmacological and clinical testing during development, knowledge of their ecotoxicity is poor. One major concern is that antibiotics found in sewage effluent may cause increased resistance amongst natural bacterial populations (Willis, 2000).

The debate over risks associated with chemicals in the environment represents more than just another disagreement in the scientific community. It has opened the door to a new way of thinking about the onset of uninherited diseases, the nature of scientific investigation, and the role of scientific knowledge in the policymaking process. For example, research evidence on endocrine disruption collected over the last few years has changed dramatically the way we think about chemical risks. In part, this change has also been attributed to the precautionary principle, as a new approach to environmental policy forged in Europe. The term "precautionary approach" declares an obligation to control the dangerous substances even before a definitive causal link had been established between the chemicals and health or environmental effects, and represents a radical departure from traditional approaches to risk assessment and particularly risk management, which includes an integration of the assessment, communication and mitigation of risks.

Risk Assessment

Risk assessment is for chemicals for both the aquatic and terrestrial environment usually involves calculation of the predicted exposure concentration (PEC) and the predicted no effect concentration (PNEC) and their ratio (PEC/ PNEC) on the basis of toxicity data for aquatic or soil organisms or alternatively equally simple calculations for higher animals, including humans (Bound and Voulvoulis, 2004). Regulatory approaches based on risk assessment have seriously failed to anticipate some of the deleterious effects of chemicals. For example, the impact of organochlorine pesticides on birds (Hickey and Anderson, 1968; Edwards, 1973; Ratcliffe, 1980; Newton and Haas, 1984) and mammal populations (Chanin and Jeffries, 1978), the adverse effects of PCBs on the health of humans and ecosystems (Stringer and Johnston, 2001; Harrington and Macdonald, 2002), the uptake and bioaccumulation of polybrominated diphenyl ethers (PBDEs) and the endocrine disrupting effects of tributyltin (TBT) and many other persistent organic pollutants (POPs), were not predicted.



The precautionary principle

In environmental policy, the precautionary principle has emerged as a driving force behind new legislative mandates aimed at reducing public health risks from exposure to harmful environmental contaminants, even before the scientific community has reached consensus on the exact mechanism that may cause adverse effects in humans. The key element is the justification for acting in the face of uncertainty. The precautionary principle is thereby a tool for avoiding possible future harm associated with suspected, but not conclusive, environmental risks

(Grandjean et al., 2004). Since policy makers require scientific information in order to manage risk, the gap in knowledge has been partially filled by the precautionary principle (Burger, 2003). The precautionary principle can be controversial, and critics support the need to wait for "sound science" before taking "costly" regulatory action. However, risks associated with human and ecological health as a result of exposure to environmental pollutants are difficult to assess and accurately quantify. For example, direct human evidence on the endocrine effects of environmental chemicals has been slow to accumulate because of inherent sample size limitations of exposed populations and over-conservative hypothesis testing approaches. Indeed, even huge population-based studies of hormone replacement therapy have been inconclusive regarding both benefits and risks (Gochfeld, 2003). The endocrine disruption hypothesis has also unleashed a revolution in toxicity theory. The traditional theory that 'the dose makes the poison' has proven inadequate in explaining the complex workings of the endocrine system.

Risk Management

Today, the need for managing risks associated with environmental pollutants is great. Although more research is needed to elucidate the full scope of potential adverse implications resulting from environmental pollutants, there is much scope to take mitigating action and opportunities for prevention. The precautionary principle has provided the foundations for building a new risk regulatory pattern under scientific uncertainty. The management of possible risks can still be effective and useful, even if the uncertainty associated with the risk assessment process is high. The new approach to risk management is through an integrated framework, where there is a better balance between precaution and reality. Although the need for scientific evidence is detrimental to limiting uncertainty, there might still be scope for mitigation measures when for example the benefits associated with those measures outweigh the costs involved. The proposed scientific framework for the management of chemicals is based on an environmental risk-benefit analysis tool, which uses the conceptual model of 'sources - pathways – impacts' for the presence of chemicals in the environment (Figure 1). Following this, sources, pathways and impacts can be managed in order for risks to be reduced. Management of the 'sources' could cover restrictions on production, applications and disposal of products containing hazardous chemicals, such as happened in the case of DDT and TBT. Similarly, focusing on pathways,

action could focus on improving removal through wastewater treatment or leachate treatment before disposal to waters from sewage works and landfills respectively.

