



CHEMTrust

Protecting humans and wildlife
from harmful chemicals

PHARMACEUTICALS IN THE ENVIRONMENT: A GROWING THREAT TO OUR TAP WATER AND WILDLIFE.





This report was produced by CHEM Trust, a UK charity working to protect humans and wildlife from harmful chemicals. CHEM Trust's particular concerns relate to chemicals with hormone disrupting properties, persistent chemicals that accumulate in organisms, the cocktail effect and the detrimental role of chemical exposures during development in the womb and in early life. CHEM Trust strongly supports the conservation of biodiversity and believes in the importance of wildlife protection. Furthermore, monitoring wildlife populations can provide vital insights into contaminant related threats to human health.

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Glossary

ANSES	French National Agency of Food, Environment and Work Place Safety (Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail)
BAT	Best Available Techniques
BCF	Bioconcentration Factor, that is the ratio of the concentration of a chemical in an organism to the concentration of the chemical in the surrounding environment
BREF	BAT Reference Document in the context of the Industrial Emissions Directive
CIP	Chemicals Investigation Programme
EA	Environment Agency of England and Wales
EEA	European Environment Agency
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency (formerly EMEA)
EMEA	European Agency for the Evaluation of Medicinal Products (superseded by EMA)
EPAR	European Public Assessment Report
EQS	Environmental Quality Standard, which is the concentration of a particular pollutant in water, sediment or biota which should not be exceeded in order to protect human health and/or the environment.
EQSD	Environmental Quality Standards Directive
ERA	Environmental Risk Assessment
Estrogens	17 β -estradiol, estrone and estriol are natural estrogens, although the former is also used in Hormone Replacement Therapy (HRT) and the latter two are also used in pharmaceuticals. 17 α estradiol and 17 α -ethinyl estradiol originate from the contraceptive pill
GCMS	Gas Chromatography-Mass Spectrometry
IED	Industrial Emissions Directive (2010/75/EU)
LCMS	Liquid Chromatography-Mass Spectrometry
Metabolite	Slightly altered form of a pharmaceutical or other chemical that has passed through an animal or human. This may or may not still have similar activity
NGO	Non Governmental Organisation
NOEC	No Observed Effect Concentration
NSAID	Non-Steroidal Anti-Inflammatory Drug
Product of environmental transformation	Slightly altered form of a pharmaceutical or other chemical that has been transformed in the environment (eg. by sunlight or water)
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
REACH	European Union regulation (2006/1907/EC) concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
SAICM	Strategic Approach to International Chemicals Management
SEPA	Scottish Environmental Protection Agency
STWs	Sewage Treatment Works
UKWIR	UK Water Industry Research
WFD	Water Framework Directive (2000/60/EC)
WWTP	Waste Water Treatment Plant

1.

Executive Summary

The pollution of the environment resulting from the increasing use of human and veterinary pharmaceuticals poses a threat to wildlife and also humans via drinking water supplies. However, monitoring and controlling the presence of pharmaceuticals in the environment is difficult and currently inadequate.

Pharmaceutical residues have already devastated some wildlife populations. Furthermore, some pharmaceuticals have also been found in otters and fish, but there is still inadequate research into their effects on mammals, fish and invertebrates in the wild. Unfortunately, it is likely that many effects on wildlife will pass unnoticed, especially where smaller species are concerned.

Between 1990 and 2007 in the EU, the retail value of the market for prescription and non-prescription human medicines quadrupled (Bio IS, 2013). Global per capita consumption is increasing, a trend which looks set to continue with our ageing population. Unfortunately, generally 30-90% of the active ingredient is excreted after ingestion and can enter the environment via sewage treatment works (STWs). In addition, incorrect disposal of unwanted drugs can add to the problem, such that pharmaceuticals in the environment are a rapidly growing problem.

Wildlife has already suffered from exposure to residues of pharmaceuticals. The two most notable harmful effects include the deaths of millions of vultures in Asia due to the use of an anti-inflammatory pain killer in cows, and the widespread feminisation of male fish caused to some extent by exposure to synthetic estrogens used in the birth control pill and for treating menopause-related problems.

However, many other more subtle effects have been reported in animals and there is a paucity of monitoring

data, such that there is little doubt that other pharmaceuticals will also be found to be causing effects in future. Aquatic wildlife is exposed to low levels of many pharmaceuticals, and as many rivers and groundwaters are also used as drinking water for humans, or as irrigation water for food crops, measures which reduce wildlife exposure will also benefit people.

The types of pharmaceutical products raising concern from the perspective of their potential effects on wildlife include (but are not limited to): antibiotics (for infections); anti-cancer drugs (to treat cancer); antidepressants (to treat depression); anti-parasitics (to treat parasites); non-steroidal anti-inflammatory drugs (NSAIDs) (for reducing inflammation to ease joint pain and stiffness); beta-blockers (for hypertension and heart problems); lipid regulators (to reduce cholesterol); oral contraceptives and hormone replacement therapies and analgesics (to treat pain).

Human exposure can arise from tap water or from food chain contamination. Crops can take up some pharmaceuticals from soil fertilised with manure or sewage sludge. With regard to harmful effects on human health from environmental exposure to pharmaceuticals, it has been suggested that antibiotics, anti-parasitics, anti-fungals and anti-cancer medicines might prove to be the most important, because these are designed to kill organisms or cells.

Furthermore, there is also concern that antibiotics in the environment may contribute to the increasing problem of antibiotic resistance in bacteria.

There are still many gaps in our understanding of the effects of pharmaceuticals in the wide range of organisms in the environment, particularly as the potential effects



Vulture [Credit: i-Stock/perreten]

cannot always be predicted from their therapeutic effects on humans or from tests on a few species. Coupled with this, is the problem of trying to identify whether there might be adverse effects due to the 'cocktail effect', that is the simultaneous exposure to low levels of many such substances and other pollutants in the environment, such as pesticides.

Some pharmaceuticals are persistent in the environment, while others seem to be continuously present in the environment because of their ubiquitous use. They are all designed to be biologically active and to cause specific effects, so perhaps it should not be surprising that many can affect wildlife at low doses.

A global review has found that 713 pharmaceuticals (of which 142 are transformation products) have been looked for in the environment and 631 have been found above their detection limits (IWW, 2014). Sixteen pharmaceutical substances were reported at many locations worldwide. These were: diclofenac (for pain and inflammation); carbamazepine (an anti-epileptic); ibuprofen (for pain and inflammation); sulphamethazole (an antibiotic); naproxen (for pain and inflammation); trimethoprim (an antibiotic); paracetamol (for pain); clofibril acid (from the lipid lowering drug); ciprofloxacin (an antibiotic); ofloxacin (an antibiotic); norfloxacin (an antibiotic); acetylsalicylic acid (aspirin, a pain killer); as well as the sex hormonally active substances, estrone, 17 β -estradiol, 17 α -ethinyl estradiol and estriol (IWW, 2014).

Several pharmaceutical substances have been found at very low levels

in drinking water, but as there is no legal requirement to monitor such substances in tap water, data are patchy. At present, the levels of individual pollutants are low but little is known about the long term health implications and there is concern regarding potential 'cocktail' effects. In order to afford adequate protection of human health, CHEM Trust considers that there is a need for far greater scrutiny of the levels of pharmaceuticals in tap water.

Reducing wastage and ensuring the least environmentally damaging pharmaceutical is used should be part of effective strategies to protect the environment. However, given that some pharmaceuticals will inevitably be required, improved sewage treatment is a necessity in some areas.

The challenge ahead is not only to ensure adequate data provision and effective regulation, but also to raise awareness and educate doctors, veterinarians, pharmacists and the public on the important role that they must play in reducing pollution at source. For example, doctors and veterinarians should prescribe the least environmentally damaging drug available for a disease. Furthermore, the public should be encouraged to reduce unnecessary consumption and take-back unwanted drugs so that they can be disposed of properly.

There are around 3000 pharmaceutical products authorised in the EU, with the numbers used in each Member State varying between 850-3000. More research is undoubtedly needed because as yet there are not even analytical techniques to monitor many of the

pharmaceuticals in use today in water or in soil. A priority is to identify those specific medicines likely to cause most harm and to try to prevent damage.

This report reviews the current knowledge, outlines the extent of the problem and makes some recommendations. It highlights that the current legal framework in the EU needs significant improvement in order to protect wildlife and humans from harm. Moreover, it notes the need for global action to address this important emerging issue of growing concern.

1.1 Key recommendations

The pharmaceutical industry must:

- Accept their responsibility for comprehensive environmental stewardship of their products. They should accept responsibility for their products from cradle to grave, and moreover – under the polluter pays principle - should pay for pollution control measures and monitoring.
- Start developing drugs that are ‘green by design’.

UK and other EU National governments should:

- Act to reduce usage of veterinary medicines in agriculture and aquaculture.
- Ensure sewage treatment works (STWs) are improved so that they remove pharmaceutical pollution from waste waters. There is also a need for continued research and development to optimise water treatment technologies. In particular the water industry should ensure that STWs are as energy efficient as possible and move to the use of renewable energy sources in order to reduce climate impacts.
- Ensure there are effective take-back schemes for unused medication.
- Bring together stakeholders – including manufacturers, regulators, doctors, veterinarians, pharmacists and consumer groups – to agree strategies and methods for reducing the levels of harmful pharmaceuticals in the environment.
- Support stronger and more effective measures on pharmaceuticals and veterinary medicines at EU level.

Recommendations for the EU include:

- Strengthen the environmental aspects of the system for authorising medicines, including better testing and more consideration of environmental impacts.
- Ensure that all EU countries have effective take-back schemes for unused medicine.
- Implement an environmental classification scheme for pharmaceuticals, with environmental authorities having full access to safety data on new medicines.
- Develop a phased approach for establishing and addressing the environmental risks of older pharmaceuticals.
- Strengthen standards for, and monitoring of, pharmaceuticals in (i) drinking water, (ii) sewage sludge, (iii) food and (iv) the environment.

At the global level:

- There is a need for enhanced global co-ordination, monitoring, and capacity building, particularly in developing countries. To this end, pharmaceuticals in the environment should be agreed to be an emerging policy issue under the auspices of the United Nations Environment Programme’s global Strategic Approach to International Chemicals Management (SAICM) (see section 4).

2. Introduction

Hundreds of active chemicals used in human and/or animal medicines (and their metabolites and degradation products) contaminate water and soil. Some of these pharmaceuticals are persistent, while others, which are termed pseudo-persistent, are continuously found in the environment because they are discharged frequently and extensively. Pharmaceuticals have a very wide range of effects and, for example, some of these substances are endocrine disruptors (eg. synthetic hormones) and some are designed to kill bacteria (eg. antibiotics).

Pharmaceuticals in rivers can threaten drinking water resources and aquatic wildlife. Levels worldwide can range from nanograms per litre (ng/L) (or parts per trillion 10^{12}) to milligrams per litre (mg/L) (or parts per million 10^6) in highly polluted rivers (and also in ground-waters). However, in the EU, pharmaceuticals are typically found at low levels.

