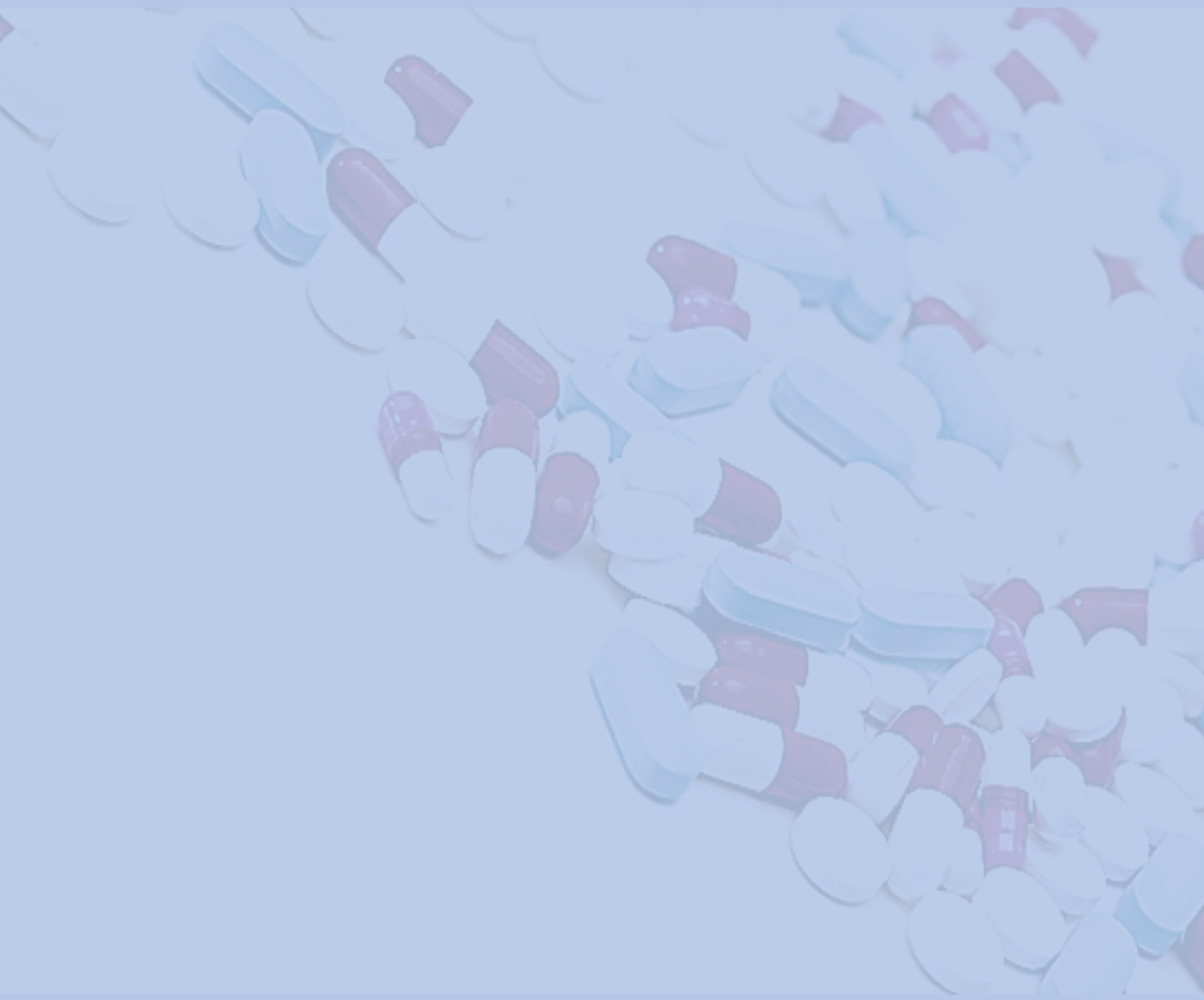
Pharmaceuticals in European freshwater: The need for green pharmacy



