Document 19

Brussels, 10 April 2018

Dear Commissioner Andriukaitis,

We write in relation to the risks to human health and the environment posed by releases of pharmaceuticals into the environment. In particular, we are very concerned about how these releases affect ecosystems and are contributing to the development of antimicrobial resistance (AMR), one of the major threats to human health today. We would like to discuss with you the opportunities that the Commission has in the coming months to spearhead action against the global rise of drug resistance, including within the framework of its Proposal for a Regulation on veterinary medicinal products and its upcoming Strategic Approach to Pharmaceuticals in the Environment.

In its report on *Frontiers 2017: Emerging Issues of Environmental Concern*, UN Environment identifies growing AMR linked to the discharge of drugs and particular chemicals into the environment as one of the most worrying health threats today.[1] Indeed, experts view the promotion of antibiotic resistant bacteria as "by far the greatest human health risk" posed by the presence of pharmaceutical residues in the environment and note that, in addition to fostering the spread of resistant pathogens, antibiotic residues can also turn harmless environmental bacteria into carriers of resistance.[2]

Europe's AMR burden in terms of lives lost, morbidity, healthcare costs and productivity losses is much greater than currently available statistics suggest. Recent projections estimate a 15-fold increase in morbidity in Europe due to AMR by 2050, with 390,000 deaths every year as a result of drug-resistant infections.[3] The use of antibiotics in intensive livestock farming promotes the development of resistant bacterial strains and the environment plays not only an important role in the spread of those, but also wildlife organisms and ecosystem services are at risk.[4]

We are concerned that the pharmaceutical industry is currently excluded from any kind of environmental legislation, which is untenable in the light of the risk that pharmaceutical pollution poses to the environment and to human health. We expect legislative action from the Commission to tackle this issue, similar to the regulation of the chemical industry through REACH.

Since AMR is a quintessential cross-border issue, it is important that the EU-One Health Action Plan against AMR is supported by policy measures and legislation in other areas, along the lines with those proposed in our recent briefing[5] on policy options to be considered in the context of the Strategic Approach to Pharmaceuticals in the Environment and the proposal for a Regulation on veterinary medicinal products[6] to ensure that we tackle the problem in a comprehensive way.[7]

We would therefore like to request a meeting with you to discuss the main policy measures available to successfully tackle this problem.

Yours sincerely,

epha

Changing Markets Foundation

HCWH Europe

EEB

PAN Germany

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4 Ecological Impacts of Veterinary Pharmaceuticals: More Transparency - Better Protection of the Environment http://www.pan-germany.org/download/veterinary_pharmaceuticals/tierarznei-EN-160321-web.pdf
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How to tackle the environmental pollution by Veterinary Pharmaceuticals? http://www.pan-germany.org/download/tierarzneimittel/PositionStatement_ENGL_F.pdf
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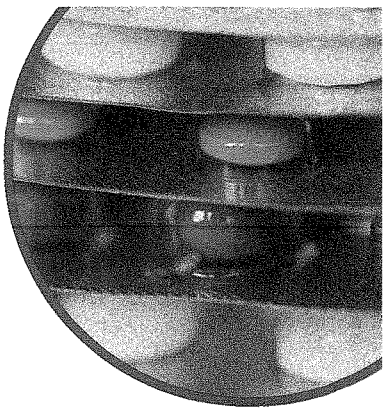
Health Care Without Harm



Antimicrobial resistance

A HCWH Europe position paper

Pharmaceuticals

October 2017

Introduction

What is antimicrobial resistance (AMR)?

Antimicrobial resistance (AMR) develops when microorganisms become resistant to the antimicrobial drugs used to treat them - this leads to treatments becoming ineffective, infections persisting, and an increased risk of infections spreading.[1] AMR is a broad term that refers to resistant viral, parasitic, fungal, or bacterial diseases, but resistance to antibiotics is of particular concern, as it is considered one of the greatest global threats to public health.[2]

Why should society be concerned about AMR?

Each year, antimicrobial-resistant infections cause 25,000 deaths in the European Union[3], 700,000 deaths worldwide[4], and generate annual costs of at least €1.5 billion in the EU alone.[3] The World Health Organization (WHO) reports that 480,000 people worldwide are affected by multi-drug resistant tuberculosis each year, and that the fight against HIV and malaria is also further exacerbated by AMR.[5]

A lack of research and development (R&D) could result in a shortage of alternative antimicrobials in the future. Approximately 10 million annual deaths caused by AMR are forecast for 2050 unless there is significantly more investment in R&D, a reduction in the amount of antimicrobials used, and attention to the control of infectious diseases in both human and veterinary fields.[6]

Antibiotic resistance, "the single greatest challenge in terms of infectious diseases today"[7] represents a threat for developed and developing countries alike.[2,8] Whilst widely acknowledged as a global threat, antibiotic resistance has not yet received enough public and governmental attention.

The spread of AMR

Pharmaceutical disposal - an unrecognised factor of AMR

AMR is primarily caused by inappropriate use and overuse of antibiotics in humans and animals, but increasingly evidence shows that pharmaceutical waste from excretion and disposal (including effluent from the pharmaceutical manufacturing process) is also a concern in the development of resistance.[9-12]

Another significant factor of AMR is disposal of drugs; there is insufficient implementation of collection schemes for unused and expired medicines throughout Europe.[13] Inappropriate disposal of antimicrobials: flushing them down the toilet or the sink for example, results in environmental pollution.[14] Sewage treatment systems are inadequate for the complete removal of active pharmaceutical ingredients in waste water, which can contribute to the spread of resistance.[9, 15, 16]

A reservoir for the spread of resistance

Since their discovery in the 1940s, antibiotics have become essential medicines.[1, 2] Recent studies have proven, however, that antibiotic waste from manufacturing sites doesn't just pollute the

environment, but is also a reservoir of resistant microbes.[10-12, 17-20] According to a 2013 report by the European Executive Agency for Health and Consumers, of all the risks humans face from medicinal product residues in the environment - AMR poses the greatest risk.[21]

Research has demonstrated how antibiotic resistance proliferates in the environment - bacteria are able to share genes with each other through a process called horizontal gene transfer, which can fuel the rapid spread of resistance among pathogens.[22] Through this process, genes that are resistant to antibiotics can move between bacterial cells and species.[23, 24]

Some particular environments are considered 'hot-spots' where antimicrobial resistance is more likely to emerge: 'hot-spots' include areas with poor pharmaceutical manufacturing practices, or where expired or unused drugs are disposed inappropriately e.g. toilets, sinks, or household refuse. Areas where pharmaceuticals are used in aquaculture or agriculture are also considered 'hot-spots'.[10-12, 19, 20] Currently the majority of national and global actions to tackle the spread of AMR do not take into account this release of antibiotics into the environment.

The pharmaceutical industry is known to contribute to antimicrobial contamination of the environment through their manufacturing practices.[11, 25, 26] Many pharmaceutical producers, attracted by cheaper labour and capital costs and weaker environmental protection laws, have outsourced their manufacturing outside of Europe.[25, 27] Active pharmaceutical ingredients (known as APIs) are the substances within medicine that are biologically active in order to have an effect on the patient (human or animal). China is the world's largest producer and exporter of APIs, currently supplying up to 90% of all antibiotic APIs; the majority of these are then processed in India before being sold on to markets worldwide.[25, 27, 28]

The unmonitored discharge of API-rich effluent into rivers and waterways in China and India has been shown to contribute to the proliferation of resistant bacteria.[10, 25, 26] This is not only problematic for local populations' health; the resistant bacteria can also spread across the world through international trade and travel.[25, 29] Normally the highest source of antimicrobials in the environment is excretion from humans and animals, yet in areas of pharmaceutical manufacturing, direct emissions of APIs are proven to be a much greater source. Every day 44kg of ciprofloxacin is discharged within effluent running into the Godavari River in China – water in this river contains concentrations of ciprofloxacin 1000 times higher than the amount required to kill certain bacteria.[26]

Currently there is little published information available concerning global quantities of APIs produced every year and where they are produced. The lack of data and transparency on these issues is cause for concern that low prices for pharmaceuticals could be indicative of low manufacturing standards, resulting in environmental pollution.[6] Problematically, current legislation fails to properly address this issue: The European Medicines Agency's "Guideline on the environmental risk assessment of medicinal products for human use" states that before receiving market authorisation, pharmaceutical products should undergo an environmental risk assessment.[30] This requirement does not apply, however, to antimicrobials placed on the market before 2006 when the guidelines came into force, and no risk assessments on the development of AMR in the environment are required. There is no scientific evidence that products placed on the market before 2006 are of less environmental concern than new products.