Almost everyone has taken medicines which have been prescribed by a doctor, or bought over the counter in a pharmacy, and in the EU medicines are now used in vast quantities. In 2007, the market for prescription and non-prescription medicines for human use in the EU was worth around €214 billion (£169.7 billion) at retail prices up from €48 billion (£38 billion) in 1990 (Bio IS, 2013). Global per capita consumption is on the increase (Ronnlund T, EEA, 2010), a trend which looks set to continue with our aging population.

Medicines often significantly improve our quality of life, but little is known about the long-term implications for wildlife and humans as residues of these drugs find their way into the wider environment. Pharmaceuticals have been specifically designed to be biologically active and although much is known about their effects at therapeutic doses, much less is known about their effects due to long-term, low-level exposure.

Despite several research projects that have raised some concerns there are still many gaps with regard to understanding the effects of

pharmaceuticals on the wide range of organisms in the environment, particularly as the potential effects cannot always be predicted from their therapeutic effects on humans or from tests on a few species. Coupled with this, is the problem of trying to identify whether there might be adverse effects due to the 'cocktail effect', that is the simultaneous exposure to low levels of many such substances and other pollutants in the environment, such as pesticides.

The types of pharmaceutical products raising concern from the perspective of their potential effects on wildlife include (but are not limited to): antibiotics (for infections); anti-cancer drugs (to treat cancer), antidepressants (to treat depression); anti-parasitics (to treat parasites); NSAIDs (non-steroidal anti-inflammatory drugs for reducing inflammation to ease joint pain and stiffness); beta-blockers (for hypertension and heart problems); lipid regulators (to reduce cholesterol); oral contraceptives and hormone replacement therapy (for birth control and the menopause) and analgesics (to treat pain) (see UBA, 2014a; Isidori et al., 2007; PHARMA, 2014).

This briefing is focussed on the environmental impacts of our modern reliance on medicines. It particularly highlights the need to protect wildlife, but as many rivers and groundwaters are also used as drinking water for humans, or as irrigation water for food crops, measures which reduce wildlife exposure may also benefit people. At the end of this briefing a number of important recommendations are made for reducing the unwanted human and environmental impacts of pharmaceuticals.

2.1 Routes to the environment

A considerable proportion of the original drug can be excreted unchanged such that in general, between 30-90% of the orally administered dose is excreted as active substance in the urine or faeces of animals and humans. This means that discharges from hospitals and municipal sewage works are important routes by which pharmaceuticals reach the environment. Indeed, in the EU, with regard to pollution by human pharmaceuticals, it will be the normal use, as well as the incorrect disposal of medicines down the lavatory, that is likely to be more problematic than the discharges from production sites. In contrast, in developing countries, such as India, very high levels of pharmaceutical residues have been reported downstream of some production facilities (Fick et al., 2009). Nevertheless, in some areas in the EU, discharges from production will be an important source.

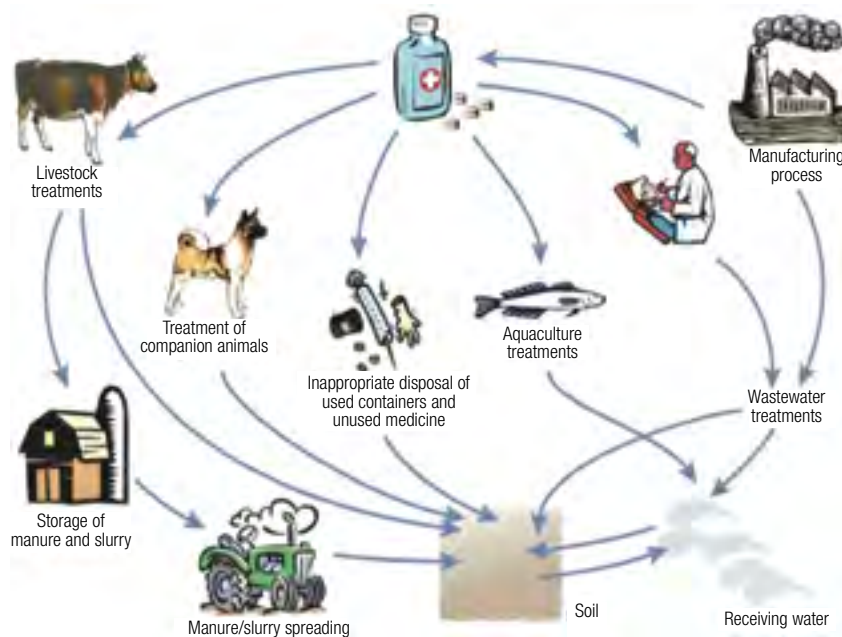
For veterinary drugs, intensive animal husbandry and aquaculture can result in significant releases of pharmaceuticals into the environment. Manure and slurries are important routes by which veterinary medicines, in particular, can contaminate land, and similarly certain human pharmaceuticals can also find their way into the environment from the use of sewage sludge on agricultural land. For example, several pharmaceuticals, derived from sewage sludge, have been shown to have the ability to transfer to crops (Wu et al., 2010), and similarly, antibiotics have been found in food plants (lettuce, corn and potato) grown using animal manure (Dolliver et al., 2007).

Composting does tend to reduce the levels of these pharmaceuticals, but for those drug residues which do end up in the soil, unfortunately, little is known about their fate and behaviour and particularly the effects of these substances on soil microbes. Landfills accepting sewage sludge can

also produce leachate with significant amounts of pharmaceuticals. However, the three main sources by which human pharmaceuticals result in widespread contamination of rivers are:

- i) From the incorrect disposal of unwanted drugs down the drain or down the lavatory (and then via STWs).
- ii) As a result of the medicine being consumed and either it, or a metabolite, being excreted and ultimately being released via a STWs, or from STWs after dermal applications are washed off the skin during bathing.
- iii) From pharmaceutical production sites or medical facilities either via waste water treatment plants (WWTPs) or via direct discharges.

Pharmaceuticals: Routes to the Environment



(Taken from Boxall ABA (2004). The environmental side effects of medication, EMBO Vol.5, No.12, p1111. Reproduced with permission from EMBO Reports)

3. Pharmaceutical regulation in the EU



Man holding 3 bottles of pills [Credit: i-Stock/shorrock]

In the EU, pharmaceuticals require licencing (marketing authorisations) before they can be placed on the market, and in order to obtain such a licence for a new product, a pharmaceutical company must demonstrate its quality, safety and efficacy. The body that coordinates this in the EU for human medicines is the European Medicines Agency (EMA), based in the UK. If only individual country authorisation is sought, then this falls to the Member State's regulatory authority. In the EU, there are 4 possible authorisation procedures from which industry can choose. These include the centralised authorisation procedure (EU wide), the national authorisation procedure (single Member State), the decentralised procedure (where the applicant applies for authorisation in more than one Member State), or the mutual recognition procedure (where a drug already authorised in one Member State is allowed to be used by one or more other Member States). Even in the centralised procedure, the national authorities are very much involved in the assessments, e.g. acting as rapporteurs.

In the EU there are around 3000 pharmaceutical products authorised, with the amounts used in each Member State varying between 850-3000 (Bio IS, 2013). The laws and processes by which human and veterinary medicines are regulated in the EU are comprehensively set out in chapter 8 of the Bio Intelligence Service Report, "*Study on the environmental risks of medicinal products*" (Bio IS, 2013). This CHEM Trust document will therefore not repeat all the procedures for authorisation and the legal constraints, except to highlight some of the large number of shortfalls which need to be remedied.

As of 2014, a revision of the EU veterinary medicines Directive 2001/82/EC and other legislation on veterinary medicines is well underway, with a Commission proposal being adopted on 10th September. The Commission stressed that this proposal was needed to reduce the regulatory burden and to increase the number of medicines available to prevent and treat diseases in animals. The proposed regulation would make it possible to keep certain antibiotics solely for human use, and also it would introduce stricter controls over the use of medicated feed, in particular banning antimicrobials in food as a preventative measure or as a growth promoter (EC, 2014). However, there are concerns that the final regulation will focus too much on reducing industry costs, rather than on improving health protection.

3.1 Regulation of marketing authorisations of veterinary and human medicinal substances (Directives 2001/82/EC and 2001/83/EC)

In the case of a veterinary medicine, it is possible for the results of the environmental risk assessment (ERA) to lead to a refusal of a marketing authorisation. However, for human medicines the ERA cannot, in itself, result in the rejection of an application to market a pharmaceutical. This means that the pharmaceutical industry has little incentive to try to design human drugs which do not damage the environment.

In addition, ERAs may be of poor quality, or be totally absent in the case of older products. Specifically:

- ERAs are lacking for most human medicinal products, because legislation only requires them on new products authorised after 30 October 2005.
- Many ERAs are inadequate, because a phased approach to data generation operates, with more information only required if phase 2 is triggered. This means that some environmentally damaging properties may not be discovered, because phase 2 may not be triggered, as this is based on the level of exposure. Indeed, there are some examples (see Bio IS, 2013, p126) of medicines that have harmful environmental effects when present in the environment at concentrations less than those which trigger phase 2. Moreover, these exposure triggers for both human and veterinary medicines do not take into account metabolites or products of environmental transformation.
- Similarly, in the second phase of the ERA there are again 2 tiers (A and B) and only if certain triggers are exceeded (eg. the predicted environmental concentration is greater than the predicted no effect concentration (PEC>PNEC)) does the more detailed consideration required in tier B kick-in. In tier A of Phase 2, the likely impact of the substance is assessed using

a range of standard tests, but the second tier (tier B) involves more detailed investigations into effects in sediments or water or soil or wherever is likely to be most exposed. Unfortunately, the predicted no effect concentrations may be only based on acute toxicity studies rather than chronic effects. Furthermore, the trigger value to undertake tier B of phase 2 does not take into account potential mixture effects, which are quite possible given the likelihood of substances with similar effects already being present in the environment. This means that tier B is all too often not required.

- Another factor which leads to poor quality ERAs, is that the EMA committee looking at these for human medicines does not have to have anyone specifically appointed for their expertise in ecotoxicity and environmental risk assessment.
 - Also, the quality of the ERAs may vary greatly between products and when submitted in different Member States.
 - For veterinary medicines, a PBT assessment (which assesses its potential to persist, bioaccumulate and cause toxic effects) only needs to be conducted in Phase 2 of the ERA. This means that if the trigger values (ie. likely to be in the environment above a certain concentration) are not met, then there will be no PBT assessment. This situation for veterinary medicines needs to be changed because a PBT assessment is crucial to determine the potential for long term effects.
- For human medicines, the situation is better, because a PBT screening is always required, and if considered relevant, a further assessment should be performed as in the REACH PBT assessment. This is regardless of whether the substance's environmental concentrations meet the trigger value under phase 1.
- Another shortfall of the ERA, is that it relates to the medicinal product as a whole and not the active ingredient, and so the totality of exposure is not

considered because there may be more than one medicinal product on the market utilising the same (or similar) active ingredients.