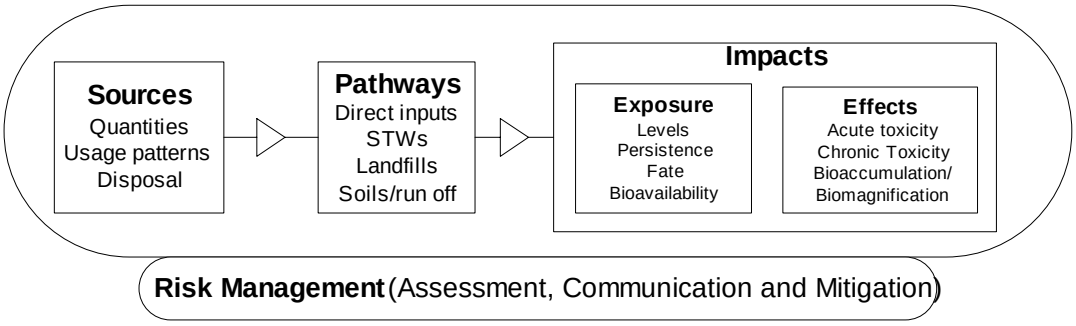


Figure 1. Risk management framework for chemicals in the environment

Risk management for pharmaceutical compounds

Sources: Around the world thousands of tons of pharmacologically active substances are used annually. A large proportion of an administered dose may be excreted, unchanged while metabolites can be converted back to the active compound via bacterial action, and thus ending up in STWs. Disposal of out of date or unwanted medicines may occur via the sink/toilet or in household waste, which is then incinerated or taken to landfill sites. For example, records of drug use in the UK are kept by the Department of Health (prescribed drugs) and the Proprietary Association of Great Britain (over the counter medicines), and details of the twenty-five most used prescription pharmaceuticals in England, by weight were obtained from the statistics division (SD1E) of the UK Department of Health. Data from 2000 prescription items dispensed by community pharmacists, appliance contractors, dispensing doctors and prescriptions submitted by doctors for items for personal administration are sown in Table 1 (Jones et al., 2002).

Table 1. The 25 most used pharmaceuticals by weight in England in 2000

Compound Name	Therapeutic Use	Amount used per year (kg)
Paracetamol	Analgesic	390954.26
Metformin hydrochloride	Anti-hyperglycaemic	205795.00
Ibuprofen	Analgesic	162209.06
Amoxycillin	Antibiotic	71466.83
Sodium valproate	Anti-epileptic	47479.65
Sulphasalazine	Anti-rheumatic	46430.43
Mesalazine (systemic)	Treatment of ulcerative colitis	40421.72
Carbamazepine	Anti-epileptic	40348.75
Ferrous sulphate	Iron supplement	37538.52
Ranitidine hydrochloride	Anti-ulcer drug	36319.24
Cimetidine	H_2 receptor antagonist	35654.20
Naproxen	Anti-inflammatory	35065.98
Atenolol	β-blocker	28976.55
Oxytetracycline	Antibiotic	27195.11
Erythromycin	Antibiotic	26483.78
Diclofenac sodium	Anti-inflammatory & Analgesic	26120.53
Flucloxacillin sodium	Antibiotic	23381.47
Phenoxymethylpenicillin	Antibiotic	22227.59
Allopurinol	Anti gout drug	22095.64
Diltiazem hydrochloride	Calcium antagonist	21791.50
Gliclazide	Anti-hyperglycaemic	18783.11
Aspirin	Analgesic	18105.89
Quinine sulphate	Muscle relaxant	16731.26
Mebeverine hydrochloride	Anti-spasmodic	15497.35
Mefenamic acid	Anti-inflammatory	14522.77

Pathways: Most human pharmaceuticals are released by excretion from the patient or, to a lesser extent, in aqueous waste produced by manufacturing. Recent studies have demonstrated that there is incomplete elimination of many pharmaceuticals during sewage treatment and levels at high ng to low µg per litre concentrations have been found in surface water, groundwater and marine systems (Ayscough et al., 2000). Sewage treatment plants (STPs), may therefore be reasonably expected to be the main point of collection and subsequent release into the environment (Figure 2). In addition, disposal of waste medicines by the general public is often considerable (Slack et all., 2004). The public is under no obligation to return unused or life-expired medicines to pharmacists for safe disposal and such action is often dependent on whether clear advice is given, for example, in any accompanying patient information leaflet and in America even these guidelines do not apply (Daughton and Ternes, 1999a). Drugs disposed can end up in landfills, again posing a threat to surface and groundwater (Ahel et al., 1998). In practice therefore, the majority of people will either flush unused drugs down the drain (where they will eventually pass to a STP) or dispose of them in domestic refuse which will ultimately enter domestic waste landfill sites or, to a lesser extent, be incinerated. Both of these routes represent a risk to the environment (Ternes, 2000b).

The majority of compounds are unlikely be degraded in a STWs and most are unlikely to sorb to sludge, and therefore could be discharged to rivers. This leads to serious consequences in certain parts of the UK, where water is supplied through direct abstractions and in dry periods a large proportion of the flow may be made up of treated sewage effluent. Such a high rate of abstraction and reuse means there is possibility that pharmaceuticals and/or their metabolites might enter the public water supply.