A recent study attempts to fill in the research gap and has proposed to establish "safe levels" of APIs in manufacturing waste. These "safe levels" were calculated by estimating the minimal selective concentrations i.e. the lowest concentration of an antibiotic at which resistance can still occur and predicting the no-effect concentrations i.e. the maximum concentration of an antibiotic below which no resistance can occur.[31]

The health sector's contribution to the AMR crisis

Millions of inappropriate antibiotic prescriptions are written every year, which further fuel the development of resistance.[32] Inappropriate prescribing occurs for a number of reasons: due to a lack of information doctors may prescribe a drug for a resistant infection, or prescribe antibiotics for a viral infection, and second or third-line antibiotics are sometimes prescribed when a first-line antibiotic would have sufficiently worked. Without rapid diagnostic tests, doctors still prescribe antibiotics based on immediate assessments of patients' symptoms; in many cases, antibiotics are prescribed prophylactically because they are cheaper in comparison with available diagnostic tests.[6]

When standard treatments don't work anymore, infections become harder or impossible to control, thus increasing the risk of infections spreading; combined with prolonged illness and lengthier hospital stays, the risk of fatality grows.[2]

Information regarding over-the-counter i.e. non-prescription sales of antibiotics is inconsistent and difficult to obtain in many countries. Despite a European Union Council recommendation that antibiotics are used as prescription-only medicines in Member States[33], it is believed that in some areas of Southern and Eastern Europe 20%-30% of antibiotics consumed are non-prescription.[6, 34]

Antibiotics and antibiotic-resistant bacteria are present in both hospital and municipal sewage systems, and while the healthcare sector may be thought of as a large source of pharmaceuticals in wastewater, hospitals only account for less than 10% of pharmaceuticals in the municipal wastewater (by weight).[15, 35] Excretion of drugs and poor disposal practices in the community means there are larger quantities of pharmaceuticals in municipal waste water.

Statistics have shown that awareness campaigns are effective in informing and educating their audiences about important health issues including antibiotic-use.[36] One successful campaign to reduce antibiotic-use during the 2000 influenza season in Belgium resulted in a 36% reduction in the prescription of antibiotics.[37]

Antibiotic use in food production contributes to the spread of resistance

When used to treat infections in agriculture and aquaculture, antimicrobials, especially antibiotics, are very important for animal health and welfare, as well as food security. At the global level, however antimicrobials are mostly used to prevent infections and compensate for poor animal husbandry practices and/or to promote growth.[6, 38] The exact quantity of antimicrobials used in food production worldwide is unknown due to insufficient data, but it has been shown that in some regions - antimicrobials are used more often for animals than for humans - in the U.S. more than 70% (by weight) of the antibiotics considered medically important for human health are used in livestock.[39]

Last-resort antibiotics are those prescribed if all other antibiotics have failed; when they are used in livestock this can increase the threat of AMR. Antibiotics lose their efficacy in humans when they are routinely absorbed in low levels in the food chain.[40] This is the case of colistin - whilst not widely used in humans, (as it can cause kidney failure[41]), it remains an important last-resort antibiotic that is administered when an infection hasn't responded to other drugs.[6] The widespread use of colistin in treating animals, however, has led to resistance in animal pathogens which has implications for humans. A recent scientific paper reports the discovery of transferable colistin resistance in both animals and humans in China.[42]

Some frequent antibiotic-use practices in animals are problematic, such as growth promotion, prophylactic use i.e. preventive use in the absence of infection, and metaphylactic use i.e. treating a group animals when only a small number of individuals show signs of infection. Metaphylactic use aims to prevent infections spreading, but it actually leads to gross overuse of antibiotics and contributes to antibiotic resistance.[39] The problem is exacerbated by cramped conditions, allowing resistance to spread rapidly. The most contentious use of antibiotics, however, is non-therapeutic use for growth promotion, which was banned in the EU in 2006[43], but is still permitted for use in the US.

Other, non animal-based food products may also be contaminated with antimicrobial resistant bacteria and/or antimicrobial resistance genes. Ingredients intentionally added during food processing (such as starter cultures, probiotics, bioconserving microorganisms, or bacteriophages), can spread antimicrobial resistant bacteria.[44] Such bacteria can also be spread through cross-contamination (e.g. when raw food is mixed with other ingredients). Whilst cooking processes often kill resistant bacteria, raw food products pose a substantial risk of transferring antimicrobial resistance to humans through consumption.[44]

Actions at the global level

The World Health Organization (WHO) urges Member States to adopt the WHO Global Action Plan on Antimicrobial Resistance as a basis for their own national priorities and specific contexts. This plan, adopted by the 68th World Health Assembly in May 2015, aimed to have national plans in place by May 2017.[45]

The European Commission contributed to the development of the WHO action plan and is currently involved in implementation.[46] The key points of the action plan to tackle AMR include:

- Awareness and education campaigns
- Improving knowledge of AMR through surveillance
- Infection prevention and control measures
- Optimising antimicrobial-use in humans and animals
- R&D and investment.[1]
- Implementing good manufacturing practices - however, this neglects to include environmental criteria.

As part of its Global Action Plan, The WHO recognised the impact that antibiotic use in agriculture can have on the spread of drug resistance, and therefore requires Member States to incorporate actions for dealing with the veterinary use of antimicrobials in their national action plans.[1] This issue has been also recognised by The Food and Agriculture Organisation of the United Nations (FAO) and The World Organisation for Animal Health (OIE) – all three organisations collaborate in sharing responsibilities in tackling AMR.[47] The FAO plays a key role in supporting all actors to adopt measures that minimise the use of antimicrobials and to prevent the development of AMR.[48] The OIE promotes the responsible and prudent use of antimicrobial agents in veterinary medicine and improved knowledge and monitoring of the quantities of antimicrobials used in animal husbandry.[49]

There is also international cooperation among countries through an Intergovernmental Task Force on Antimicrobial Resistance, which reports to the Codex Alimentarius Commission.[50] The EU collaborates closely with the USA, Canada, and Norway to address AMR through the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) established in 2009.[51] The European Commission also collaborates with the Organisation for Economic Co-operation and Development (OECD) to assess the economic impact of AMR.[46, 52]

There is a common consensus at the international level that unnecessary use of antibiotics in animals and agriculture represents a major concern for human health.[6] Recent G7 statements recognised the urgent need for national efforts in sharing best practices and promote the prudent use of antimicrobials.[53, 54, 55, 56] A political declaration to combat the global threats posed by AMR was adopted this year by the 71st United Nations (UN) General Assembly - Member States should develop multisectoral national action plans on AMR, which must be in line with the WHO Global Action Plan.[8]

Actions at the the EU level

The European Commission's Action plan against the rising threats from Antimicrobial Resistance (2011-2016) outlined the main actions for its implementation amongst Member States, and identified areas where measures are most needed.[57] This Action plan aimed to ensure appropriate use of antimicrobials across Member States: within the plan, the European Commission proposed measures to prevent the spread of microbial infections and encouraged innovative research and development of antimicrobial drugs. The plan describes the need for international collaboration to address the risks of resistance spreading via international trade, travel, and the environment. An important target included in this plan was strengthening the regulatory framework on veterinary medicines and on medicated animal feed.[57] Environmental criteria in implementing good manufacturing practices to combat AMR, however, is not included within this action plan either.

In June 2017, the European Commission published A European One Health Action Plan against Antimicrobial Resistance (AMR).[58] This second action plan recognises AMR as a growing threat on a global level and aims to strengthen actions containing this crisis and to promote the EU as a best practice region. Within this latest action plan, the European Commission for the first time acknowledges environmental aspects leading to AMR, but only to cover knowledge gaps. There is no mention of the industrial pollution in the supply chain.

The European Commission is currently working on a new regulation on veterinary medicines, which will propose new policy measures to tackle AMR by ensuring proper use of antimicrobial drugs in farming practices. (For further information, please read *Food pathways to antibiotic resistance: A call for international action*)

HCWH Europe recommendations on AMR

AMR currently poses one of the greatest threats to global public health, an important focus for stakeholders worldwide should be to find strategies to improve production standards and minimise the release of antimicrobials into the environment throughout their life cycle (production, use, and disposal).

HCWH Europe therefore urges the European Commission to work with international governments and regulators to establish evidence-based targets for maximum levels of antimicrobial API discharge associated with the manufacture of pharmaceuticals. These targets should be enforced at international level, regardless of products' origins. The goal should be to manage the pharmaceutical waste stream and control API discharge associated with the manufacture of pharmaceutical products.

In this international context, HCWH Europe also calls on the European Commission to develop a guideline with measurable goals, which should include feasible targets and monitoring systems to reduce the overuse and inappropriate use of antimicrobials in human and agricultural practices.

1. Achieve zero discharge and eliminate the release of antimicrobials into the environment from manufacturing plants

Governments need to strengthen laws to eliminate pollution, monitor antimicrobial discharges into the environment rigorously, impose fines, and withdraw licences if needed - the ultimate aim should be a zero discharge policy. National governments and regulators around the world need to expand the regulatory framework for Good Manufacturing Practice (GMP), to include environmental safety. GMP legislation (Directive 91/412/EC[59] and Directive 2003/94/EC[60]) should require antimicrobial production facilities to apply environmental safety standards to achieve a zero discharge and should be validated through an independent auditing system.

2. Enforce the development of minimum manufacturing standards to prevent pharmaceutical waste that leads to AMR

More attention should be paid to environmental safety throughout the regulatory framework for authorisation procedures for medicinal products.[61] Manufacturers need to be held responsible for their antibiotics on the market and they should be held accountable for pharmaceutical pollution that leads to AMR.