- Another problem that does not serve to drive up the quality of the assessment is that ERAs are not publicly available in many cases due to commercial confidentiality concerns. At the Member State level, the availability of the environmental information varies from one country to another. A number of competent authorities in some Member States publish a public assessment report, but others do not. For example, Belgium, Bulgaria, the Czech Republic and Romania do not publish information on the ERA results for public review (Bio IS, 2013).

For every human medicine granted a central marketing authorisation, the EMA publishes a scientific assessment report called the European Public Assessment Report (EPAR). Some of these, but not all, contain a section called ecotoxicity / environmental risk assessment, although this can be very short. Similarly, in EPARs for veterinary medicines, the reference to the ERA can be just one sentence stating that it has been provided. This situation needs to be improved.

Other problems exist, which are not due to poor or absent ERAs. In particular, risk mitigation measures may be imposed on the applicant for a marketing approval, and for example, for a veterinary medicine such a measure might be that the animals have to be stabled for a certain number of days after treatment. However, there is no EU legal obligation to carry out monitoring to ensure that these conditions are followed.

Nevertheless, Regulation 726/2004 (as amended) provides a mechanism whereby when urgent action is essential to protect humans or the environment, a Member State may suspend the use of either a veterinary or human pharmaceutical in its territory.

3.2 Regulation of pharmaceuticals as water pollutants

Directive 2000/60/EC of the European Parliament of the Council establishing a framework for Community action in the field of water policy (the Water Framework Directive (WFD)), as amended by its daughter directives, the Environmental Quality Standards Directive (EQSD) (2008/105/EC) and the Priority Substances in Water Directive (2013/39/EC)

European regulators have, so far, taken little concrete action to address pharmaceuticals in water.

The original Water Framework Directive (WFD) provides a framework to deal with chemical pollution affecting water. The Environmental Quality Standards Directive (EQSD) amends the WFD to mandate the creation of a priority list of substances, which have been prioritized for action on the basis of risk to or via the aquatic environment. 'Priority substances' must be monitored in water (or sediments and biota) at set frequencies and progressively reduced. Annex X of the WFD, as amended by the EQSD in 2013, currently contains 45 'priority substances', none of which is an active pharmaceutical ingredient.

Some years ago, a proposal from the European Parliament to review 4 medicinal products with a view to possibly adding them to the priority substance list was postponed. These substances were amidotrizoate, carbamazepine, lopamidol and diclofenac, although as noted below, the latter has now at least made it on to the 'watch list'.

In 2012, the Commission proposed the inclusion of 3 pharmaceuticals on the list of 'priority substances'. These were 17 α -ethinyl estradiol (used in the contraceptive pill), 17 β -estradiol (endogenous estrogen and used in hormone replacement therapy) and diclofenac (a painkiller). Following intense industry pressure,

this was not agreed and the compromise reached during the political negotiations led to these 3 pharmaceuticals being placed on the first 'watch list' with the aim of gathering monitoring data to support future reviews of the priority list and "for the specific purpose of facilitating the determination of appropriate measures to address the risk posed by these substances."

According to Directive 2008/105/EC (EQSD), the 'watch list' mechanism was needed to provide high-quality monitoring information on potentially polluting substances in the aquatic environment to support future prioritisation. The substances targeted include those for which the available monitoring data are either insufficient or of insufficient quality for the purpose of identifying the risk posed across the EU. Thus, the 'watch list' was brought in to identify a limited number of substances which would be monitored EU-wide for up to 4 years (Carvalho, 2014).

A report from the EU Joint Research Centre (JRC) recommended that in addition to diclofenac, 17 β -estradiol and 17 α -ethinyl estradiol, which are already agreed for the 'watch list', an additional 7 substances should be included in the first 'watch list'. Two of the additional substances it proposed were pharmaceuticals; the antibiotic, erythromycin, and trichlorfon, which although now banned as a pesticide, is still used as veterinary pharmaceutical (Carvalho, 2014).

The priority list is revised every 4 years and therefore 'watch list' substances for which a significant risk at EU level is confirmed could be included in the next revision of the priority substances list.

'Priority hazardous substances' consist of substances for which Member States should implement necessary measures for the cessation or phasing out of emissions, discharges and losses, while for the 'priority substances', there is still a need to progressively reduce their levels. For the contraceptive pill and other pollutants this would mean a big investment in the level

of treatment at certain STWs in EU Member State level, including the UK. Given that the combined exposures to hormone disrupting substances in certain rivers pose a threat to fish and probably other species, such investment is crucial. Implementing the necessary improvements at STWs is needed to protect wildlife while still enjoying the benefits of modern medicine. However, improving STWs will require accelerated research and the development of new and more efficient approaches, which include maximising the use of renewable energy to combat effects on climate.

Directive 2013/39/EU regarding priority substances in the field of water policy.

In this Directive, the European Commission is instructed to look further into the problem of water pollutants, and in particular to come up with proposals to handle the problem of pharmaceuticals in the environment.

Directive 2013/39/EU states in "Article 8c: the Commission shall, as far as possible within two years from 13 September 2013 develop a strategic approach to pollution of water by pharmaceutical substances. That strategic approach shall, where appropriate, include proposals enabling, to the extent necessary, the environmental impacts of medicines to be taken into account more effectively in the procedure for placing medicinal products on the market. In the framework of that strategic approach, the Commission shall, where appropriate, by 14 September 2017 propose measures to be taken at Union and/or Member State level, as appropriate, to address the possible environmental impacts of pharmaceutical substances, particularly those referred to in Article 8b(1), with a view to reducing discharges, emissions and losses of such substances into the aquatic environment, taking into account public health needs and the cost-effectiveness of the measures proposed."

Therefore, by 13th September 2015, the European Commission must come up with a strategic approach for water pollution by pharmaceuticals, which has environmental objectives and takes into account public health needs as well as cost effectiveness.

Furthermore, by 14th Sept 2017 the Commission has to propose actual measures to address environmental effects of pharmaceutical substances.

3.3 Regulation of drinking water

As regards the protection of drinking water, EU law requires that Member States take measures necessary to ensure that water intended for human consumption is free from substances in concentrations that constitute a potential danger to human health, with emphasis on the precautionary principle.

However, there is no specific legal requirement in EU law to monitor the levels of pharmaceuticals in drinking water.

3.4 Pharmaceuticals as soil pollutants

The issue of soil contamination by medicinal products is not covered at EU level, and the majority of national laws in Member States also do not cover this specific issue. Thus, although there is UK legislation relating to heavy metals in sewage sludge applied to land, there is no obligation to monitor or regulate pharmaceutical residues present in sewage sludge (Bio IS, 2013).

Nevertheless, 7 pharmaceuticals have been looked for in sewage sludge from UK STWs and all were found to be present. Six were monitored in sludge from 28 STWs and found to be present at the mean concentrations in mg/kg dry weight shown in parenthesis: ibuprofen (0.27); propranolol (0.14); erythromycin (0.06); ofloxacin (0.22); oxytetracycline (7.63); fluoxetine (0.13). Diclofenac was monitored at 7 STWs and found with a mean concentration of 0.06. However, although soil PNECs for pharmaceuticals do not exist, the investigators predicted that soil concentrations after application of the sludge to land posed negligible environmental risk for these pharmaceuticals (Jones et al., 2014).

3.5 Research Activities

There are also EU research initiatives looking at the environmental effects of many of the older pharmaceuticals which were on the market prior to the requirement for an ERA. For example, the Innovative Medicines Initiative is a joint undertaking between the European Union and the pharmaceutical industry association (EFPIA), and its project called Ecorisk Prediction is to develop a science-based methodology to assist in ERA by using knowledge from pre-clinical and clinical studies and mode-of-action to predict effects of pharmaceuticals on wildlife. It aims to address public and regulatory concern relating to old pharmaceutical products and to prioritize the large number of non-evaluated pharmaceuticals for a future assessment programme.

In addition, there are several other research groups working to assess the potential environmental effects of pharmaceuticals, some of which have received funding from the European Commission (eg. see PHARMAS http://cordis.europa.eu/project/rcn/97551_en.html).

4. International action on pharmaceuticals

There is also growing realisation of the need for wider international action. For example, with respect to veterinary pharmaceuticals there is a trilateral (EU-Japan-USA) programme aimed at harmonising the technical requirements for veterinary product registration, including environmental impact assessment guidelines (<http://www.vichsec.org/>). Indeed, it is clear that pollution of the environment with pharmaceutical residues is now a matter of global concern as this issue has been nominated for consideration as an emerging policy issue under the Strategic Approach to International Chemicals Management (SAICM). Adopted by the International Conference on Chemicals Management on 6 February 2006 in Dubai, SAICM is not a legally binding global treaty, but it is a global policy framework to foster the sound management of chemicals.

Peru, Uruguay and the International Society of Doctors for the Environment (ISDE) nominated Environmentally Persistent Pharmaceutical Pollutants (EPPPs) as an emerging issue under SAICM. However, as of 2014 it remains to be seen whether this will be approved. More information can be found on the following SAICM web page: http://www.saicm.org/index.php?option=com_content&view=article&id=458:epi-eppp&catid=222:saicm-emerging-policy-issues&Itemid=687.

CHEM Trust supports the proposal to include pharmaceuticals in the environment as an emerging global issue under SAICM, and to this end, responded to the official SAICM consultation. (See <http://www.chemtrust.org.uk/widespread-pollution-by-pharmaceuticals-should-be-discussed-internationally-at-saicm/>).

The European Commission has already accepted that the *“pollution of waters and soils with pharmaceutical residues is an emerging environmental problem and also an emerging public health concern”* (COM(2008)666), so hopefully other nations will agree that this issue merits being accepted as a global emerging issue.

5. Pharmaceuticals in the environment



Otter [Credit: iStockphoto]

The global view

Contamination of rivers with pharmaceuticals is widespread, with hundreds of drugs found at low levels. The most comprehensive analysis of the current state of knowledge on the environmental contamination by pharmaceuticals worldwide can be found in the report, *“Global occurrence of pharmaceuticals in the environment.”* This work was done for the German Environment Agency (UBA), in order to support SAICM discussions, and although full publication will likely not be completed until the middle of 2015 (see IWW & Adelphi) a summary of the findings is available (IWW, 2014).

The project has compiled measured environmental concentrations of human and veterinary pharmaceuticals reported in all five United Nations (UN) regions and compared consumption data and future trends in these regions. In addition, they will make an assessment of the relevance of different emission pathways (manufacturing, use, disposal) and evaluate the role of infrastructure, population, pharmaceutical availability, agricultural practice, etc. on the emissions of pharmaceuticals into the environment. A database, including many maps, on the global relevance of pharmaceuticals in the environment has been developed (IWW, 2014).

This global review found that 713 pharmaceuticals (of which 142 are transformation products) have been looked for in the environment and 631 (of which 127 are transformation products) have been found above their detection limits (IWW, 2014).