DIVISION OF GLOBAL SUSTAINABLE DEVELOPMENT, UNIVERSITY OF WARWICK: 2021

Pharmaceuticals in European freshwater: The need for green pharmacy

Overview:

- Pharmaceutical compounds in the environment present a major risk to wildlife, and human medicine.
- Current water treatment techniques are inadequate and increase the abundance of antibiotic resistance genes.
- Local strategies of labelling drugs based on environmental impact are effective and scalable- influencing prescribers and users of drugs to choose more sustainable medicines.
- Drug takeback schemes have potential to reduce entrance of drugs into the environment.
- Agricultural techniques lead to the further spread of pharmaceuticals and aquaculture is responsible for large amounts of antibiotics entering water systems.

Executive Summary:

Pharmaceutical compounds entering the environment present a major risk to human medicine, wildlife and biodiversity. The main source that compounds enter the environment is via water systems- leaching from farmland, human excrement and aquaculture. Current water treatment facilities are inadequate and are known to increase antibiotic resistance in bacteria. Strategies to influence prescribers and drug users have proven successful on a local scale, and drug takeback schemes have the potential to significantly reduce entrance of drugs into the environment. Such schemes are scalable to the whole of the EU. Many used and excreted drugs remain active in the environment, and therefore impact the physiology and behaviour of wildlife. Certain endocrine disrupting compounds are known to cause problems with human development and reproductive health- both in men and women. Many pharmaceutical compounds are currently found in drinking water, food and the environment. Compounds found include over the counter drugs such as painkillers, and prescription drugs: antibiotics and human hormones, amongst others, but at a low concentration that a

therapeutic dose is not reached for humans of any particular drug. It is preferable to limit routes of entry over relying on innovation and further research due to uncertainty, and time constraints- compounds build in concentration over time.

Foundational science: Discussion & Analysis:

Evidence of Pharmaceutically active compounds (PhACs) and endocrine disturbing compounds (EDCs) has been found in seafoods across Europe [1]. PhACs are designed to have a specific biological effect upon an animal at low doses such that wildlife or humans will be affected by the drug in the intended fashion [2]. There is a notable impact upon fish behaviour caused by low concentrations of PhACs currently observed in river waters across Europe [3, 4]. Marine physiology is also already being impacted by PhACs and EDCs in freshwaters- presence of estrogens in river environments has led to feminisation of male fish in rivers, leading to intersexed fish [5], a clear example of the huge ecological impact that PhACs are capable of causing. Feminisation of fish can result in loss of biodiversity, and available breeding stock, as the sexual capabilities of the fish are impacted [5].

Despite most studies finding low risks to human health, few include consideration of all exposure pathways, or the impact of a multitude of PhACs mixing at once [6]. Similarly, bioaccumulation is rarely a considered phenomenon: bioaccumulation is the increase in concentration of certain substances over time in consumers. [7] PhACs are present at the bottom of a food chain, and the compounds remain in the consumer such that over its lifetime a large dose an animal's tissues contains a significant amount of the substance of interest- a predator will then eat a large number of those animals resulting in a dose equivalent of the lifetime consumption of the prey animals eaten. This results in large doses of PhACs in seafoods than is present in water.

PhACs and EDCs are difficult to remove using conventional water treatment methods, with antibiotic resistance genes being most difficult [8]. Several academics consider antibiotic resistance a larger risk to human health than toxicity or negative effects of PhACs [8-10]. Secondary water treatment facilities increases numbers of antibiotic resistance genes present during processing of the water, as bacteria will release plasmids for resistance when treated,

allowing other bacteria to pick up resistance genes [8]. Increased antibiotic resistance will lead to major disruption to current medical techniques as antibiotics become less effective. eventually making routine surgery incredibly risky if no alternative is found. Waiting on pharmaceutical companies to produce sustainable medicines should not be relied on, due to the time taken for this to occur. The cost or efficacy differences from currently used PhACs may make use of such new drugs unfeasible regardless of their low environmental impact. Therefore, it is preferable to limit exposure of PhACs to the environment. The common routes that PhACs take into the wider environment, particularly into freshwater can be seen in figure 1.