Manufacturing standards should be developed amongst all Member States to address this issue. These standards should apply across all stages of the supply chain with transparency regarding the source of APIs, emissions of manufacturing waste containing APIs, and environmental assessment of the discarded APIs. These standards should be applied to products for both human and animal use that are sold in Europe, regardless of where they are produced. Environmental criteria, as a matter of good manufacturing practice, should be included in the market authorisation procedure for medicinal products sold in the EU.

3. Require environmental risk assessment for all antimicrobials

HCWH Europe recommends that an Environmental Risk Assessment (ERA) covering all stages of the pharmaceutical substance's life cycle should be a mandatory part of the marketing authorisation process for antimicrobials.[62]

4. Add requirements to assess the risk for development of AMR

The ERA for antimicrobial substances should include a risk assessment for development of AMR - this would improve current knowledge on risks associated with antimicrobials presence in the environment.[62]

5. Last-resort antibiotics and those medically important for human use should be reserved for human use only

Last-resort antibiotics should not be prescribed for veterinary use, but only for human therapy. HCWH Europe calls upon regulatory bodies and international organisations (WHO, FAO, and OIE) to agree on a harmonised list of last-resort antibiotics that are critical to human health and should be banned from agricultural use.

6. Restrict prophylactic and metaphylactic use of antimicrobials in livestock

Antimicrobial drugs, especially antibiotics, must not be used to improve performance (e.g. physiological and reproductive performance) or to compensate for poor animal husbandry. HCWH Europe recommends that the EU should adopt the position of the European Parliament's Environment and Public Health Committee on prophylactic and metaphylactic use of antimicrobials in livestock.[63] Prophylactic use of antimicrobials should be limited to single animals and only when prescribed by a veterinarian. Metaphylactic use should also be restricted: only individual animals that are clinically ill or show a high risk of infection should receive antimicrobial treatment. Sick animals should also be physically separated from the healthy to reduce the risk of infections spreading.

7. Work towards developing legislation for Member States to enforce regulations that prevents over-the-counter sales without prescription

It is the role of the EU regulatory body to establish legislation for prescription-only use of antibiotics and ensure that this is enforced nationally in Member States. This measure should record and monitor the data regarding quantities of antibiotics sold for both human and veterinary use.

8. Develop guidelines for informed prescription practices to reduce the unnecessary use of antibiotics

Better prescription practices need to be developed and implemented to reduce the problem of resistance spreading. Governments across the EU must legislate that doctors' decisions to prescribe antibiotics must be evidence-based and supported by up-to-date surveillance information and that testing technology is applied when available.[6]

9. Support the establishment of a harmonised collection scheme system for antimicrobials throughout the EU

At the EU level, guidelines are needed to support the setup and improvement of take back schemes foreseen in Directive 2004/27/EC.[64] Take back schemes should be expanded and strengthened across the EU to prevent unused antibiotics reaching the environment. Collaboration between Member States to establish a harmonised collection scheme system for antimicrobials should be encouraged through common guidelines and targets.

10. Promote research into environmentally-responsible ways to treat sewage and prevent the release of antibiotic resistant bacteria

Further research is needed on how to improve the wastewater treatment to prevent antibiotic resistant bacteria being released into the environment without resorting to the use of toxic chemicals.

11. Promote research into environmentally-responsible waste disposal methods

Further research is needed on how to improve antibiotic waste disposal methods to prevent the release of toxic chemicals in the environment.

12. Develop EU-wide awareness campaigns to:

a. Educate the public on correct consumption and disposal of antimicrobials

Educational campaigns could help promote proper disposal practices and help patients understand that demanding antimicrobials from health professionals or buying them over-the-counter without the necessary knowledge is harmful as it contributes to AMR.

b. Train health professionals on responsible prescribing practices

Healthcare professionals can influence patients' use of antimicrobials, and they should be actively involved in reducing the misuse and overuse of this category of drugs. For example, doctors can optimise prescription practices to ensure that antibiotics are prescribed and dispensed of prudently. Pharmacists are also well placed to advise patients about how to follow a correct therapy of antibiotic drugs, and to help reduce the risk for accumulation of unused antibiotics that become waste and can end up in the environment.

Hospitals and health systems should become leaders in educating staff, patients, and communities about the link between healthy and sustainable food to long-term wellbeing. Health professionals can also play an important role in advocating for policy changes at the hospital administrative level to prioritise purchasing antibiotic-free meat.

c. Educate farmers on the responsible use of antimicrobial drugs

Farmers and agricultural workers should also be educated about the consequences of unnecessary antimicrobial-use in agriculture.

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59. Directive 91/412/EC laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products. OJ L228/70, 17.8.91.
60. Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. OJ L 262/22, 14.10.2003.
61. European Commission (2016) *Authorisation procedures for medicinal products.*
62. Agerstrand M, Berg C, Björlenius B *et al.* (2015) *Improving Environmental Risk Assessment of Human Pharmaceuticals.* Environ. Sci. Technol 49: 5336–5345.
63. European Parliament News (2016). *Superbugs: curb use of today's antibiotics, and develop new ones, urge MEPs.*
64. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use.

HCWH Europe Recommendations on pharmaceuticals in the environment - September 2016

Health Care Without Harm (HCWH) Europe[1] is the European arm of a global not for profit NGO whose mission is to transform healthcare worldwide so that it reduces its environmental footprint, becomes a community anchor for sustainability, and a leader in the global movement for environmental health and justice. HCWH's vision is that healthcare mobilises its ethical, economic, and political influence to create an ecologically sustainable, equitable, and healthy world.

HCWH Europe works towards promoting a reduction of pharmaceuticals in the environment by collaborating with the health sector, the pharmaceutical industry, and other NGOs, and has recently launched a Safer Pharma campaign that aims to raise awareness, educate the general public and healthcare professionals, and to promote policies that reduce pharmaceutical emissions throughout their entire life cycle (in their production, use, and disposal). Therefore, HCWH Europe calls on the European Commission to develop a strategic approach that protects both the environment and human health. HCWH Europe invites governments, the pharmaceutical industry, and other relevant stakeholders to play an active role in the global effort to reduce pharmaceutical pollution - to protect both public health and the environment in the long-term.

What is the scale of the issue?

In the right place, pharmaceuticals save lives and prevent disease, but it is well known that pharmaceuticals in the environment represent a global pollution problem - over 631 different pharmaceutical agents or their metabolites have been detected in 71 countries on all continents.[2] They are already damaging the environment[3] and in the long-term, they could cause widespread damage to human health.

Worldwide revenue from the sales of pharmaceuticals has almost doubled over the last 10 years, from $559.9 billion in 2004 to $1,057 trillion in 2014, and is expected to grow more over the coming years, with aging populations and improved access to healthcare.[4] The European Union (EU), is the second largest consumer of human medicinal products in the world (24% of the global production), after the United States.[5]

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[1] Health Care Without Harm (HCWH) Europe. https://noharm-europe.org

[2] Aus der Beek T, Weber FA, Bergmann A, Hickmann S, Ebert I, Hein A and Küster A, (2016). Pharmaceuticals in the environment-Global occurrences and perspectives. *Environ Toxicol Chem*, 35(4), pp.823-35. http://www.ncbi.nlm.nih.gov/pubmed/26666847

[3] Kümmerer K, (2010). Pharmaceuticals in the environment: sources, fate, effects and risks. *Environmental Science and Pollution Research*, 17(2), pp.519-521.

[4] Statista (The Statistics Portal) (accessed 2016). http://www.statista.com

According to a recent German Environment Agency report,[6] about 4,000 Active Pharmaceutical Ingredients (APIs, the part of the medicine that is biologically active in order to have an effect on the body), are being used in prescription drugs, over the counter therapeutic drugs, and veterinary drugs.

APIs are designed to be highly biologically active in humans and can have unintended effects on other species.[6] Even low amounts of APIs in the environment can have far-reaching effects on ecosystems.[7]

Pathways into the environment

Various categories of pharmaceutical residues have been detected in surface water, sewage effluents, groundwater, drinking water, manure, soil, and other environmental matrices. [2,8,9,10,11,12,13,14,15,16]

Pharmaceutical residues can enter the environment during the production, consumption, and disposal of pharmaceuticals.[17] Pharmaceutical manufacturing is a source of pharmaceutical

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[5] Académie Nationale de Pharmacie (2008). Médicaments et environnement. http://www.acadpharm.org/dos_public/1_Rapport_Med_Env_version_JMH_def_JPC.pdf

[6] German Environment Agency (2016). *Pharmaceuticals in the environment - the global perspective*. p.3. https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/pharmaceuticals_in_the_environment_0.pdf

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[8] Kümmerer K, (2009). The presence of pharmaceuticals in the environment due to human use – present knowledge and future challenges. *Journal of Environmental Management*, 90(8), pp.2354–2366.

[9] Touraud E, Roig B, Sumpter JP and Coetsier C, (2011). Drug residues and endocrine disruptors in drinking water: risk for humans? *International Journal of Hygiene and Environmental Health*, 214(6), pp.437-441.