In 71 countries, pharmaceuticals have been detected in the environment. Sixteen pharmaceutical derived substances were found in surface

water, groundwater or drinking water in each of the UN regional groups. These were: diclofenac (for pain and inflammation); carbamazepine (an anti-epileptic); ibuprofen (for pain and inflammation); sulphamethazole (an antibiotic); naproxen (for pain and inflammation); trimethoprim (an antibiotic); paracetamol (for pain); clofibrac acid (from the lipid lowering drug); ciprofloxacin (antibiotic); ofloxacin (antibiotic); norfloxacin (antibiotic); acetylsalicylic acid (aspirin, a pain killer); as well as the sex hormonally active substances, -estrone, 17 β -estradiol, 17 α -ethinyl estradiol, and estriol (IWW, 2014). Of these, diclofenac has received the most monitoring and has been detected in water in around 50 countries.

Many pharmaceuticals will ultimately be transported to the marine environment. For example, in the coastal Baltic Sea off Germany, several pharmaceuticals have been reported. These include 17 ethinyl estradiol, clofibrac acid, ibuprofen, carbamazepine, gemfibrozil, diclofenac, bezafibrate, naproxen and propyphenazone (HELCOM, 2010). There is now an ongoing project, coordinated by the Swedish Medical Products Agency, to make the Baltic Sea Region a lead in sustainable development for pharmaceuticals.¹

When viewing the results of various targeted monitoring activities, it must be remembered that analytical detection methods are available only for some of the thousands of pharmaceuticals manufactured and analytical methods are not yet standardized internationally, so detection limits may vary. Moreover, although pharmaceuticals have also been found in manure and soil, there is much less monitoring of soil levels as compared to water samples.

¹http://meeting.helcom.fi/c/document_library/get_file?p_l_id=18975&folderId=1272499&name=DLFE-43705.pdf

5.1 Data on presence and levels in the UK environment

Reports on pharmaceuticals in the environment have also been published by many national government or regulatory agencies, and references to these can be found in the global report (IWW & Adelphi). In the UK, for example, there are approximately 3000 pharmaceuticals licenced for use (ACHS/06/29B), but for only a relatively small percentage of these are there any environmental monitoring data available.

The Environment Agency (EA) of England and Wales has undertaken work to assess the levels and effects of some pharmaceuticals. Their first report on the topic, entitled *“Review of Human Pharmaceuticals in the Environment”* was published in 2000². This reviewed information on the occurrence, fate and effects of human pharmaceuticals, and noted that the following human pharmaceuticals had been detected in sewage effluent or in the aquatic environment: salbutamol; aspirin; paracetamol; diclofenac sodium; ibuprofen; diazepam; combined ethinyl estradiol, erythromycin; trimethoprim; propranolol hydrochloride; carbamazepine; erythromycin ethylsuccinate; naproxen; oxytetracycline; estrogen conjugated with progestogen; timolol maleate; estradiol with progestogen; estradiol; estrogens conjugated; combined ethinyl estradiol; clarithromycin and ciprofloxacin.

In light of the results, the EA conducted a second study, called the *“Targeted Monitoring Programme for Pharmaceuticals in the Aquatic Environment”*, which was published in 2003.³ This report describes a screening process to rank pharmaceuticals based on their relative risk to the aquatic environment. A short targeted monitoring programme

was undertaken for 12 of the higher priority pharmaceuticals. Ten pharmaceutical compounds, including: ibuprofen; mefenamic acid; diclofenac; propranolol; dextropropoxyphene; erythromycin; trimethoprim; tamoxifen; sulfamethoxazole and acetyl-sulfamethoxazole were detected in STW final effluent samples, and all of these except tamoxifen and sulfamethoxazole, were detected in the river downstream. Two substances, paracetamol and lofepramine, were not detected in any of the effluent or river water samples.

Regarding monitoring of veterinary pharmaceuticals by the EA, there was a similar approach to that followed for human pharmaceuticals in the environment. The EA published in 2002 a *“Review of Veterinary Medicines in the Environment”*⁴, and a subsequent *“Targeted Monitoring Study for Veterinary Medicines in the Environment.”*⁵ In the latter study, 18 compounds were judged worthy of monitoring based on a risk-based ranking approach. However, only 7 were selected for targeted monitoring. Apart from enrofloxacin and its metabolite ciprofloxacin, all of the other 6 compounds monitored for (doramectin, ivermectin, lincomycin, oxytetracycline, sulfadiazine and trimethoprim) were detected in one or more environmental compartment such as soil, water or sediment. Concentrations of antibacterials in soils ranged from 0.5 µg/kg (micrograms of trimethoprim per kilogram of soil) to 305 µg/kg (oxytetracycline). Maximum concentrations of antibacterials in water ranged from 0.02 µg/L (trimethoprim) to 21.1 µg/L (lincomycin); the parasiticides (doramectin and ivermectin) were not detected. Concentrations of antibacterials in sediment were 0.5–813 µg/kg for trimethoprim and oxytetracycline respectively and

those for doramectin and ivermectin were 2.7 and 4.9 µg/kg respectively.

Since this time the EA has not done any specific research on pharmaceuticals and does not currently undertake any specific routine monitoring for pharmaceuticals. However, the EA has been involved in some key projects. For example, the EA was on the board of a UK Water Industry Research (UKWIR) project, the aim of which was to prioritise pharmaceuticals in terms of their potential impact⁶. UKWIR were engaged by the water industry, the Environment Agency and other UK regulators to manage a £25M programme (The Chemicals Investigation Programme or CIP) to investigate the presence and control of a range of substances likely to be found in sewage.

In the 1st phase of the CIP, 160 STWs were monitored and it was found that in the majority, the final effluent concentrations of erythromycin, oxytetracycline, ibuprofen, propranolol, fluoxetine, diclofenac, 17β-estradiol and 17α-ethinyl estradiol exceeded the currently estimated UK PNECs of 0.01 µg/L or the proposed Environmental Quality Standards (EQSs), which for diclofenac, estradiol and ethinyl estradiol are 0.1, 4x10⁻⁴, and 3.5 x 10⁻⁵ µg/L respectively. However, dilution in the receiving water might ensure compliance with the estimated or proposed standards for these chemicals, although in some cases, there may be insufficient dilution, such that additional management options are needed (Gardner et al., 2012).

A 2nd phase of the CIP is planned for spring 2015. This will measure pharmaceuticals identified as high priority in the earlier project, in both the influent and effluent of over 40 STWs in England (Wilkinson, 2014). The substances to be monitored include:

² https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/290277/strp390-e-e.pdf

³ http://www.freshwaterlife.org/projects/media/projects/images/5/83919_ca_object_representations_media_596_original.pdf

⁴ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/290328/sp6-012-8-tr-e-e.pdf

⁵ https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/290533/schoo806blhh-e-e.pdf

⁶ <http://ukwir.forefront-library.com/reports/14-ww-17-16/97495>

diclofenac; ibuprofen; atorvastatin; ortho-hydroxyatorvastatin; para-hydroxyatorvastatin; propranolol; atenolol; erythromycin; norethromycin; azithromycin; clarithromycin; ciprofloxacin; metformin; ranitidine; carbamazepine; 10,11-epoxycarbamazepine; sertraline; nortriptyline; fluoxetine; tamoxifen; estrone; 17 β -estradiol and 17 α -ethinyl estradiol (Wilkinson, 2014b).

The EA has now invested in GCMS (gas chromatography-mass spectrometry) and LCMS (liquid chromatography-mass spectrometry) scanning tools for their own laboratories. In future, the data gathered from using these tools on several samples will be reviewed to provide information on a number of chemicals, including some pharmaceuticals (Wilkinson, 2014).

CHEM Trust considers that there is a need for the EA to instigate a routine monitoring programme for several 'high concern' pharmaceuticals and to take a more active role in ensuring protection of the environment.

5.2 Levels reported in EU biota and bioaccumulation concerns

One of the very worrying properties of some environmental pollutants is their potential to bioaccumulate. Bioaccumulation occurs when higher levels are found in biota as compared to their surroundings.

Invertebrates

One mechanism of bioaccumulation is for invertebrates to accumulate a chemical, and then for this chemical to further accumulate in the animals that eat the invertebrates.

In a laboratory experiment, Boxall and colleagues showed that the freshwater shrimp (*Gammarus*

pulex), in particular, could take up relatively high concentrations of certain pharmaceuticals and that the level of bioaccumulation depended on the species. Bioconcentration factors (BCFs) ranged from 4.6 to 185,900 and increased in the order moclobemide < 5-fluoruracil < carbamazepine < diazepam < carvedilol < fluoxetine (with fluoxetine, an antidepressant, being most bioconcentrated). Similarly, a study which dosed the marine mussel (*M. galloprovincialis*) for 7 days with 0.03-300 ng of fluoxetine per litre, reported BCFs ranging from 200-800 (Franzellitti et al., 2014).

In water boatman (*N. glauca*) the bioaccumulation was less. Here, BCFs ranged from 0.1 to 1.6 and increased in the order 5-fluorouracil < carbamazepine < moclobemide < diazepam < fluoxetine < carvedilol (with carvedilol, used for high blood pressure, being most bioconcentrated) (Meredith-Williams et al., 2012). These data highlight the need for monitoring the levels of pharmaceuticals in invertebrates in the wild, because unfortunately, at present, there is a paucity of such data.

Otters

Richards and co-workers (2011) have reported the presence of the NSAIDs, diclofenac and ibuprofen, in hair from otters collected from 6 English counties. They noted the need for further studies to identify residue loads in the otters and their prey to fully assess the pervasiveness of these compounds and potential risks. These drugs add to the pollution load, adding to the other chemicals to which otters are exposed. (See <http://www.chemtrust.org.uk/home/otter-health-pollutants/>)

Fish

The ability of fish to accumulate high levels of certain pharmaceuticals is alarming. For example, in a study in Sweden, 23 pharmaceuticals have been detected in 7 wild fish (perch)

samples (Fick et al., 2011). Also in Sweden, ciprofloxacin (an antibiotic) has been detected in fish at an average concentration of 6 μ g/kg (wet weight) (Sternbeck & Osteras, 2009 – see Helcom, 2011).

The antidepressant (citalopram) and painkiller (propoxyphene) have similarly been reported in the liver of perch in the Baltic Sea in the Stockholm region at concentrations of 0.1 and 0.25 μ g/kg respectively (see Wennmalm, 2008).

Moreover, in Texas, some other antidepressants, including fluoxetine, sertraline and their active metabolites (norfluoxetine and desmethylsertraline, respectively) have been found accumulating in muscle, liver and brain tissues of 3 different fish species, a phenomenon which was dubbed, "fish on Prozac" (Brooks, 2014).

Similarly, bioaccumulation of the sex hormone, levonorgestrel, has been reported in rainbow trout exposed experimentally to undiluted effluent from STWs in Sweden, such that the levels in the fish were similar to those used therapeutically in humans (Fick et al., 2010). And even Baltic Sea salmon has been found to contain 17 α -ethinyl estradiol (from the contraceptive pill) at a concentration of 0.9 μ g/kg (wet weight) (Andersson et al., 2006).

