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Human pharmaceutical products in the environment – The "problem" in perspective

David Taylor *, Thomas Senac

wca environment, Brunel House, Volunteer Way, Faringdon, Oxfordshire SN7 7YR, UK
Sanofi, 9 rue President Allende, F–94255 Gentilly Cedex, France

HIGHLIGHTS

- The human pharmaceutical group are no more of a problem than other group of micropollutants.
- Individual pharmaceuticals may pose problems but should be dealt with case by case.
- A satisfactory ERA is needed for all micropollutants including pharmaceuticals.
- Faulty problem diagnosis can lead to inappropriate solutions and wasted resources.

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ABSTRACT

Concerns about the potential for significant environmental impact from residues of human pharmaceuticals emerged at the beginning of the 21st century. Since then there has been an exponential rise in the number of publications and conferences on this "problem". However, this intense focus on human pharmaceuticals is misplaced. Pharmaceuticals do not consist of a coherent group of substances with similar chemical, structural, biological or toxicological properties. Pharmaceuticals are only identifiable from their use: in other words substances can be divided into two classes, those that are used as pharmaceuticals and those for which a possible pharmaceutical use has not yet been discovered. For example, nitroglycerine, Warfarin and dimethyl fumarate, initially sold respectively as an explosive, a rodenticide and a mould inhibitor have subsequently all been used as pharmaceuticals.

As analytical science advances, an increasing range of environmental contaminants, including pharmaceuticals, is being identified at sub μg L^{-1} concentrations. Although, human and environmental exposure to these contaminants will be low, all of them need to be subjected to risk assessment on a case by case basis. Many of these substances, including human pharmaceuticals, may have little, if any, impact on human health or the environment, however for some substances there may be a significant risk and in these cases appropriate action should be taken. However considering all human pharmaceuticals as a special case, isolated from the wider range of emerging contaminants, is scientifically unjustifiable and diverts resources away from the consideration of other substances that may be of considerably more significance.

1. Introduction

The rapid development of highly sensitive and automated analytical instrumentation in the latter part of the 20th century has meant that in the 21st century we can now see a large number of substances in the aquatic environment that were previously undetectable, despite having potentially been present for many years (Richardson and Bowron, 1985). In the majority of cases, this was seen merely as an interesting observation and although these substances came to be called "emerging contaminants" there appeared to be little overt concern at their discovery. However, pharmaceuticals, as a class of substances, came in for special attention for two reasons: firstly John Sumpter and his team (Purdom et al., 1994; Sumpter and Jobling, 1995) in their investigation of fish feminisation in UK rivers had identified that ethinyl estradiol (EE2), a pharmaceutical used in birth control and hormone replacement therapies, was probably a contributory factor to this effect and, in laboratory studies, had been shown to be active at a few ng L^{-1}, similar to concentrations then being detected in surface waters. Secondly it was recognised that data on the ecotoxicology of pharmaceuticals was very sparse with little data on chronic effects. The

* Corresponding author. Tel.: +44 (0) 7827 336485.
E-mail address: david.taylor@wca-environment.com (D. Taylor).

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question that then arose was: are all pharmaceuticals as ecotoxciologically potent as EE2 or is this an exception? If EE2 was not exceptional, then, in the light of our new knowledge on the levels of pharmaceutical residues in the aquatic environment, there might be a serious problem.

Since 2000 a multitude of studies and reviews e.g. United Kingdom (Ayscough et al., 2000), Sweden (SMPA, 2004), Korea (Park, 2005), Norway (Grung et al., 2007), European Union (Roig, 2010)) have been published on this subject, the majority of which have reached broadly similar conclusions;

- Pharmaceuticals can now be detected at ng L^{-1} concentrations in the majority of surface waters whereas previously they were present but invisible.
- The principal route to the environment is from their excretion from patients, although discharges from manufacturing and inappropriate disposal of unused and life expired products can also make a contribution.
- Concentrations are such that adverse consequences for human beings and acute impacts on wildlife are considered to be very unlikely.
- Data are currently insufficient to determine if long term exposure to these concentrations poses a significant risk to wildlife populations. However the potency of EE2 does appear to be exceptionally high.

However pharmaceuticals as a class of substances are still being singled out for special attention, with voluminous amounts of environmental research being published annually. Much of this research adds very little, if any, value since it mainly identifies environmental presence or hypothesises potential environmental risks related to pharmaceuticals without trying to assess environmental risk at environmentally relevant concentrations. In addition, considerable effort is being devoted to how to curtail the release of all pharmaceuticals to the environment despite knowing that among the different sources, the main one is from patient's excretion. Although some of the proposed mechanisms could be considered as simple good practice, others, such as the upgrading of wastewater treatment plants, could be both resource and carbon intensive.