[10] Kümmerer K (ed.), (2008). *Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks* (third edition). Berlin Heidelberg, Springer-Verlag.

[11] Buerge IJ, Buser H-R, Poiger T and Müller MD, (2006). Occurrence and Fate of the Cytostatic Drugs Cyclophosphamide and Ifosfamide in Wastewater and Surface Waters. *Environ. Sci. Technol.*, 40 (23), pp.7242–7250.

[12] Daughton CG, (2016). Pharmaceuticals and the Environment (PiE): Evolution and impact of the published literature revealed by bibliometric analysis. *Science of the Total Environment*, 562, pp.391-426.

[13] Klatte S, Schaefer H-C and Hempel M, (2016). Pharmaceuticals in the environment – A short review on options to minimize the exposure of humans, animals and ecosystems. *Sustainable Chemistry and Pharmacy.* In press.

[14] Küster A and Adler N, (2014). Pharmaceuticals in the environment: scientific evidence of risks and its regulation. *Philos Trans R Soc Lond B Biol Sci*. 369(1656). http://www.ncbi.nlm.nih.gov/pubmed/25405974

[15] Kümmerer K, (2010). Pharmaceuticals in the Environment - Annual Review of Environment and Resources. *Environment and Resources*, 35(1) pp.57-75. http://www.annualreviews.org/doi/full/10.1146/annurev-environ-052809-161223

[16] BioIntelligence Service (2013). *Study on the environmental risks of medicinal products – Final report.* http://ec.europa.eu/health/files/environment/study_environment.pdf

pollution that can be exacerbated by weak environmental legislation in countries that produce many of the APIs for pharmaceutical products globally.[18]

Pharmaceuticals also enter into the environment during the use phase of their life cycle - by human excretion via wastewater, and animal excretion via runoff from agricultural areas and discharges from aquaculture.[15]

Another route is through incorrect disposal - the most common forms of incorrect disposal are when unused medicines are flushed down the toilet or sink, or when they are disposed of in waste bins destined for landfill sites.[19]

According to Directive 2004/27/EC[20] (relating to medicinal products for human use), EU Member States have an obligation to implement appropriate collection schemes for unused pharmaceutical products. However, no guidelines have been provided on the implementation of these schemes.[19] As a consequence, a number of studies[21, 22] have highlighted significant differences between Member States in terms of collection schemes. Currently, there is deficient and scattered data regarding the implementation and efficiency of collection schemes for unused pharmaceuticals throughout Europe, which makes it unclear whether all EU countries have fulfilled their obligations.[19] Current wastewater treatment plants are unable to completely destroy or remove pharmaceuticals. The amount of these pharmaceuticals remaining after treatment depends on the substance(s) in question, their initial concentration, and the treatment methods employed.[16, 23] Consequently, pharmaceutical residues can re-enter terrestrial systems, spread to surface waters and agricultural lands, and can ultimately end up in drinking water,[24,25] and accumulate in vegetables and fish.[26,27,28,31]

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[17] Thomas KV and Langford KH, (2010). Point sources of human pharmaceuticals into the aquatic environment. In: Kümmerer K and Hempel M (eds), (2010). *Green and Sustainable Pharmacy*, pp.211–223. Berlin Heidelberg, Springer-Verlag.

[18] SumOfUs (2015). *Bad Medicine: How the pharmaceutical industry is contributing to the global rise of antibiotic-resistant superbugs.* https://s3.amazonaws.com/s3.sumofus.org/images/BAD_MEDICINE_final_report.pdf

[19] HCWH Europe (2013). *Unused pharmaceuticals, where do they end up? A snapshot report of European collection schemes.* https://noharm-europe.org/sites/default/files/documents-files/2616/Pharm%20Report_WEB.pdf

[20] Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. OJ L 136/34, 30.4.2004. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf

[21] Volmer G, (2010). Disposal of pharmaceutical waste in households – A European Survey. In: Kümmerer K and Hempel M (eds), (2010). *Green and Sustainable Pharmacy*, pp.165–178.

[22] Taylor D and Poulmaire M, (2008). *An initial survey of unused and expired medicine take-back schemes in the European Union.* Poster Presentation. KNAPPE International Conference. Nimes, France.

[23] Köhler C, S Venditti S, Igos E, Klepiszewski K, Benetto E and Cornelissen A, (2012). Elimination of pharmaceutical residues in biologically pre-treated hospital wastewater using advanced UV irradiation technology: A comparative assessment. *Journal of Hazardous Materials*, 249-240:70-77.

[24] World Health Organization (2012). *Pharmaceuticals in drinking-water.* http://www.who.int/water_sanitation_health/publications/2012/pharmaceuticals/en/

[25] Huerta-Fontela M, Galceran MT and Ventura F, (2011). Occurrence and removal of pharmaceuticals and hormones through drinking water treatment. *Water Research*, 45(3): 1432–1442.

Causes for concern

At present, there is little published information, and a lack of transparency regarding the quantities of APIs produced per year, or the amounts that are being discharged into the environment.

Designed to be biologically active, APIs are also developed to remain unchanged and stable during their passage through the body, which means they often persist outside the body and as a consequence, can accumulate in the environment. Therefore, these substances have the potential to significantly impact both the environment and non-target organisms.[12,19]

Recent scientific literature has provided various examples of animals and other organisms exposed to pharmaceuticals in water or soil.[2, 6, 14] Animals are also exposed when they feed on other animals which have been medicated, and behavioural, physiological, and histological effects have been observed in animals exposed in this way.[7, 27, 31] The most dramatic environmental effect witnessed in relation to pharmaceuticals was the near extinction of vultures feeding on animals that have been treated with diclofenac in Pakistan.[29,30]

Through water and food consumption, humans can be unintentionally exposed to pharmaceutical residues.[31] Although it has already been proven that low concentrations of pharmaceuticals in the environment can affect animals and other organisms, little is understood about their effects on humans.[13, 31]

There are 3 groups of pharmaceuticals that are particularly active in low concentrations and therefore have attracted the attention of researchers and policy-makers: endocrine-disrupting pharmaceuticals (i.e. hormones), anti-cancer treatment drugs (which are toxic to living cells by design), and antibiotics (because of the threat of the development of antibiotic resistant bacteria).[15]

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[26] Jelic A, Gros M, Ginebreda A, Cespedes-Sánchezd R, Ventura F, Petrovica M and Barcelo D, (2011). Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment. *Water Research*, 45(3), pp.1165-1176.

[27] Arnold KE, Ross Brown A, Gerald T, Ankley GT and Sumpter JP, (2014). Medicating the environment: assessing risks of pharmaceuticals to wildlife and ecosystems. *Phil. Trans. R. Soc. B* 369: 20130569.

[28] Sarmah AK, Meyer MT and Boxall ABA, (2006). A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. *Chemosphere*, 65(5), pp.725-759

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[30] Green RE ,Taggart MA, Senacha KR, Raghavan B, Pain DJ, Jhala Y and Cuthbert R, (2007). Rate of Decline of the Oriental White-Backed Vulture Population in India Estimated from a Survey of Diclofenac Residues in Carcasses of Ungulates. *PloS One*, 2(8).

[31] HCWH Europe (2014). *How doctors can help reduce pharmaceutical pollution.* https://noharm-europe.org/documents/how-doctors-can-help-reduce-pharmaceutical-pollution

However, there are also problems surrounding other categories of drug substances, as was recently highlighted by Stockholm County Council in their categorisation of immunosuppressants (drugs that lower the body's ability to reject a transplanted organ), heart medications, and anti-acne medications among the pharmaceuticals of moderate concern.[32]

Policy context

In recognition of the growing problem of pharmaceuticals in the environment, the UN Strategic Approach to International Chemicals Management (SAICM), adopted 'Environmentally Persistent Pharmaceutical Pollutants' as an emerging policy issue in their process in autumn 2015.[33] In their 2012 report, the World Health Organization (WHO), stressed the importance of prioritising the emerging issue of pharmaceuticals in drinking water in the overall context of water safety management, including microbial and other chemical risks that may threaten the safety of drinking water.[24]

In Europe, according to Article 8c of Directive 2013/39/EU[34] (a directive regarding priority substances in the field of water policy), the European Commission has been asked to develop a strategic approach to address water pollution by pharmaceuticals by September 2015. This deadline has come and gone, and a lack of action by the Commission means that there is a continued risk to public health, health systems, and the environment from pharmaceutical pollution.