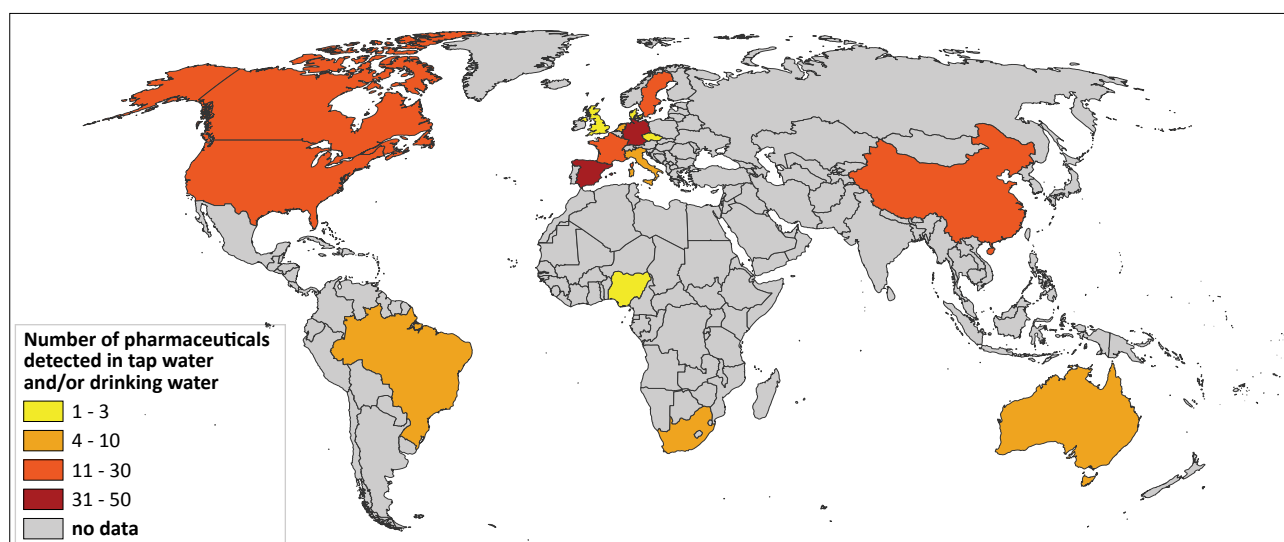
Nevertheless, for the most part, unfortunately there is inadequate information on the levels of pharmaceuticals in biota in the food web, particularly the marine environment. This means that it is difficult to assess whether wildlife are at risk.

5.3 Pharmaceuticals in drinking water

UK

A UK study published in 2011 has revealed the presence of several pharmaceuticals in drinking water (Boxall, 2011). The study found that 6 out of the 17 pharmaceutical substances monitored for were present in tap water. However, this will not reflect the situation for the bulk of the 3000 pharmaceuticals licenced in Britain, because this study focussed on pharmaceuticals that were considered to have high predicted exposure concentrations amongst other properties. This study was therefore considered likely to provide a 'worst case' assessment of potential human exposure to pharmaceuticals via drinking water in England and Wales. If only the parent molecule of solely therapeutic drugs are considered, then from this study 3 substances can be counted as contaminants which have been found in drinking water in Britain, and these are carbamazepine, ibuprofen and naproxen. This is because included in the 6 substances reported were benzoylecgonine (a metabolite of cocaine, which as well as being used in medicine, also has a lot of illegal recreational usage), caffeine (found in tea and coffee as well as certain drugs) and carbamazepine epoxide (a metabolite of carbamazepine).

Number of pharmaceuticals found in drinking water worldwide.



(Notes:

1. Caffeine is excluded, because although it is used in some pharmaceutical formulations, it is ubiquitous due to its presence in coffee and tea.
2. In addition, this map excludes drugs which are also used recreationally, and therefore, for example, cocaine and its metabolite, benzoylecgonine, are not included.)

(See IWW Water Centre 2014; <http://pharmaceuticals-in-the-environment.org>).

Another potential drinking water contaminant that has been the focus of some attention is 17 α -ethinyl estradiol from the contraceptive pill. According to the report by Bio Intelligence Service, it has been reported in surface waters and drinking water in several countries including the UK, USA, Canada, Brazil and Germany (Bio IS, 2014). However, in England and Wales, the only data on pharmaceuticals in drinking water that the Drinking Water Inspectorate holds is from the 2011 study by Boxall and colleagues as outlined above (Marsden, 2014). They are unaware of any research that shows the presence of pharmaceuticals derived from the contraceptive pill in UK drinking water (Marsden, 2014b).

The report about ethinyl estradiol being found in UK tap water seems to originate from a 1989 paper by Aherne and Briggs, which according to a review in 2000 by the EA reported levels in the range of not detected to 4ng/L (nanograms per litre) (EA, 2000). Nevertheless, it should be noted that it is extraordinarily difficult to reliably measure very low concentrations and studies conducted many years ago are particularly suspect.

That said, 17 α -ethinyl estradiol is excreted by women and is present in many surface waters (probably at typical concentrations of between 3 and 30 pg/L (picograms per litre) in developed countries (Hannah et al., 2009)). Therefore, it is conjectured here that it is likely to be present in some drinking waters at exceedingly low concentrations. However, the question is whether this is of any concern for human health.

Other pharmaceuticals reported in UK drinking water in pre-1991 studies, include bleomycin (an anti-cancer drug), clofibrac acid (lipid regulator) and diazepam (sedative) (see EA, 2000). It seems that this information has been missed from the map shown above, which reports just 3 pharmaceuticals found in UK drinking water, whereas these earlier studies suggest that at least 7 pharmaceuticals have at some time been reported in UK tap water.

In Scotland, there has been a similar lack of monitoring for human or veterinary pharmaceuticals in drinking water supplies and when asked, the Drinking Water Quality Regulator was not aware of any specific research carried out on the subject in Scotland. Moreover, because most sources in Scotland are derived from upland rivers or lochs where there is no, or very limited, human input upstream, the Regulator considered that the potential for human pharmaceuticals be present in raw waters used for drinking water was much reduced (Byers, 2014).

France

The French Ministry of Health, together with ANSES (the French Agency for Food, Environmental and Occupational Health & Safety), have evaluated the presence of some pharmaceuticals in order to assess the risks posed by contaminated drinking water. ANSES (2011) reported that some 19 pharmaceuticals or their residues have been found in drinking water in France.

These include: caffeine; oxazepam (for anxiety); paracetamol (for pain); carbamazepine and its epoxy derivative (for epilepsy); losartan (for hypertension); gadolinium (a metal used as a contrast agent in medical magnetic resonance imaging); hydrochlorothiazide (for water retention); ketoprofen (for inflammation and pain); salicylic acid (aspirin for pain); ibuprofen and its derivative (for inflammation and pain); naftidrofuryl (for circulatory problems); danofloxacin (antibiotic used in cattle); florfenicol (antimicrobial used in cattle); ofloxacin (antibiotic); ramiprilate (for hypertension and heart problems); tylosine (antibacterial used in many species) and 17 β estradiol (the female sex hormone secreted by women).

Of these, apart from caffeine, the 3 drugs found at the highest levels included salicylic acid at 115ng/L, oxazepam at 91ng/L, and the derivative of ibuprofen at 85ng/L. Another study reported 25 pharmaceutically active substances in drinking water in France, and a notable addition included atenolol (for hypertension) (Vulliet et al., 2009).

Germany

In Germany, residues of the following drugs were reported in drinking water in 2001: clofibrac acid (which can arise from clofibrate taken to lower cholesterol); N-(phenylsulfonyl)-sarcosine; propyphenazone (for inflammation and pain); diclofenac and DDT related substances (Heberer, 2001).

However, more up to date information about the pharmaceutical substances reported in drinking water may be found in the data collated by the IWW and Adelphi project, which indicates that between 31 and 50 pharmaceuticals have been found in drinking water in Germany (see <http://pharmaceuticals-in-the-environment.org>).

6. Harmful effects of pharmaceuticals in the environment



Discharge pipe [Credit: i-Stock/Deuelpics]

6.1 Pharmaceuticals in the environment are affecting wildlife

Unfortunately, pharmaceuticals in the environment have already been reported to have had devastating effects in wildlife. Several species have been affected, including fish and birds. Moreover, of course it must be recognised that many effects on wildlife will pass unnoticed, especially where smaller species are concerned.

The contraceptive pill

In many locations downstream of STWs, male fish have been feminised and have been found to have reduced sperm production. There are now numerous reports of male fish abnormally making the female egg yolk protein and with eggs in their testes. Ethinyl estradiol, a component of the contraceptive pill, has contributed to causing these effects, often in combination with other hormones or hormone mimicking substances (Jobling, 2003).

This phenomenon was first reported in the UK, but has since been found to be widespread in many countries. A very high proportion of intersex gudgeon fish has also been reported in the Dore river downstream of a pharmaceutical production plant making steroid drugs in France (Sanchez et al., 2011). It is now clear that ethinyl estradiol can impair reproduction in fish populations (Kidd et al., 2007).

Diclofenac

In Asia, the anti-inflammatory drug, diclofenac, caused the death of thousands upon thousands of vultures between 1996 and 2007. Diclofenac was mainly given to cattle for relief of pain or inflammation associated with disease or wounds. As the meat of cattle is not eaten by people in India, vultures would feast on them and take up all remaining diclofenac residues.

Unfortunately, it took some time to find that vultures are particularly sensitively to even low doses of diclofenac (Oaks, 2004).

Nevertheless, it seems that it is not just vultures that might be at risk, as diclofenac concentrations in rivers in many parts of the world exceed the predicted no effect concentration (PNEC) (see map below taken from IWW, 2014). In 35 countries the measured concentrations in waters, on occasion, exceeded the 0.1 µg/L PNEC, a figure close to the concentration in laboratory tests at which damage to fish was observed. For example, in an experiment on rainbow trout, the lowest observed effect concentration for cell damage in liver, kidney and gills was 1 µg/L (Triebkorn et al., 2004; and see SCHER, 2011). Also, for example, a laboratory study has reported that environmentally realistic concentrations of diclofenac can impair the osmoregulatory ability of the shore crab (*Carcinus maenas*) (Eades & Waring, 2009).

The proposed environmental quality standard (EQS) for diclofenac in surface water in the EU is also 0.1 µg/L (as an annual average), such that Member States will have to regularly monitor the concentrations of this substance and develop mitigation measures in the event that this EQS is exceeded.