Water contaminated by PhACs can go on to pollute both crops and soil, causing disruption to soil systems and the microbiota present. Pollution of crops by PhACs will impact the health of consumers. Once contaminated water is spread on croplands, PhACs can form complexes with minerals in the soil [11], and remain for long periods of time, but they are not highly available to plants in this state, reducing the availability of ions for plant growth. PhACs may then be transformed into more toxic compounds via interaction with the environment. They can be broken down by the sun's UV rays, by heat, or from bacteria [11-13]. Little is known about substances that are produced from broken down PhACs in the environment, and hundreds of substances may be made, as certain bacteria may break drugs down into more or less toxic substances than others [12] . Additionally, PhACs may not complex in the soil, and will be moved via rainfall- leading to leaching into groundwater systems and being taken up by crops or animals. Furthering a wider impact on the environment. Several PhACs are biodegraded by bacteria present in the environment. Ibuprofen is known to significantly impact growth of aquatic microorganism communities [11], and can have toxic breakdown products [14]. The high levels of uncertainty surrounding environmental breakdown of many PhACs suggests that more care should be taken to avoid this happening- ideally by stopping the PhACs reaching the environment in the first place.

Human reproductive health is known to be impacted in similar ways to wildlife reproductive health. PhACs and specifically EDCs have been associated in higher levels of testicular, ovarian and breast cancers, and decreasing levels of fertility [15, 16]. These increases are significant even when cultural change is considered- birth rates are decreasing due to it no longer being

a priority for many people to have children [16]. PCOS and other diseases are also indicated as consequences of high levels of pollution. It may therefore be cheaper in the long term to control polluting substances to reduce incidence of such diseases than it would be to develop new treatments and treat increasing numbers of people for reproductive diseases.