Stockholm County Council (SCC), is proactively addressing pharmaceutical pollution as part of its preventative environmental health work at a regional level in Sweden. It has developed an online database with environmental information on approximately 800 pharmaceutical substances. SCC uses this data to develop recommendations for the "Wise List"[35] - a formulary of essential medicines for patient care in the Stockholm region. Although the Wise List primarily focuses on medical benefits and side effects, when multiple pharmaceuticals have the same benefits, the environmental classification can be considered. Use of the Wise List is not mandatory, but more than 80% of the pharmaceuticals prescribed by the SCC health system are in accordance with the recommendations in the Wise List.[31]

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[32] Stockholm County Council (2014). *Environmentally classified pharmaceuticals, 2014-2015.* http://www.janusinfo.se/Global/Miljo_och_lakemedel/Miljobroschyr_2014_engelsk_webb.pdf

[33] Environmentally Persistent Pharmaceutical Pollutants (EPPPs) at International Conference on Chemicals Management (ICCM) 4 autumn 2015 in Geneva http://www.saicm.org/index.php?option=com_content&view=article&id=520&Itemid=714

[34] Directive 2013/39/EU amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy. OJ L 226/1, 24.8.2013. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32013L0039&from=EN

[35] Stockholm County Council Drug and Therapeutics Committee (2015). *The Wise List.* http://www.janusinfo.se/Documents/Kloka_Listan/The-Wise-List-2015.pdf

HCWH Europe's recommendations for the reduction of pharmaceuticals in the environment

1. Minimise the entry of pharmaceuticals into the environment throughout their life cycle

We need a multi-sectoral, multi-stakeholder approach that includes pharmaceutical companies, doctors, veterinarians, pharmacists, academics, patients, the general public, hospitals, care homes, water and waste companies, and legislators to minimise and prevent the release of APIs into the environment throughout their life cycle (i.e. in their production, use, and disposal). All policies and forms of engagement to this end should be applied using the precautionary principle (whereby in cases where scientific data do not permit a complete evaluation of the risk, withdrawal from the market should be considered for products that are likely to be hazardous). Member States need to set reduction targets with measurable impacts and annually report publicly on the reduction achieved.

2. Achieve zero discharge and eliminate the release of pharmaceuticals into the environment from manufacturing plants

Governments need to strengthen laws to eliminate pollution, monitor rigorously, impose fines, and withdraw licences if needed. The ultimate aim should be a zero discharge policy. National governments and regulators around the world need to expand the regulatory framework for Good Manufacturing Practice (GMP), to include environmental safety. The GMP legislation (i.e. Directive 91/412/EC[36] and Directive 2003/94/EC[37]), should require pharmaceutical production facilities to apply environmental safety standards to achieve a zero discharge goal.

3. Increase transparency and improve consistency along the supply chain

Pharmaceutical companies should know their supply chains, insisting on consistently high standards throughout. Companies need to report publicly on their environmental and worker safety standards. This will prevent multinational pharmaceutical corporations operating double standards in low, middle, and high-income countries, whereby they maximise profits by importing APIs from countries with weak regulatory systems. This needs to be equally applied to medicinal products for both human and veterinary use.

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[36] Directive 91/412/EC laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products. OJ L228/70, 17.8.91. http://ec.europa.eu/health/files/eudralex/vol-5/dir_1991_412/dir_1991_412_en.pdf

[37] Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. OJ L 262/22, 14.10.2003. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf

4. *Extended producer responsibility - make the pharmaceutical industry accountable for pharmaceutical waste throughout the life cycle*

The pharmaceutical industry's accountability for the impact of their products should not end at the point of sale. The Extended Producer Responsibility concept, already established in the automotive and electronics sectors,[38] also needs to be applied to the pharmaceutical sector. Pharmaceutical manufactures should contribute to financing collection schemes under the extended producer responsibility clause of the Waste Framework Directive.[39]

5. *Assess the potential environmental risks of all pharmaceuticals*

Most of the pharmaceuticals detected in the environment were authorised prior to 30th October 2005, when the 'Guideline on the environmental risk assessment (ERA), of medicinal products for human use',[40] came into force. Pharmaceuticals authorised before this date currently do not require an ERA. This exemption should be removed and an ERA conducted when renewing the market authorisation of any pharmaceutical. This should be based on the "No data no market" principle that applies to chemical substances regulated under the REACH Regulation.[41]

6. *Use green procurement as a tool to switch to pharmaceuticals with a lower environmental impact*

Public procurers can send a clear signal by setting environmental criteria for tendering in order to drive change in the market, using the Public Procurement Directive[42] to purchase socially responsible and environmentally sound pharmaceuticals. The joint UN Procurement project is an example of procurers working with supply companies to shift towards procuring more sustainable products.[43] Stockholm County Council is also facilitating green procurement by publishing the best available data on the persistence and likelihood of environmental impact from specific APIs.

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[38] Organisation for Economic Co-operation and Development (OECD) (accessed 2016). *Extended Producer Responsibility*. http://www.oecd.org/env/tools-evaluation/extendedproducerresponsibility.htm

[39] Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives (Article 8). http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008L0098&from=EN

[40] European Medicines Agency (2006). *Guideline on the environmental risk assessment of medicinal products for human use.*
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf

[41] Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals. OJ L 396, 30.12.2006. http://eur-lex.europa.eu/legal-content/en/TXT/PDF/?uri=CELEX:02006R1907-20160401

[42] Directive 2014/24/EU on the public procurement and repealing Directive 2004/18/EC. OJ L 94/65 28.3.2014. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014L0024&from=EN

[43] United Nations Informal Interagency Task Team on Sustainable Procurement in the Health Sector (SPHS) (2016). *Saving Lives Sustainably*. http://savinglivesustainably.org

7. Encourage rational use and improve education about pharmaceuticals

Over-prescription and overuse, especially of antibiotics, needs to be reduced. The rational use concept[44] should be reinforced by including environmental criteria in the curricula of medical, pharmacy, and nursing schools. Prescription guidelines for medical professionals need to be tightened and enforced.

8. Improve wastewater treatment

Wastewater treatment technologies are crucial components in the water management process. Wastewater treatment technologies need to be improved at municipal level and not just at a hospital level, as many patients continue treatment at home. Technologies that remove or destroy pharmaceutical contaminants in wastewater should be further developed and emission limits continuously lowered. Implementing advanced wastewater treatment technologies will reduce pharmaceutical pollution and in the longer term could completely eliminate environmental releases.

9. Dispose of unused pharmaceuticals safely

The inappropriate disposal of pharmaceuticals, such as by flushing them down the toilet, results in environmental pollution[16,19] and needs to be eliminated. Take-back schemes should be harmonised and expanded across the EU to prevent unused pharmaceuticals from reaching the environment. Member States should implement non-incineration treatment for all healthcare waste, including pharmaceuticals. Introduce clear labelling on each package on how to dispose of unused medicine that will guide doctors, pharmacists, nurses, and patients. Data on collection and disposal should be gathered and published annually.

10. Develop comprehensive legislation to reduce the impact of pharmaceuticals on the environment

Pharmaceuticals should not be treated differently than other groups of chemicals such as pesticides, biocides, and industrial chemicals. Models from other regulatory approaches that are already in place should be applied when drafting the strategic approach to pollution of water by pharmaceutical substances. In addition to this, the EU must develop comprehensive legislation to address the other means by which the pharmaceutical industry can affect the global environment and human health. Mandatory targets, systematic reporting, enforcement, and stakeholder engagement are all necessary to achieve this goal.

For more information about HCWH Europe, please visit: www.noharm-europe.org or email: europe@hcwh.org

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[44] World Health Organization. *Essential medicines and health products.* http://www.who.int/medicines/areas/rational_use/en/

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POLICY OPTIONS FOR REGULATING PHARMACEUTICALS IN THE ENVIRONMENT

Releases of pharmaceuticals into the environment: an issue of growing concern

Over 100,000 tonnes of pharmaceutical products are consumed globally every year (24% in Europe). During their manufacture, use and disposal, Active Pharmaceutical Ingredients (APIs) as well as other chemical ingredients are released into the environment (BIO Intelligence Service, 2013).

A very substantial share of pharmaceutical production now takes place overseas. This is particularly the case for antibiotics and other generic medicines. China produces 80-90% of antibiotic APIs and Indian companies lead the production of finished dose products. There have been numerous high-profile pollution scandals at antibiotics production sites in both China and India, resulting in the spread of drug-resistant bacteria (Changing Markets, 2016). Possible downstream pollution from manufacturing plants has been observed in the EU and other parts of the world (BIO Intelligence Service, 2013).

APIs are released in high amounts to the environment during human and veterinary consumption of drugs, as between 30 and 90% of an oral dose is excreted in urine as an active substance. A global review shows that over 600 different APIs have been detected in the environment (Lyons, 2014), in some cases at levels that pose a high risk to the environment. Pharmaceuticals have also been monitored in drinking water, waste-water, sewage sludge and soils (BIO Intelligence Service, 2013).

3000 APIs are marketed in the EU as human or veterinary drugs. Although the environmental impact of most of these substances is widely unknown, several API are known to persist and to accumulate in the environment. Examples of ecotoxicological effects of APIs include the contraceptive ethinylestradiol, which impairs the reproduction of exposed fish populations; the effects of various antibiotics on environmental bacteria and algae or the decline of vulture populations due to poisoning with diclofenac when feeding on animals carcases (BIO Intelligence Service, 2013).

The most relevant pharmaceuticals for the environment are anticancer medicinal products; hormonally active substances and antibiotics. Hormonally active APIs such as EE2 (which is present in the birth control pill) or paracetamol (over-the-counter pain reliever and a fever reducer) can disrupt the normal functioning of the endocrine system.