A recent research paper, using modelling data and comparing with

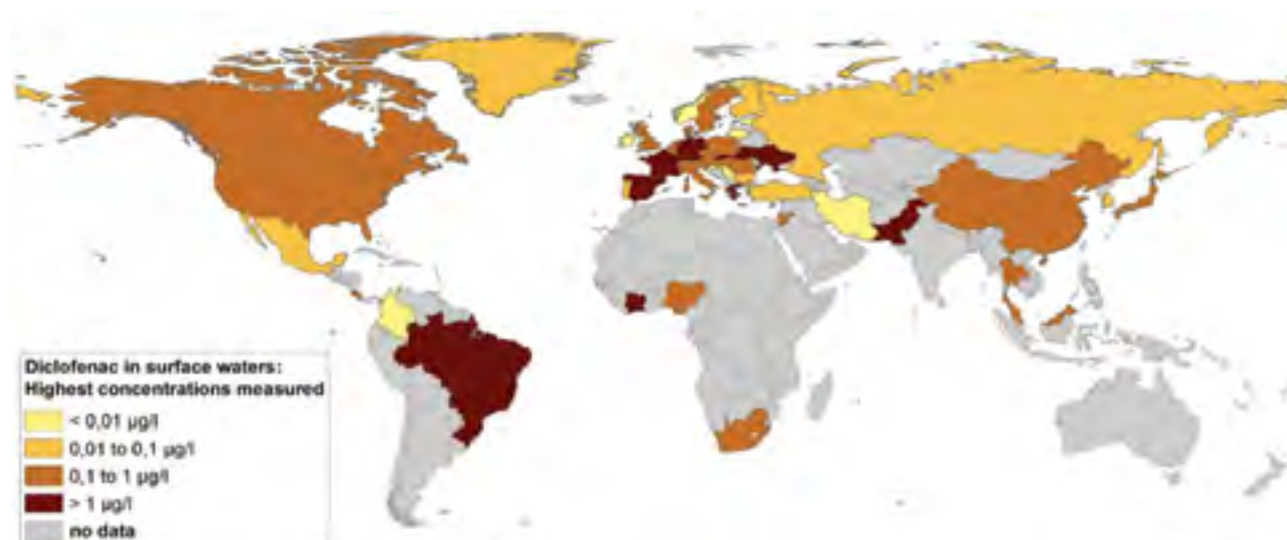
actual available data, suggested that in the UK, the EQS for diclofenac might be exceeded in 4.5% of river reaches. However, it also suggested that the EQS (0.1 µg/L) for diclofenac might be overly conservative (Boxall et al., 2014). In support of this opinion, one research group has concluded that diclofenac probably does not harm rainbow trout or zebra fish at concentrations up to 320 µg/L. They considered that this indicates a sufficient safety margin for fish populations, because concentrations of diclofenac in European rivers are in the range of ng/L to low µg/L (Memmert et al., 2013).

Nevertheless, the diclofenac example illustrates that the environmental effects of some pharmaceuticals can be staggering. Based on the existing proposed EQS, just 10 tablets of a typical 50mg dose of diclofenac are enough to pollute up to 5 million litres of water!

In March 2014, a petition was sent to the Commission from some environmentalists who were concerned about EU vultures and were dismayed that diclofenac was now available on the EU market.⁷ They suggested that an immediate ban on veterinary diclofenac was needed to protect EU birds and also to “send

a crucial signal encouraging African countries to stop the spread of diclofenac, which is already affecting the highly endangered populations of African vultures.” CHEM Trust was a signatory to this petition.

Maximum diclofenac concentration in surface waters in comparison to ecotoxicologically derived Predicted No-Effect Concentration (PNEC) of 0.1 µg/L.



(Reproduced with thanks to IWW Water Centre 2014; <http://pharmaceuticals-in-the-environment.org>).

⁷<https://www.change.org/en-GB/petitions/janez-potočnik-european-union-diclofenac-the-vulture-killing-drug-is-now-available-on-eu-market-ban-it-now>

Anti-parasitics

Ivermectin is a veterinary drug that has caused effects in the wild. It is used to kill parasites on cattle, sheep, goats, birds, pigs and horses. It is available in the UK, with many internet-based selling sites.⁸

Much of the drug is excreted in the faeces and being insecticidal, residues of ivermectin in cow dung can reduce the number and variety of insects in the dung. Residues adversely affect certain types of fly larvae, appearing to inhibit larval development and/or prevent pupation from taking place. This could be detrimental to wildlife, particularly birds reliant on cow dung as an important invertebrate food source.

Avermectins (the class of anti-parasitics which includes ivermectin) may therefore be affecting populations of birds and bats in some areas because of their effect of reducing the quantity of food available (McCracken, 1993). In addition, ivermectin and related substances can also delay dung degradation, leading to the fouling of pastures (McCracken & Bignal, 1991; Liebig, 2010) (For a review of the effects of the avermectins, milbemycins and spinosyns, which are collectively called macrocyclic lactones, see Lumaret et al., 2012)

The EA has also reported a number of pollution incidents involving other anti-parasitic medicines, such as cypermethrin and diazinon, used in sheep dips. These incidents have been caused by the release of the veterinary medicine to water either from farmyard and road surfaces or from grazing animals entering streams.⁹

Anti-parasitics in fish farming

Other anti-parasitics that cause concern are those used in fish farming for the treatment of sea lice. For example, emamectin benzoate is

widely used in the Scottish salmon farming industry and this is highly toxic to marine crustacean.

The typical licence held by fish farmers under the Controlled Activities Regulations requires farm operators to report to the Scottish Environmental Protection Agency (SEPA) the results of self-monitoring of sea-bed residues of certain sea lice treatments, including emamectin benzoate. However, many farms fail to provide such data and furthermore, some fish farms have reported levels in excess of the EQSs set by SEPA to protect marine flora and fauna.

There are some anecdotal reports of sea lice treatment chemicals harming wild shellfish. For example, dead and dying *Nephrops* (also known as the Norway lobster or Dublin Bay prawn) were reported in creels in Loch Shell following sea-lice treatments carried out at fish farms in 2010 (Linley-Adams, 2012).

Antidepressants

Another group of pharmaceuticals that have raised concerns with regard to the effects on wildlife are the antidepressants. For example, Fong and Ford (2014) have concluded that there is strong evidence to suggest that antidepressant pharmaceuticals are affecting aquatic invertebrates at concentrations now commonly found in the environment.

They noted that since antidepressants act by modulating the neurotransmitters serotonin, dopamine and norepinephrine, aquatic invertebrates that possess transporters and receptors sensitive to activation by these pharmaceuticals are potentially affected by them. Many biological functions within invertebrates are under the control of serotonin, including reproduction, metabolism, moulting and behaviour.

In a recent review of the biological

effects of antidepressants, just a few of the effects reported in laboratory studies included altered spawning and larval release in bivalves and disrupted locomotion and reduced fecundity in snails.

In crustaceans, the effects reported included altered behaviour in freshwater amphipod, and altered marine amphipod photo- (light stimulated) and geotactic behaviour (movement based on the earth's gravity for orientation).

In crayfish, altered aggressive behaviour was reported, in cuttlefish altered learning, and in daphnia, altered reproduction and development (see review Fong & Ford, 2014). Fluoxetine has also been reported to be relatively potent with regard to its toxicity to green algae (Oakes et al., 2010).

Moreover, Franzellitti and co-workers noted alterations in a range of biomarkers for sub-lethal toxicity in the marine mussel (*M. galloprovincialis*), after a 7 day dosing regime with fluoxetine encompassing a range of environmentally relevant values (0.03-300ng/L).

However, more research is needed to confirm some of the concerns raised in these laboratory studies and to find out just what effects antidepressants are causing in the wild.

Anti-inflammatory and analgesic: Ibuprofen

Ibuprofen is causing particular concern with regard to its potential environmental effects, and for example, a recent research project has suggested that ibuprofen poses an unacceptable risk at 49.5% of river reaches across 22 catchments in Britain, due to likely exceedance of its predicted no effect concentration (PNEC) of 0.01 µg/L (Boxall et al, 2014).

⁸See for example:-

<http://poultrykeeper.com/poultry-medication/ivermectin-for-worms-lice-mites>

http://www.vetuk.co.uk/horse-wormers-ivermectin-horse-wormers-c-540_174_1233

<http://www.hyperdrug.co.uk/Ivomec-Classic-Cattle-Sheep-Injection/productinfo/IVOME/>

⁹Environmental exposure to cypermethrin released to the farmyard - VMO2502

<http://randd.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=0&ProjectID=13945>

Ibuprofen has been reported to have a number of effects in laboratory studies, including endocrine disruption. For example, in the water flea (*Daphnia magna*), the 21 day reproduction NOEC (no observed effect concentration) was <1.23 mg/L; and for Japanese rice fish (*Oryzias latipes*) the NOEC in a 120 day survival test was 0.0001 mg/L.

In addition, ibuprofen affected several endpoints related to reproduction of the fish, including induction of vitellogenin in male fish, fewer broods per pair, and more eggs per brood. Parental exposure to as low as 0.0001 mg/L ibuprofen delayed the hatching of eggs, an effect which is environmentally relevant because this may increase the risk of being predated (Han et al., 2010).

Low concentrations of ibuprofen (10-100ng/L) have also been reported to cause behavioural effects (decreased activity) in crustaceans (eg. *Gammarus pulex*, which is often referred to as a shrimp) (De Lange et al., 2006).

Other medicines

Other pharmaceuticals which have been reported to cause effects at levels similar or near to those reported in the aquatic environment include:

- Oxazepam (a benzodiazepine sedative) - alters behaviour and feeding rate of wild European perch (*Perca fluviatilis*) at concentrations encountered in effluent-influenced surface waters (Brodin, 2013). The perch exhibited increased activity, reduced sociality and higher feeding rate.
- Carbamazepine (antiepileptic) - causes effects in mussels (*Mytilus galloprovincialis*) (Martin-Diaz et al., 2009).
- Gemfibrozil and bezafibrate (both lipid lowering drugs)- reported to cause effects on immune system of mussels (Canesi et al., 2007).
- Clofibric acid (a metabolite of lipid regulators) - reported to cause effects on reproduction in fish, including detrimental effects to fish sperm (Runnalls et al., 2007).
- Clotrimazole (an antifungal) - affects marine microalgal (periphyton) communities at very low concentrations (Porsbring, 2009).
- Antibiotics - can cause harm to environmental bacteria and algae. For example, environmental concentrations of chlortetracycline are in a range that clearly inhibits the protein biosynthesis activity of planktonic bacterial communities (Brosche, 2010). And a mesocosm study (which utilises a large controlled area outside) found that sulfadiazine affected soil bacteria and altered species distribution (Hammesfahr et al, 2008).

Also, for example, an EU funded research project (PHARMAS) has also highlighted that model predictions show that ciprofoxacin and levofloxacin in some European rivers may approach concentration levels that could trigger ecological effects¹⁰.

In addition to the examples given above, there are other examples of subtle effects in aquatic and terrestrial animals that have been seen in studies looking at the potential effects of long-term, low-level exposure to pharmaceuticals (Boxall, 2004; Brausch et al., 2012).

A review looking at data for England and Wales on 12 pharmaceuticals has suggested, based on comparing modelled environmental concentrations with ecotoxicity data, that those which might generate concern at some locations include not only ibuprofen, but also carbamazepine, fluoxetine, simvastatin and orlistat (Boxall et al., 2014).

¹⁰http://www.ecologic.eu/sites/files/event/2014/summary_and_presentation_ragas_20131121.pdf

6.2 Could pharmaceuticals in the environment be affecting human health?

People can be exposed to pharmaceutical residues in their diet in a number of ways, including via crops (from uptake due to the use of contaminated manure and sewage sludge), fishery products, meat and dairy products, as well as from drinking contaminated tap water.