2. What makes pharmaceuticals "different"?

Pharmaceuticals are but one class of micro contaminants that emerged at the end of the 20th century due to major improvements in analytical science. Although the initial interest in them could be explained by the lack of data combined with the concern that they all might be extremely potent, why does the interest continue? What is it about pharmaceuticals that results in this major differentiation from other micro contaminants?

Pharmaceuticals are not a class of substances like phthalates or PCBs. They have no chemical, physical, structural or biological similarities. Pharmaceuticals can be simple aromatic molecules like the anaesthetic propofol,[1] simple aliphatic molecules like the vasodilator, nitroglycerine[2] or more complex but still relatively low molecular weight molecules like the statin, atorvastatin.[3] Increasingly, new pharmaceuticals are likely to be very heavy molecular weight biopharmaceuticals such as insulin.

In fact the only common factor which unites pharmaceuticals is their use: a substance is identified as a pharmaceutical only if it is used as a human (or animal) medicine. Thus any substance, in theory, might be identified, at some point, as a pharmaceutical and a number of pharmaceuticals are also used for non pharmaceutical purposes. For example the vasodilation properties of nitroglycerine were only discovered after its invention by Alfred Nobel as the active constituent of dynamite. Similarly, the discoverers of Warfarin[4] at the University of Wisconsin in 1948 would be amazed that at the beginning of the 21st century this rat poison is still the most prescribed anticoagulant in the world. This is not just a historical oddity. The most recent example is dimethyl fumarate which has been widely used as a mould inhibitor. It is interesting to note that a year after the European Union applied the new REACH regulation to impose severe restrictions on its use as a mould inhibitor (EU, 2012), dimethyl fumarate (Tecfidera) was granted a pharmaceutical marketing authorisation by the European Union for use against multiple sclerosis (EMA, 2013).

So it is clear that any chemical substance, either natural or synthetic might be used as a pharmaceutical and it is also clear that all substances are capable of causing harm to the environment or to human health at some concentration. In which case why are pharmaceuticals as a group being treated as if they were different to all other emerging microcontaminants? A number of arguments are regularly advanced but none of them stand up to scrutiny.

The most frequent reason put forward is that pharmaceuticals are different to other emerging contaminants because they have been designed to be biologically active. As a consequence it is felt that they will be significantly more harmful that other substances and also that with some additional effort they could be further designed to be more environmentally friendly. This however represents two fallacies since pharmaceuticals are "discovered" rather than designed and they are not necessarily more biologically active than any other substance.

Many people have an idealised picture of the medicinal chemist sitting at a computer using molecular construction software to design pharmaceuticals to treat specific diseases. However the process is one of discovery rather than design. Scientists in discovery teams use targeted and automated high throughput screening techniques to search existing chemical databases for molecules that show efficacy at impacting the target pathway, or receptor, identified by the research team looking at the cause of the disease. In the majority of cases several lead compounds will be identified that have some activity in the chosen area. These are then subjected to further structural optimisation to maximise their efficacy and safety. Although this might be considered to be drug design, in essence it is based on making relatively minor modifications to an existing chemical structure.

Our current inability to design drugs *ab initio* also makes it more difficult to specifically produce pharmaceuticals that have lower environmental persistence. However, although 'environmental friendliness' is not a key driver in pharmaceutical research, there are two reasons why this is not, in reality, a significant concern. Firstly, even if all the 3000 + existing pharmaceuticals on the EU market had been originally designed to degrade by 90%, we would still be discussing the issue of pharmaceuticals in the environment. Currently it is the presence of detectable residues combined with the absence of sufficient data on chronic environmental exposures that is causing concern. A 90% reduction in current environmental residue concentrations would simply have reduced them from a range of 1.0–0.01 μg L^{-1} to a still easily detectable 0.1–0.001 μg L^{-1}.

Secondly the next generation of pharmaceuticals will, in any case, have much lower environmental persistence than those currently on the market. This is because making new pharmaceuticals more effective for the patient also reduces environmental

[1] 2,6-Diisopropylphenol.

[2] 1,2,3-Trinitroxypropane.

[3] (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid.

[4] (RS)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)- 2H-chromen-2-one.