The presence of antibiotics in the environment contributes to the development of antimicrobial resistance (AMR), one of the major emerging threats to human health today. AMR burden in terms of lives lost, morbidity, and healthcare expenses and productivity losses is much greater than currently available statistics suggest - 25,000 deaths in 2007 - (ECDC, 2009) and projections estimate a 15 fold increase in

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morbidity in Europe due to AMR by 2050 with 390,000 deaths (Deloitte Sustainability, 2017). While many questions remain unanswered regarding the transmission dynamics between antibacterial agents in the environment and the development and spreading of drug resistance in people, it is clear that the rise of so-called superbugs could throw us back into a "pre-antibiotic era", with all the serious consequences this would entail for healthcare systems and people. From treating complex diseases including cancer, diabetes, pneumonia or HIV/AIDS, to performing surgeries to childbirth, AMR could put an end to many key achievements in health of the last century given the crucial role played by antibiotics (EPHA, 2017).

PHARMACEUTICALS, AN UNREGULATED INDUSTRY

Despite the high concerns on the threats posed by pharmaceuticals, their releases into the environment are almost unregulated:

- Information on environmental impacts of APIs is not available to the public or authorities. Accessibility is generally limited to risk assessors only.
- The assessment of the environmental risks is only compulsory for the Human Medicinal Products (HMP) placed on the market after October 2005, therefore, it covers only a minority of pharmaceuticals. Submitted Environmental Risk Assessments (ERA) may be incomplete or altogether absent from the marketing application (in Germany, for the top 10 human medicinal products found in surface water not a single ERA was available).
- ERAs' results are not considered for the decision on granting market authorisations of HMP, and the proposed risk mitigation measures are not binding.
- There are insufficient monitoring requirements and no specific emission limits in place for API releases from manufacturing plants in or outside Europe.
- Good Manufacturing Practices do not take into account the risks that medicinal products may pose to the environment and human health at the manufacturing stage.
- There are no limits in place for the content of pharmaceuticals in drinking water, in surface water, or waste water, not even from hospitals' effluents.
- Although pharmaceuticals contain hazardous substances, there are no specific regulations for the management of most human and veterinary medicinal products waste (only cytotoxic and cytostatic substances are regulated).
- There is no obligation to monitor or regulate medicinal pharmaceuticals present in sewage sludge or in manure used in agriculture.

REGULATORY NEEDS

As well as other chemical pollutants such as pesticides, biocides or industrial chemicals, the emission of pharmaceuticals into the environment needs to be regulated:

- **To ensure adequate information and transparency on the environmental impacts of pharmaceuticals.**
- **To ensure adequate and reliable evaluation of environmental risks of pharmaceuticals.**

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- **To prevent environmental releases of pharmaceuticals throughout their life-cycle.**
- **To control emissions of pharmaceuticals to the environment when prevention is not feasible.**

A. To ensure adequate information and transparency on environmental impacts.

Information on the ecotoxicological properties is lacking for most of the pharmaceuticals on the market. Existing information is provided in the ERA performed by industry and is scarce, scattered in individual reports, heterogeneous, incomplete and not publicly available. Toxicological effects occurring at low doses such as alteration in natural behaviours (activity, feeding rates, sociability), are normally not taken into account. Relevant studies from peer-reviewed literature are generally not included in the ERA performed by the pharmaceutical companies. Information on the presence of medicines in different environmental compartments is also scarce and heterogeneous as there is no obligation to monitor APIs in the environment, not even in water. Environmental impacts are only included in the reporting of adverse events of the veterinary pharmacovigilance system and, in any case, are reported relatively infrequently through the established tools.

Policy options:

✓ **Include medicinal and veterinary products under all of REACH titles.**

Medicinal and veterinary ingredients are exempted from most titles of REACH Regulation, including registration, evaluation and authorisation. The amendment of REACH to include pharmaceutical ingredients under all of its titles would ensure the generation of information on its ecotoxicological properties through the registration process and would improve the environmental risk assessment of APIs at all life cycle stages of pharmaceutical products. In order to avoid the bad quality and noncompliance problems of industrial chemical registrations, the registration files for APIs should be prepared by independent labs, nominated by ECHA although paid by industry. The costs could be shared by all the companies marketing the same APIs. As with industrial chemicals, deadlines could be established to ensure that all APIs in the market are registered in the near future. Priority should be given to those APIs with higher environmental relevance and used in higher volumes in the EU.

✓ **Public centralised EU electronic register of environmental impacts of API (human and veterinary).**

An alternative to the amendment of REACH, would be to create a specific register on the environmental impacts of all APIs marketed in the EU, based on the experience from REACH and also from the pesticides and biocides registration systems. In order to avoid the bad quality and non-compliance problems of existing systems, the registers of APIs should be prepared by an

independent lab as suggested above. This register would be public and accessible online in the same way as the REACH, pesticides and biocides registers.

✓ **Effective ecopharmacovigilance system both for human and veterinary pharmaceuticals.**

The EU legislation for HMP (Directive 2001/83/EC) should be amended in order to introduce environmental impacts reporting requirements in the human pharmacovigilance system. The importance of reporting environmental impacts, in particular AMR, should be promoted among professionals and authorities and the reporting tools should be simplified.

✓ **Inclusion of most relevant API in priority substance list and setting Environmental Quality Standards for these pollutants.**

In 2007 the German Advisory Council on the Environment (SRU) recommended examining the possibility of including pharmaceuticals in the list of priority hazardous substances. Environmental Quality Standards (EQS) are set for these substances in surface waters (river, lake, transitional and coastal). However, in 2018 there are still no pharmaceuticals included as priority substances despite the fact that this was already proposed by the Expert Group on Review (SG-R) of the Priority Substances in 2009.

Six pharmaceuticals have already been included in the Watch List [1] for surface waters including the painkiller diclofenac, two synthetic hormones 17-beta-estradiol (E2) and 17-alpha-ethinylestradiol (EE2) and three antibiotics (erythromycin, clarythromycin, azythromycin). No pharmaceutical is included in the Watch List for groundwater. Monitoring results show high risk levels for several of these API[2]. These APIs should immediately be included in the list of priority hazardous substances and Maximum Allowable Concentration (MAC) limits shall be set to the maximum technical feasible "detection limit". Additional relevant pharmaceuticals should be included both in the surface and in the groundwater watch lists. Improved monitoring results and target objectives to achieve a good chemical status will enable the identification of the sources and most cost-effective measures that could be taken upstream to prevent pollution.

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1 The Watch list is a mechanism to provide high-quality monitoring information on the concentrations of potentially polluting substances in the aquatic environment to support future prioritisation exercises. The mechanism is aimed at emerging pollutants and other substances for which the available monitoring data are either insufficient or of insufficient quality for the purpose of identifying the risk posed across the EU.

2 See EEB Briefing The environmental and health impacts caused by emissions of APIs to the environment.

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- ✓ **Establish and enforce greater transparency across pharmaceutical supply chains** by obliging companies to disclose in full the origin of their products at each step of the chain and down to the company name and factory where they were manufactured.

B. Ensure adequate, reliable and transparent evaluation of environmental risks of APIs.

"A reliable and relevant prospective risk assessment procedure is the backbone of an effective and successful environmental policy." (Ågerstrand, 2015)

The European Medicines Agency (EMA) guidelines for human and veterinary pharmaceuticals describe how the ERAs for human and veterinary pharmaceuticals should be performed. Important deficiencies of these guidelines that need to be tackled have been identified. The following recommendations from Ågerstrand (2015) should be implemented:

"1. Require environmental risk assessment also for products put on the market before 2006

We recommend that environmental risk assessments are performed also on products approved before the European Medicines Agency's guideline came into force. This would provide relevant environmental information for all active pharmaceutical ingredients that could be found in the environment.

2. Add requirements to assess the risk for development of antibiotic resistance

We recommend that information that enables assessment of the risk for increased antibiotic resistance development is included in the environmental risk assessment for antibiotic substances. This would provide a more accurate picture of the risks connected to the environmental occurrence of antibiotics and their risk to human health.

3. Perform only one environmental risk assessment per active pharmaceutical ingredient

We recommend that pharmaceutical companies that produce/import the same active pharmaceutical ingredient submit a joint environmental risk assessment instead of each company producing a separate one for the same substance, in line with the REACH Regulation's 'one substance, one registration' principle. This would increase consistency, and reduce animal testing as well as duplication of work.

4. Refine the tiered approach

We recommend that the tiered approach is refined to include pharmacological and toxicological data from the drug discovery process, as well as bioconcentration data. This would improve the

prioritisation process so that the ecotoxicity testing is focused on the most problematic substances and the most relevant test species.

5. Perform mixture toxicity assessments on active pharmaceutical ingredients with similar modes of action

In order to overcome the cocktail effect problem, we recommend that environmental risk assessments are performed for groups of active pharmaceutical ingredients with similar modes of action. This would enable a more accurate environmental risk assessment.