Residues in food

EU legislation for veterinary medicines defines some maximum residue levels (MRLs) in food of animal origin (meat), and therefore requires some monitoring. However, no legal limits currently exist for human pharmaceutical residues in meat or fish arising, for example, from uptake from contaminated soil or water.

In our view research should be undertaken to determine the human pharmaceuticals most likely to be found in food, and monitoring studies should be instigated to determine actual levels found.

Drinking water

No standards currently exist for pharmaceuticals in drinking water, so water companies do not routinely look for them. Therefore, most of the information that is available comes from targeted research studies.

Worldwide, concentrations in surface, ground and partially treated water are typically less than 0.1 µg/L (= 100 ng/L), and concentrations in treated drinking water are generally below 0.05 µg/L (WHO, 2012).

The quality of the waste water treatment and the drinking water treatment is, of course, an important determinant of human exposure via

tap water. CHEM Trust considers that there is a need for far more monitoring of pharmaceutical residues in tap water with a focus on those with a high predicted exposure to therapeutic dose ratio.

The effects of such contamination needs to be determined particularly considering effects from long-term exposure and effects from exposure to multiple contaminants, albeit at relatively low levels.

The World Health Organization (WHO) has noted that *“The substantial margins of safety for individual compounds suggest that appreciable adverse impacts on human health are very unlikely at current levels of exposure in drinking water.”* (WHO, 2012).

Given the typically very low levels of pharmaceuticals in drinking water, some toxicologists have suggested that someone would have to drink the equivalent of several Olympic swimming pools to be affected,¹¹ but such assessments have only considered that drug in isolation, not with all the other drugs and contaminants to which we are now exposed.

Furthermore, all water on the earth is part of the same finite stable pool and as more pharmaceuticals are consumed, there is a risk that the levels of pharmaceuticals in drinking water will increase. In every UN region of the world, some pharmaceuticals have been found in drinking water / tap water (see section 5.3).

Possible impacts of human exposure

It should of course be recognised that just because we are now able to measure many substances at very low concentrations, it does not mean that they are always going to cause harm. However, there is a lack

of knowledge about the long-term effects of low level exposure to even single pharmaceuticals, let alone multiple pollutants.

Antibiotics, anti-parasitics, anti-mycotics (anti-fungals) and anti-cancer medicines are groups of chemicals intended to kill their target organism or target cells, and therefore it has been suggested that these sorts of substances might prove to be the most important with regard to negative effects on human health due to environmental exposure.

A particular concern is that indirect environmental exposure to antibiotics and medicinal products having anti-bacterial, anti-viral or disinfectant properties may create antimicrobial or anti-viral resistance in human gut flora leading to less effective antibiotics or anti-viral medicines in future (Bio IS, 2013).

The issue of antibiotic resistance is very important, and the role that pharmaceuticals in the environment play in this phenomenon merits more attention.

¹¹<http://www.ladwpnews.com/go/doc/1475/194797/Water-Quality-News-Recent-Media-Focus-on-Pharmaceuticals-in-Drinking-Water->

7. Options for reducing environmental impacts



Lavatory crime scene [Credit: i-Stock/hidesy]

7.1 Take back and disposal

An important first step in protecting aquatic organisms is to ensure the proper disposal of unwanted drugs. This requires adequate 'take-back' schemes and education so that people are aware that flushing them down the lavatory is not appropriate.

However, at present there is no EU wide rule which requires pharmacies to participate in take-back schemes and in many Member States their participation is voluntary (Vollmer, EEA 2010). In the majority of EU Member States, a large share of unused human medicinal products (around 50% on average) is not collected and some EU Member States do not implement take-back schemes (Bio IS, 2013).

Unlike many other EU countries, in the UK, there is a legal requirement for pharmacies to take back unwanted household medicines from the public, but this does not include a duty to take back unwanted medicines from, for example, institutions such as care homes. Moreover, in the UK, this scheme is financed by local authorities and not by the pharmaceutical industry. (See report from Health Care Without Harm <https://noharm-europe.org/documents/unused-pharmaceuticals-where-do-they-end-snapshot-european-collection-schemes>)

7.2 Sensible use of medicines

Mitigating pollution from the correct use of pharmaceuticals is more complex. Consumed medicines are metabolised and often excreted in a different form, which may or may not have some biological activity. Moreover, once in the environment, inactive metabolites can sometimes be re-activated in some way.

Also, in many cases, a considerable proportion of the original drug is excreted unchanged such that in general, between 30-90% of the orally administered dose is excreted as active substance in the urine of animals and humans (Bio IS, 2013). For example, the majority of a dose of cimetidine, a drug used for dyspepsia and stomach ulcers (which also has anti-androgenic activity and can cause breast growth in men) is excreted unchanged in the urine (Mitchell et al., 1982). Similarly, sometimes more of the drug is excreted in the faeces rather than the urine, and up to 75% of the dose

of some pharmaceuticals has been found in animal faeces (Bio IS, 2013).

Options for reducing the potential environmental effects of pharmaceuticals include the education of doctors and pharmacists, so that they consider prescribing the least environmentally damaging drug that is available for treating that person. However, at present, the environmental hazard profile of a human medicine plays no role in the decision as to whether or not to authorise that medicine for use and (except in Sweden – see below) whether doctors prescribe it. This needs to change, although this not to say that the needs of people should be sacrificed to the needs of wildlife, but rather that there should be a process of thinking about how to minimise potential environmental impacts without compromising the well-being of the patient. Similarly, veterinarians should consider using the least environmentally damaging treatment for animals.

Such a system already works well now throughout Sweden, where

the Stockholm County Council in partnership with others, drew up an environmental classification of pharmaceutical products. This system has also gained international attention, and access to the system is available in Swedish and English on www.janusinfo.se. This project started with the rationale that if health care staff and patients were informed about the negative environmental impacts of various medicines, they would be able to select the medicine likely to have the least environmental impact from those available for their respective needs.

National agencies and manufacturers of pharmaceuticals are now involved and the classification of pharmaceuticals has been expanded to include not only environmental hazard, but also environmental risk. In 2010, a complete classification of all medicines on the Swedish market was completed.

Another important consideration, of course, is whether the use of any drug is really necessary.

7.3 Better sewage treatment

The operation of municipal STWs also needs to be optimised, and here for example, a particular concern are discharges of the contraceptive pill (ethinyl estradiol) and other female hormones, given as hormone replacement therapy for the menopause. As noted above, these estrogens have contributed to the feminisation of male fish in many rivers, such that there is a real need for better sewage treatment in many areas.

Many pharmaceuticals that occur in the environment are the result of medical treatments that cannot be replaced, so pollution prevention must be addressed through better wastewater treatment.

Modern methods like UV treatment or advanced oxidation process are available to reduce pharmaceutical residues, but more research is needed to find the best option in different situations, and for example, various kinds of filters, membranes and sorbents need to be evaluated (Ledin et al., EEA, 2010). Additionally, care needs to be taken to combat effects on climate, such that there is a need to consider energy efficiency and the use of renewable energy.

For some patients suffering from diseases which require treatment with highly toxic drugs, it may be necessary to stop the pharmaceutical residues in their faeces and/or urine from reaching municipal STWs and the wider environment. In this case, regional specialised hospitals with additional sewage treatment, or excretion collection schemes might be needed.

It is important that the cost of such improved sewage treatment to deal with pharmaceutical contaminants is paid for by a levy on the pharmaceutical industry, in line with the polluter pays, thereby providing an incentive to reduce usage. This is because although it could be argued that the user of the medicine is the polluter, putting such costs on the water ratepayer would not ensure that the cost of the medicines themselves better reflect their true environmental costs.

8. Recommendations



Glass of water & pile of pills [Credit: i-Stock/pixhook]

8.1 Actions required from the pharmaceutical industry

Implement environmental stewardship

There is a need for the pharmaceutical industry to accept responsibility for their products across their entire life cycle. Moreover – under the polluter pays principle – it should pay for all pollution control measures and monitoring. This will require cooperation from pharmaceutical companies and pharmaceutical industry associations.

Develop ‘green’ drugs

There is a need to incentivise the development of greener pharmacy. Where possible, drugs should be ‘benign by design’, and this could include, for example, drugs that are better absorbed during treatment or less persistent in the environment.

For example, one such incentive that needs consideration is extending the patent duration for pharmaceuticals that are ‘benign by design’. A specific label for green pharmaceuticals could also be considered.

8.2 Actions required at UK / national level

Reduce usage of veterinary medicines in agriculture and aquaculture.

The prophylactic use of antibiotics should be prohibited or at least significantly reduced in order to reduce water pollution and antibacterial resistance. Therefore, where possible, animal husbandry should be less intensive and include better hygiene provisions.

Improving the way animals are bred and kept would minimise infections and therefore reduce the need for antibiotics and other drugs. Antibiotics used in aquaculture are currently the same as those used in humans and prophylactic use of antibiotics here has been particularly high, such that this is an area which merits tough regulation.

Improve sewage treatment plants

In some areas, there is a need to improve sewage/waste water treatment. Options to be considered include, for example, activated carbon, advanced oxidation or UV. Some countries are leading the way in the advanced treatment techniques and there is a need to share information on efficacies.

Continued research and development is also needed to optimise water treatment technologies, in particular to ensure they are as energy efficient as possible. In addition, in order to reduce climate impacts, the water industry should be encouraged to increase its use of renewable energy.

Sewage leakages and overflows due to storm conditions may also undermine river quality, therefore sewage systems need to be in good order and have sufficient holding capacity. Improvements of STWs would be mandatory in some areas if the 3 pharmaceuticals on the EU priority ‘watch list’ were accepted as priority substances under the WFD.

Get stakeholder support for reducing pharmaceuticals in the environment

Representatives of interested parties should be brought together in a regular ‘round-table’ meeting, to foster support for reducing the levels of pharmaceuticals in the environment.

Such interested parties or stakeholders could include: Government authorities; pharmaceutical producers; doctors; veterinary surgeons; other health-care professionals; pharmaceutical societies; water authorities; farming and aquaculture organisations; environment and health NGOs, and consumer and patient groups.

A national action plan should be set out, which could include, just as a couple of examples, recommending that future doctors are made aware of the problem and facilitation of the roll-out of the Stockholm scheme.

There is a need for an EU wide network focussed on the issue of pharmaceuticals in the environment, and national ‘round tables’ could support and feed into such a network.

8.3 Actions required at EU level

Mandatory EU wide take-back scheme for unwanted drugs

An EU-wide take-back scheme via pharmacies should be mandatory in all countries and complemented with improved labelling, such as including the wording ‘return unused medication to a pharmacy’. Very hazardous pharmaceuticals should also have additional appropriate labelling.

Moreover, citizens should be informed about take back schemes using advertising campaigns. EU law (Directive 2004/27/EC) has required take-back schemes for unused and expired human pharmaceuticals since 2004 as Article 127b states that *“Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired.”*

Nevertheless, in some areas, the bulk of unused medicinal products are not collected or returned to pharmacies and certain Member States do not have widespread take-back schemes (Bio IS, 2013).