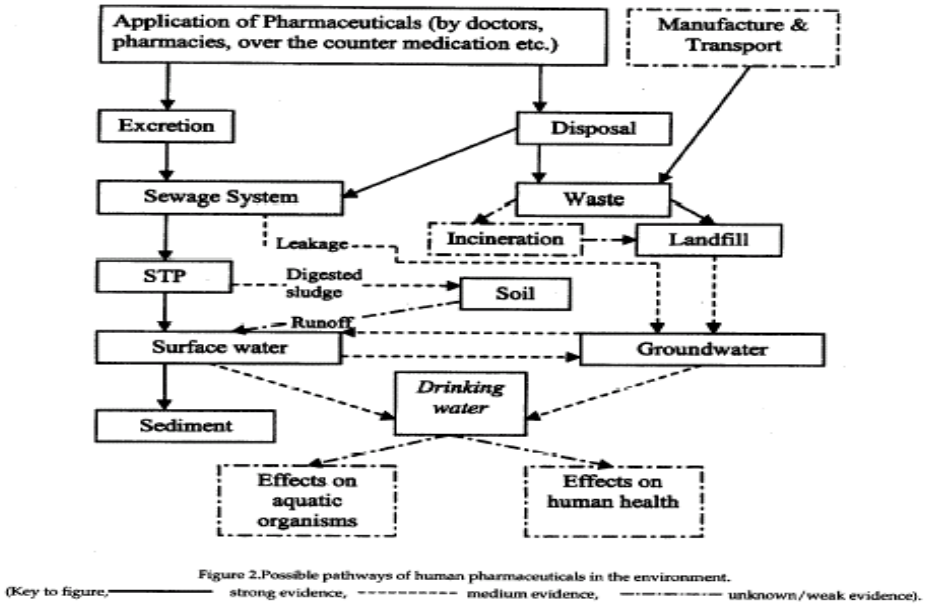


Figure 2. Pathways of human pharmaceuticals in the environment.

Impacts: In contrast to more regulated pollutants, which often have longer environmental half lives, the continual introduction of drugs through sewage effluents may have unknown consequences for aquatic organisms which can be subject to continuous exposure (Daughton and Ternes, 1999). Drugs are used to affect biochemical processes in humans so that environmental exposure of other species may induce adverse or even fatal effects on them (Rand, 1995). There are numerous concerns regarding the hazards of pharmaceutical compounds in the environment, and it is frequently recommended that more research should be done in this area. One area of particular interest is the potential for pharmaceuticals to re-enter the human body. When surface waters are used as sources of drinking water, abstraction points may often be down-stream of effluent discharge points, and groundwater sources have also been found to be contaminated with pharmaceutical compounds (Sacher et al., 2001). In densely populated urban areas with high municipal wastewater discharges and low surface-water flows there is a potential risk of drinking-water contamination by polar organic compounds (Froese et al., 1999).

It is difficult to extrapolate laboratory-based acute toxicity data to the lower concentrations and routes of exposure encountered in the environment, and there remains a wide range of issues relating to the occurrence of potential effects that requires further investigation before the environmental significance of this problem can be fully evaluated. Although advances in analytical chemistry have driven this area of research (pharmaceutical pollution at these levels was not routinely detectable even 10 yr ago and hence was not considered a threat), the development of analytical methods is still an essential part of improving uncertainty, and methods for the determination of drugs in solid phases such as sediments would also be useful (Jones et al., 2004).

It is unlikely that pharmaceutical compounds are present in the environment at concentrations high enough to cause significant harm. However, at sufficient concentrations they have been observed to induce effects in both animals and some plants, and it is possible they may have other effects that have not yet been observed. It would therefore be unwise to conclude these compounds were not having any effect until there is conclusive proof (Jones et al., 2003).

Management:
The widespread dispersion and high volume of usage of pharmaceuticals will most likely lead to a more or less constant presence, albeit in low concentrations, in rivers and other water-bodies. In addition, these compounds will have chronic, rather than acute toxic effects, for example by causing a change in behaviour that reduces the individual fitness of an organism. Poorly characterised processes warrant a more precautionary view on possible environmental fate and effects. Available scientific knowledge is less than that needed to fully assess the risks these compounds pose to the environment, and future work will need to focus on more detailed assessments of specific pathways and effects in the aquatic environment.

Due to their beneficial health effects and economic importance, the best available evidence and data will be required to fully evaluate the costs and benefits before any actions are taken to reduce inputs of drugs to the environment. Pollution control efforts could focus more on reduction, minimization, and elimination at source, where possible, while other policies could include the development of clearer labelling on medicinal products and better guidelines for the disposal of pharmaceutical compounds by patients and medical professionals. This approach

would have the potential benefit of improved consumer health (by minimizing the intake of active substances), as well as reduced health care spending.

Sewage treatment works are likely to be the most significant source of human medicinal compounds to surface waters, while the application of sewage sludge on agricultural land may also contribute a high load of drugs to the aqueous phase after runoff events. Sewage is a continuous, point source, while runoff from agriculture is diffuse, and concentrations are dependent on the application rate and runoff parameters.

Laboratory data on the toxicity of compounds gathered during product development may be able to provide useful information for risk management. The medical and social value of drugs is undoubted, but more data are needed about the ecotoxicological effects of medicines. There will also be a need to adjust the assessment to the specific environmental compartment, organism, and endpoint of the drug in question.

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