6. Mandate use of all available ecotoxicity studies

We recommend that all available ecotoxicity studies (including independent studies), of sufficient reliability and relevance, are used in the decision process. This would make better use of the available knowledge and may therefore add important information to the environmental risk assessment.

7. Include environmental risks in the risk-benefit analysis

We recommend that environmental risks are included in the risk-benefit analysis when a product is considered for market authorisation. This would increase the importance

of the environmental risk assessment and motivate pharmaceutical companies to perform the assessment on time.

8. Require review of the environmental risk assessments at regular intervals

We recommend that environmental risk assessments must be updated when significant new environmental information is available. This would bring forward the regulatory use of new scientific data and increase collaboration between stakeholders.

9. Include data from production of active pharmaceutical ingredients and formulations in the environmental risk assessments.

We recommend that the risk associated with active pharmaceutical ingredient discharges from manufacturing sites is included in environmental risk assessments when reviewing updated dossiers of products already on the market. This would increase the relevance of the assessments by including a part of the life cycle of the product responsible for the highest environmental concentrations detected.

10. Increase transparency

We recommend that environmental risk assessments and information about manufacturing sites are made publicly available. This would enable use of that information for other purposes such as research and evaluation, as well as stimulate companies to take more environmental responsibility throughout their supply chains."

C. Prevent environmental releases of APIs.

Regulatory measures to prevent releases of pharmaceuticals into the environment should be implemented similarly to measures included in REACH, biocides or pesticides legislative frameworks.

✓ **Restriction of APIs already known to pose a risk to the environment.**

As pharmaceuticals are covered by REACH Restriction title, APIs that are showing already a risk to the environment in the European Union should be restricted. The Commission should ask ECHA to prepare an Annex XV restriction dossier for these APIs. Member States where high environmental levels of APIs have been monitored could also take the lead in proposing restrictions. The scope of the restriction could include, for example, marketing limitations when safer alternatives are available; risk management measures to prevent environmental releases; or limitation of use in hospitals/health care centres that have effective of waste water treatment facilities on site.

✓ **Public procurement to favour HMPs and VMPs with low environmental impacts**

Following the example of Sweden, Members States should adopt environmental procurement criteria for pharmaceuticals and their packaging including emissions from manufacturing, content of environmentally hazardous substances, and working conditions in the production phase. Under the Swedish system, suppliers must provide the required environmental information through a freely accessible Web site, such as www.fass.se. Before being published, the information is reviewed and authorised by an independent third-party expert. (Medicinal Products Agency, 2016)

D. Reduce emissions to the environment.

Emissions of APIs to the environment should be controlled throughout the life cycle of medicines, from manufacturing (inside and outside of Europe), to consumption and waste disposal. Pharmaceutical ingredients as well as their metabolites and transformation products should be included horizontally as pollutants to be controlled in all relevant environmental legislation.

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During manufacturing of pharmaceutical products:

- ✓ **Revise the Good Manufacturing Practice (GMP) legislation to include requirements for environmental protection.**

  In order to be granted a marketing authorisation, pharmaceutical products manufacturers have to comply with GMP requirements to ensure that these products are always produced and monitored in such a manner that they satisfy quality requirements that are appropriate for their intended use. A well developed and functioning inspection system is already in place for monitoring compliance with GMP. Including environmental requirements under the GMP legislation will also have an impact on manufacturers in third countries.

- ✓ **Updating the Environmental Quality Standards Directive (EQS-D) to provide MAC values for active pharmaceutical substances.**

- ✓ **Revise relevant Best Available Techniques (BAT) reference documents (BREFs) to take into account environmental emissions of pharmaceutical ingredients during the manufacturing of pharmaceutical products.**

  The Commission shall ensure that Member States fully implement the BREF related to the Common Waste Water and Waste Gas Treatment/ Management Systems in the Chemical Sector (CWW). Member States shall review operating permits of pharmaceutical sites, implement the whole effluent assessment approach, oblige mandatory monitoring of API likely to be found in waste water (following the inventory of waste water set in BAT 2) and prevent emissions of relevant pharmaceutical ingredients in waste water through the application of more effective waste water treatment techniques. Information obtained through the application of BAT2 identifying the presence of API shall be shared with other stakeholders, in particular decision-makers, authorities and NGOs working on water protection. Possible regulatory gaps identified should be addressed through strengthened upstream control instruments (e.g. IED dedicated chapter on pharmaceuticals, REACH Regulation) and be based on recent developments in green chemistry or other findings. A more systematic link of achieving the Water Framework Directive objectives with BREF requirements shall be made. The upcoming HAZBREF initiative should address the issue of pharmaceuticals in water, considering the aforementioned elements.

During consumption

- ✓ **Obligatory prescription of APIs of high relevance for the environment.**

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EU legislation (Directive 2001/82/EC) requires prescriptions for veterinary pharmaceuticals (VMPs) which pose a potential risk to the environment, however, such an obligation does not exist for human medicinal products. The EU legislation for HMPs should be amended to require from EU MS prescription-only delivery for HMPs posing environmental risk. Guidelines should be developed both for HMPs and VMPs, for identifying environmental risk thresholds triggering prescription-only administration of APIs of high relevance for the environment.

During waste management

The large majority of unused pharmaceuticals is disposed of with municipal waste or directly in sewage. The only pharmaceutical products that are explicitly classified as hazardous waste under the Waste Framework Directive are cytotoxic and cytostatic products.

✓ **Enforce and improve provisions regarding take-back schemes in EU legislation.**

Competent authorities should ensure the enforcement of the provisions regarding take-back schemes in EU legislation on pharmaceutical products. This legislation should be amended to include specific requirements regarding Extended Producer Responsibility (EPR) and to develop an EPR system for unused medicines at the EU level, taking into account existing initiatives at MS level.

National EPR schemes should also be compliant with new minimum requirements as stipulated in revised Waste Framework Directive, to ensure the financing of the infrastructure to separate collection and proper treatment of medical waste. These EPR schemes should also be operating to reflect the waste treatment hierarchy, starting with prevention. For example, those producers offering exact amount of drugs needed rather than packaged drugs could be rewarded through fees modulation (as they will both prevent buying more drugs than needed, as well as reducing the overall amount of packaging).

✓ **Revise the Classification, Labelling and Packaging (CLP) Regulation to remove the blanket exclusion of human and veterinary medicinal products.**

This would allow the classification of relevant pharmaceuticals (in products) as hazardous (the most relevant classification would be "hazardous to the aquatic environment") and would ensure that their waste would be considered as hazardous waste and properly disposed of.

✓ **Revise the Waste Framework Directive**

To include a provision on pharmaceuticals in Annex III regarding the properties of waste which render them hazardous and to include a general provision that establishes that pharmaceutical

substances added to the priority (hazardous) substances list would automatically classify as hazardous waste.

✓ **Remind national competent authorities of the need to classify pharmaceutical wastes as hazardous waste, when appropriate**, under entry 07 05 13* (solid wastes containing dangerous substances). The Waste Framework Directive allows EU Member States to consider waste as hazardous even if it does not appear in the EU list of hazardous waste, provided it displays relevant properties.

Water

- ✓ **Update the Environmental Quality Standards Directive (EQS-D)** to provide MAC values for active pharmaceutical substances.

- ✓ **Use any future revision of** the Urban Waste Water Treatment Directive (UWWTP-D) to ensure that API are effectively treated and destroyed before further release.

- ✓ **Develop EU guidance for hospital/healthcare-centres to reduce contamination of municipal waste water with residues resulting from the use and disposal of pharmaceuticals.**

- ✓ **Amend the Groundwater Directive (GWD)** to ensure that ERA results for pharmaceutical substances are taken into account by the Commission when reviewing Annexes I and II (groundwater quality standards + list of pollutants and threshold values).

Sludge/ Manure

- ✓ **Amend the Sewage Sludge Directive** to require monitoring and establish protective limit values for relevant pharmaceutical substances and AMR microorganisms in sewage sludge.

- ✓ **Any future Commission proposal for a Soil Framework Directive** should require monitoring and establish protective limit values for relevant pharmaceutical substances and AMR microorganisms in soil.

- ✓ **Use ongoing revision of the Fertilisers Regulation** to ensure that manure, sewage sludge and water used as fertilisers or for irrigation are safe, by setting concentration limits for certain pharmaceuticals and AMR microorganisms in these materials, and by promoting good practices to reduce the risks of transfer to soils.

- ✓ **Close gaps in the BREF document on the intensive rearing of poultry and pigs** to require monitoring and establish protective limit values for relevant pharmaceutical substances and AMR microorganisms in manure and effluents. The BAT Conclusions provide a catalogue of techniques to reduce emissions of microbial pathogens to air and water from processing of manure and landspreading on farm, but do not address the use of pharmaceuticals / AMR specifically from these activities. There is just a general requirement to treat contaminated waste water, but without

specific requirement on pharmaceuticals, despite the recognition that these may end up in the manure. Building on findings gathered through the HAZBREF review, the IRPP BREF should be amended to close gaps, where necessary.