Similar take-back schemes for unused veterinary medicines are also needed.

Implement environmental classification schemes

All pharmaceuticals should be subject to an EU classification system which classifies them according to their degree of environmental hazard. The Stockholm scheme (see section 7 above) should be extended across Europe, with country specific adaptations, and in a stepwise process, whereby some countries take this forward before others. This should be accompanied by raising awareness in the medical professions and the general public.

To improve the eco-classification

and environmental risk assessment (ERA), the responsible environmental authorities should be given access to confidential data in the ERAs provided for ‘new’ veterinary and human medicines during the authorisation of the substance.

EU regulation of production sites

A systematic monitoring of emissions during manufacturing at EU level is required, in order to ensure that those that are likely to pose the greatest risk are adequately controlled.

Industrial facilities in the EU at which pharmaceutical products are manufactured are covered by the Industrial Emissions Directive (IED 2010/75/EU), which requires them to monitor and control emissions of polluting substances. However, Annex II of the IED does not yet specifically include any active pharmaceutical ingredients in the list of polluting substances for which emission limit values should be set and monitoring conducted. This annex of the IED should therefore be modified to include emission limit values for active pharmaceutical substances where relevant, for example, when environmental quality standards have been set under the Water Framework Directive through its list of priority substances or for the ‘watch list’.

There is a need to review Best Available Techniques Reference Documents (BREFs) and revise them to take into account environmental concerns related to the manufacture of medicinal products (eg. associated emission levels).

Requirements for an environmental certification of the production facilities could also be introduced in the legislation on Good Manufacturing Practice.¹² Such a

regulation would competitively benefit those companies that have already invested in sufficient wastewater treatment equipment.

Keep EU drinking water free from contamination with pharmaceuticals

The aim should be to ensure that drinking water is kept free from pharmaceutical contaminants. Mandatory monitoring for traces of pharmaceuticals should be included in the EU Drinking Water Directive and standards based on the limit of detection, in the same way that standards for pesticide contamination were based on the limit of detection.

Implement 4 important changes to EU marketing authorisations:

i) ensure more environmental testing is carried out

There is a need to require more environmental testing than is currently done, in order to create a better basis for the pharmaceutical authorities to make a first scientific estimation of the risks, particularly with regard to degradability, bioaccumulation and long-term effects. A full PBT assessment should be required for all pharmaceuticals (including veterinary medicines), similar to that required under REACH. Moreover, the pharmaceutical authorities should have the option to request further information if there are indications that the substance is hazardous.

ii) Overhaul environmental risk assessment procedures.

Ensure there is sufficient expertise in committees assessing the ERAs of pharmaceuticals. Moreover, the risk assessment should be focussed on active ingredients rather than final products, so that the total exposure

¹² GMP legislation includes Directive 2003/94/EC for human medicinal products, and Directive 91/412/EC for veterinary medicinal products.

of the environment is considered. However, in cases in which other ingredients in the product have hazardous characteristics, then consideration of the full product is also needed.

iii) Address the environmental impacts of older pharmaceuticals

The environmental hazards of older pharmaceuticals need to be established and addressed. This could be achieved through a phase-in process, which could be prioritised by presence in the environment, production volume or computer-based prediction of properties. The data required for 'phased-in existing pharmaceuticals' should be as for the new substances, but with more environmental testing as outlined in (i) above.

iv) Enable the marketing of a human medicine to be blocked if it is not needed and has poor environmental performance

As is already the case for veterinary medicines, the ERA of human pharmaceuticals should be part of the risk benefit analysis within the authorisation process, with acceptable residues depending on the therapeutic importance of the pharmaceutical. An amendment to the law on medicinal products for human use is therefore needed.

It is likely that in most cases an authorisation would be granted as the medical usefulness would continue to weigh very heavily. However, an example of when the decision-maker would be more inclined to refuse authorisation is when there were already more environmentally sound cost-effective products on the market meeting the relevant medical need.

Put the enforcement of risk mitigation measures on a legal footing

Where an unacceptable/potential risk to the environment has been identified and needs to be controlled, for veterinary medicines there may be environmental risk mitigation measures imposed as a condition of the authorisation.

Such risk mitigation measures might specify, for example, that 'treated animals should not have access to surface water for a certain number days after treatment to avoid adverse effects on aquatic organisms'. However, currently there is no legal basis for enforcement and this needs remedying.

Mandatory pharmaco-vigilance at EU and national level

Some of the adverse effects of pharmaceuticals on wildlife will likely always escape detection prior to marketing. This highlights the need for ongoing pharmaco-vigilance¹³ (being vigilant for effects which may only materialise after use) and ensuring that in key wildlife species, subtle changes to behaviour and physiology are picked up.

There is a need to rationalise and strengthen EU legislation on pharmaco-vigilance. Environmental monitoring data should be fed back into the authorisation process such that eco-monitoring data are a key part of pharmaco-vigilance.

Include several pharmaceuticals in the list of 'priority substances' under the Water Framework Directive (WFD).

All the 3 proposed pharmaceuticals, now on the 'watch list' should be accepted as 'priority substances' in the next update. If pharmaceuticals are included in the list of 'priority substances', their emissions would

have to be monitored and controlled (by being subject to limit values).

Furthermore, the European Commission and Member States should consider identifying further pharmaceuticals as 'priority substances' under the WFD, which would then lead to the application of quality standards in waters.

Implement the polluter pays principle fully for pharmaceuticals.

Many of the externalised costs currently borne, for example, by water companies, should fall to the pharmaceutical industry. For example, the costs of extra sewage treatment to reduce the levels of pharmaceuticals, the costs of any take-back schemes etc. – should all be transferred to the pharmaceutical industry.

It is important that the costs of products include their full environmental costs, in order to provide an incentive to reduce emissions of potentially harmful substances.

Amend the EU Sewage Sludge Directive to include pharmaceuticals

If sewage sludge is to be spread on farmland, there is a need to ensure that there is adequate treatment of the sludge to reduce the levels of pharmaceuticals and levels of bacteria. Adequate testing of the levels of pharmaceutical contaminants in sewage sludge is needed to ensure it is safe.

There is a need to consider imposing mandatory monitoring and restrictions of certain pharmaceuticals in sewage sludge applied to land. This would require amendment of the EU Sewage Sludge Directive to include reference to residues of pharmaceuticals.

¹³ Pharmaco-vigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse reactions and other medicine-related problems.

¹⁴See https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/290448/schoo506bktj-e-c.pdf

Ensure EU monitoring of foodstuffs for residues of pharmaceuticals

There is a need for targeted monitoring of certain foodstuffs (eg fish), particularly including produce from countries from outside the EU, for residues of pharmaceuticals (eg, antibiotics).

Moreover, there is a need to consider that human pharmaceuticals may also arise in animals used as food (due to contamination of the food chain). Currently although EU food legislation does require the monitoring of veterinary pharmaceuticals in meat, it does not refer to human pharmaceuticals.

Set up an EU database on pharmaceuticals in the environment

An EU wide database including monitored levels, effects, relevant research findings, information on the best analytic detection methods and ERAs is needed. This should be linked to any similar global initiatives.

There is no collated information at present on environmental data for active substances at the European Medicines Agency (EMA). Such information would facilitate updates of voluntary information systems as well as help establish relevant limit values based on the effect levels of the substances in various contexts.

Require accurate consumption data to be reported by Member States

Available consumption data for many EU countries are incomplete and relatively scattered. Moreover, at present it is often unclear whether this includes all or some of the following: consumption in hospital, community prescriptions, pharmacy over-the-counter sales, veterinary pharmaceuticals etc. (Bio IS, 2013).

Therefore, there is a need for a mandatory requirement on Member States to collect and provide marketing and use data of pharmaceuticals, as this would aid targeted environmental monitoring. This needs to be done annually or perhaps once every 2 years as trends in drug use can vary dramatically over time.

Reduce wastage of pharmaceuticals and unnecessary use

Doctors should be encouraged to prescribe less and instead get patients to revisit their surgery in order to cut down unnecessary waste.

The public should be educated on the alternatives to drugs and the problems with pharmaceuticals in the environment.

The over-consumption of both prescription and over-the-counter drugs needs to be tackled, and in this respect CHEM Trust very much supports the EU law which forbids the advertising of prescription only medicines to consumers and patients, and would also like to see more controls on marketing tactics that target professionals. Awareness-raising could help to reduce the need for 'end of pipe' solutions and instead foster pollution prevention.

8.4 Actions required at global level

These global activities should be taken forward by international agreement that pharmaceuticals in the environment are an emerging political issue under SAICM (see section 5).

Increase global coordination and information exchange

There is a need for a global monitoring strategy, which can be applied to map the current global situation, and feed into international coordinated efforts to reduce environmental contamination. Global coordination should ensure that the best or most appropriate detection methods are used. Moreover, such coordination would better enable comparison of levels found in various countries and help identify areas of growing concern.

There is also a need for an international network of scientists, risk managers, and others who are particularly concerned with pharmaceuticals in the environment, in order to facilitate information exchange and mutual support in research and advice on the translation of research results into policy and control actions.

International support is needed for capacity building in developing countries and countries with economies in transition, in order to support decision making.

Conduct monitoring activities for illicit and fake drugs and educate the public about their adverse effects

Many drugs are now sold on-line, without any medical scrutiny. International cooperation is needed because illegal sales need to be stamped out as far as possible.

Recreational illegal drugs and fake or improperly regulated therapeutic drugs are a cause for concern, because they will all, to some extent, end up in the environment. There is also a need to educate people about the dangers of taking mind-altering substances that are legal, often just because regulation has not caught up.

8.5 Key research needs

- **There is a need for better monitoring of the environment for pharmaceutical contaminants** (including active transformation products) in biota, water and sediments in the EU. Although there is much information on the levels of certain pharmaceuticals in the environment, for many drugs in use there is still a need to develop robust detection methods. Getting information on the presence of prioritised pharmaceuticals in the environment is often a first step to understanding the effects of these residues.
- **There is a need to develop better toxicity testing methods and biomarkers of exposure to pharmaceutical contaminants in wildlife.** A priority would be to evaluate the loads of key pharmaceuticals in aquatic predators and to evaluate their effects. More information is needed about the possible negative effects that may occur after long term environmental exposure to several pharmaceuticals both separately and simultaneously. There is therefore a need for more data on the chronic effects in wildlife and in humans, particularly including exposure during conception and other vulnerable periods of development. Better testing protocols are needed to try and better identify

the long term environmental effects of pharmaceuticals, as current standard eco-toxicity tests may be inadequate for assessing the environmental impacts of pharmaceuticals.¹⁵

- **The potential for increasing antibiotic resistance due to pharmaceuticals in the environment should be investigated in detail, and mitigation measures considered.** To determine the scale of the problem, the proportion of resistant organisms in the environment as a consequence of discharges containing pharmaceuticals needs to be robustly estimated and compared with the proportion of resistant organisms arising from excretion of resistant organisms by man and animals and the spread of resistance by plasmid transfer.

¹⁵ See https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/290448/schoo506bktj-e-e.pdf

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