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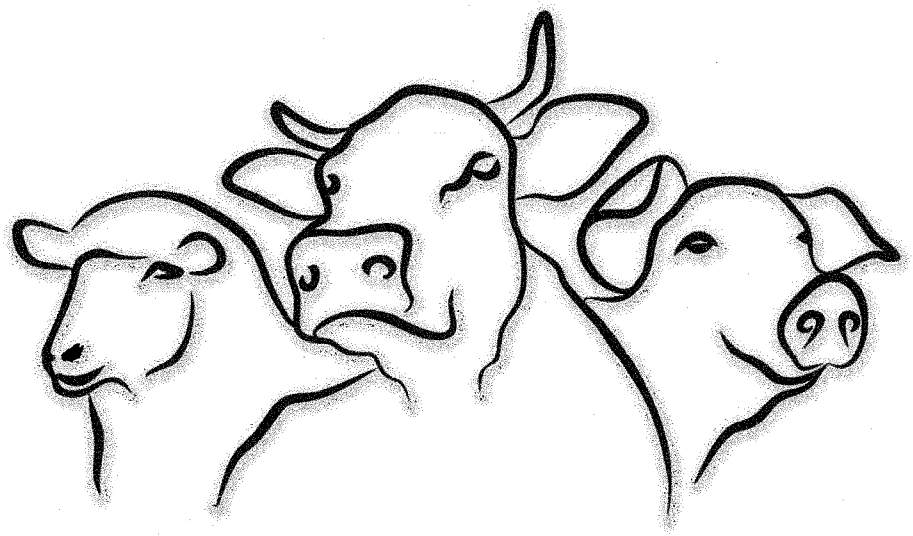
Ecological Impacts of Veterinary Pharmaceuticals: More Transparency – Better Protection of the Environment



Avoiding Environmental Pollution from Veterinary Pharmaceuticals

To reduce the contamination of air, soil, and bodies of water caused by veterinary medicinal products used in agriculture and livestock farming, effective measures must be taken throughout the entire life cycle of these products – from production and authorisation to application and disposal.

All stakeholders – whether they are farmers, veterinarians, consumers, or political decision makers – are called upon to contribute to reducing contamination of the environment caused by pharmaceutical residues and to improving protection of the environment and human health. Appropriate measures include establishing "clean" production plants, developing pharmaceuticals with reduced environmental impacts, assessing the environmental impacts of all veterinary pharmaceuticals more stringently, monitoring systematically their occurrence in the environment, converting animal husbandry practices to preserve animals' health with a minimal use of antibiotics, and enforcing legal regulations to ensure implementation of all the measures outlined here.

In the context of the revision of veterinary medicinal products legislation that is currently underway, this background paper focuses on three measures that would contribute to making information on the occurrence of veterinary drugs in the environment and their eco-toxicological effects more widely available and enhance protection of the environment from contamination with veterinary pharmaceuticals.

Introduction of a monograph system for documenting relevant environmental data and making information on the environmental impact of veterinary pharmaceuticals more widely available

PAN Germany's position is that data on the substances used in veterinary medicinal products and on their environmental impacts should be compiled in substance-based monographs and made available to the general public in databases similar to existing databases on pesticides.

For more than ten years, risk assessment in the context of authorising veterinary medicinal products has generated information on pharmaceuticals, including data on the physio-chemical properties of their active ingredients and on their environmental effects. Data collected for approval purposes are initially private property that belongs to the pharmaceutical company applying for authorisation, which must submit information from relevant test series and other data. If two different companies apply for authorisation of products with the same active ingredient, these drugs undergo the mandatory environmental impact assessments that are part of the process separately; this means that, for example, the effects of the active ingredient on model organisms are examined twice. By documenting environmentally relevant data acquired in the context of authorisation procedures in a substance-based monograph and exchanging this data between companies that have been granted authorisation of different products with the same active ingredients, the number of repetitions of test series could be reduced. As a result, environmental impact assessments could be harmonised, diverging assessments of the same active ingredient avoided, and the reduction of repeated testing with animals would contribute to enhanced animal protection. Information on the environmental occurrence, fate, and effects of active substances found in comparable products could be exchanged and published in a harmonized format: the monograph. Data on a substance's physio-chemical properties, mode of action, degradation, possible environmental consequences, its metabolic paths, and rates at which it is excreted, and so on, additional information gained from environmental monitoring, as well as data from scientific publications could be compiled and serve as a basis for assessing environmental risks.

Introduction of a monitoring system to collect data on the occurrence of (veterinary) pharmaceuticals in the environment

Information about the fate and effects of veterinary pharmaceuticals in the environment is to date inadequate. This is partly because data on the occurrence of veterinary medical products in the environment is not collected systematically and partly because eco-toxicological data collected in the context of authorisation procedures is not made available to the public, and the information acquired is not shared. Nevertheless, an appreciable volume of data on the environmental occurrence and behaviour of (veterinary) pharmaceuticals in the environment has been collected and published in recent years. To date, EU member states are not obliged to monitor pharmaceutical residues in bodies of water. However, individual and sometimes regional studies indicate that medicinal products have been found almost everywhere in surface waters in Europe and beyond. According to data from Germany's Federal Environmental Agency, more than 150 different active pharmaceutical ingredients alone have been detected in surface waters, sediments, ground water, and soil in

Germany. Many of these substances have a high potential for causing harm to fish and small aquatic organisms. Such active ingredients have been detected in surface waters at concentrations of 0.1 to 1 microgram per litre – and sometimes even higher. Long-term tests with fish, daphnia, and algae have shown that these concentrations can affect aquatic organisms. Antibiotics can inhibit the growth of plants, algae, and cyanobacteria; antiparasitics harm insects, worms, and crustaceans. Even very low concentrations of residues of endocrine-active drugs interfere with fish reproduction and can harm amphibians. And these effects do not yet take into account possible aggravated effects due to the combined action of various contaminants. Among the active pharmaceutical substances detected in concentrations above 0.1 µg/l in Germany's surface waters, there are four antibiotics used in veterinary medicine: sulfadimidine, sulfamethoxazole, erythromycin, and trimethoprim. In soil, veterinary pharmaceuticals bind to soil particles, where their germicidal, antifungal, and antiparasitic properties affect soil organisms and can have considerable negative impacts on beneficial organisms and ecosystem functions. Veterinary drugs such as sulfonamides and tetracyclines have also been detected in ground water. Even if the concentrations detected so far are low and the number of findings has been small, ground water should remain free of contamination. Contamination of veterinary pharmaceuticals in ground water is an alarming finding – not only with respect to our drinking water supplies.

PAN calls for the introduction of mandatory and coordinated monitoring of the occurrence of pharmaceuticals in soil and bodies of water. In keeping with the precautionary principle, PAN calls for applying the existing limit for active substances from pesticides and biocides in ground water of 0.1 micrograms per litre (µg/l) for a single substance and 0.5 micrograms per litre (µg/l) for the total of all such substances to pharmaceuticals, as well.

Revision of the pharmacovigilance system for veterinary pharmaceuticals to ensure monitoring of their environmental effects

Before a drug is placed on the market, it undergoes a mandatory authorisation procedure, during which its efficacy and tolerance are investigated and possible environmental risks are evaluated in an environmental impact assessment. But even if undesirable impacts are assessed in this process, monitoring a medicinal product after it has been authorised and been placed on the market is especially important, since this is the only way to observe a product in everyday use and ascertain whether it has any previously undetected (side) effects. Therefore, all pharmaceuticals are subject to statutory safety monitoring, called pharmacovigilance, by the doctors and veterinarians who prescribe them. This involves observing and reporting on the risks and side effects of drugs used in humans or animals. Unlike pharmacovigilance procedures for human pharmaceuticals, this monitoring of veterinary drugs includes possible negative effects on the environment. However, there is a discrepancy between the legal obligation to report on environmental risks in the context of monitoring a drug after it has been authorised (Directive 2001/82/EC as amended in 2004) and the current possibilities for fulfilling this obligation. The pharmacovigilance system is product-related, but contamination of the environment generally cannot be attributed to a single product. To ensure monitoring of negative impacts on the environment, at the very least the occurrence of active substances from veterinary products that have been shown to be environmentally hazardous should be checked in specific environmental matrixes. Also problematic is the fact that veterinarians are not trained to identify possible harm to organisms in soil and water. In view of current knowledge already gathered in the lab and in the field about existing contamination of soil and

PAN considers the current pharmacovigilance system to be unsuitable for monitoring possible negative impacts of veterinary pharmaceuticals on the environment. According to PAN Germany, the system must be revised or other systems of environmental monitoring have to be established.

bodies of water and about the effects of drug residues on non-target organisms and ecosystem's functioning, it is absolutely imperative that the occurrence and negative effects of veterinary pharmaceuticals in nature are systematically monitored after authorisation. Identifying the key contexts in which contamination and ecological damage occur would mean that appropriate measures to counter contamination and protect the environment could be implemented. Special attention must be paid to active ingredients and co-formulants regarded as especially hazardous to the environment, such as so-called PBT substances, which are persistent, bioaccumulative, and toxic and also accumulate in organisms; vPvB substances, which are very persistent and very bioaccumulative; and hormonally active substances, known as endocrine disrupters (EDs).

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