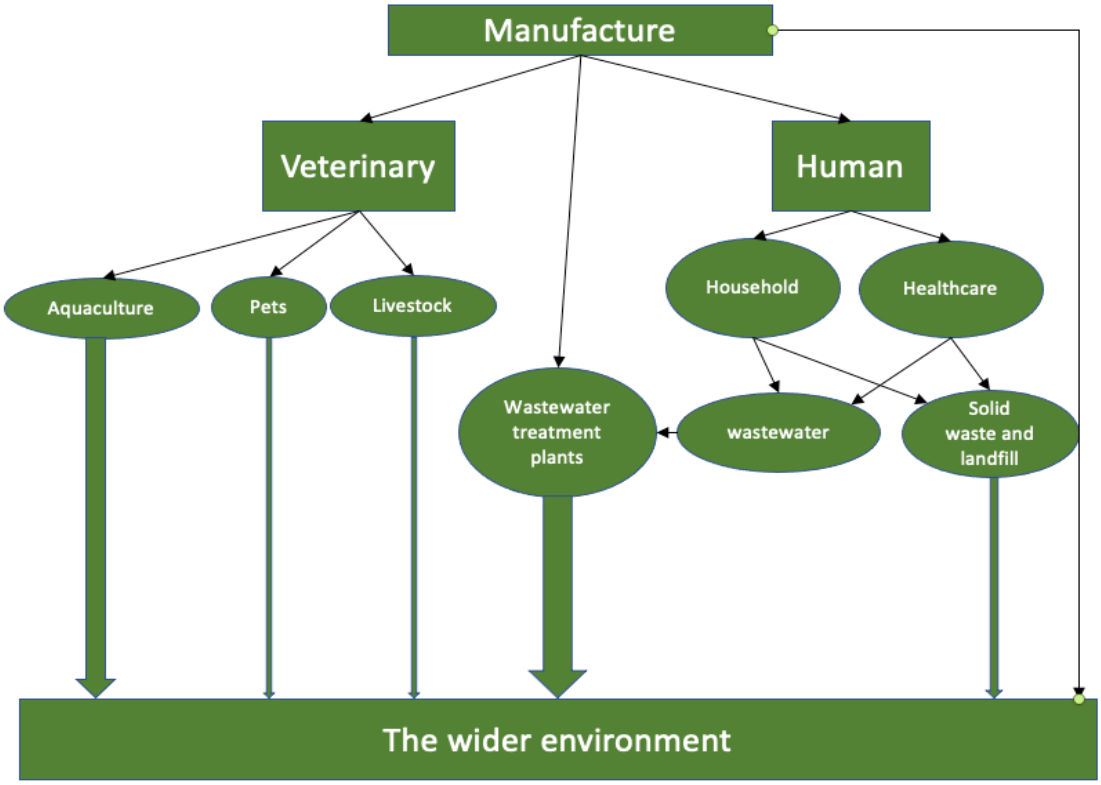


Figure 1: common routes of PhACs into the environment [17]. The wider environment referred to in this figure is primarily freshwater environments, such as lakes and rivers, but this will leach into soils and plants with time, especially if spread onto farmland.

Existing governance:

Current governance is inadequate across Europe, however governance in individual nations is better [18, 19]. Throughout Europe, release of PhACs into the environment has decreased as a by-product of projects aiming to reduce other pollutants in seawater, such as pathogens and metals [18]. However, the EU's current requirement of secondary water treatment for all cities has worsened antibiotic resistance levels [8], as such processes increase the abundance of antibiotic resistance genes in water post-treatment.

Some states have outlawed sewage spreading or incinerate solid wastes [18], which stops contaminants leaching into the environment, but this is at the loss of agricultural productivity gains from sewage-based fertilisation [20]. This leads to increased use of artificial fertilisers and pesticides to increase yields- which have significant ecological impacts of their own [21]. Select localised responses have been effective for example, Stockholm city council classifies drugs by their environmental impact in order to minimise usage of the worst offending drugs unless absolutely necessary [22]. In spain, drug take-back campaigns have been created to minimise entrance to the environment via landfill or flushing [18, 23]. Such schemes, if adopted across Europe, have the potential to be effective at reducing the entrance of PhACs into European freshwater environments. In aquaculture, there are no restrictions on use of antibiotics, so medicalised feed is used- creating a significant source of antibiotics in water systems. This is unnecessary as providing antibiotics in a controlled manner is possible, and therefore preferable [24]. The reason it does not occur is due to the time and financial costs- providing an excess of antibiotic in feeds as a preventative measure is easier.

The European Union is developing a strategic approach to PhACs in the environment [19], but their suggestions tend towards gathering further data. Improving water treatment techniques, something which is costly, can prove worse for human health in the long run when the consequences of antibiotic resistance are considered [8]. Despite this, there are clear messages to improve control of emissions from manufacture and to choose the most sustainable methods of drug delivery when possible [19], by comparing the impacts of patches, creams and tablets on the environment.

Governance recommendations:

Solutions that will target multiple types of pollutants at once are most ideal, as they will be more efficient. As consumers prefer to use more environmentally friendly products [25] It would prove effective to label PhACs based on their impact on the environment, as seen in Stockholm [22] in order to influence consumers choice for over the counter drugs. This would likely also influence decision makers involved in drug procurement. However, care should be taken to ensure that safe and effective care is always given by healthcare providers, and that unsustainable PhACs are still recommended if required. Strict controls on use of PhACs in

agriculture and aquaculture, such as limiting antibiotic use to sick and at-risk animals only. Reducing PhAC usage on farmlands such as fertilisers with sufficient incentives to use more sustainable methods, especially if such methods are associated with a lower yield. It will also reduce leaching of compounds into crops and water systems (see fig.1).

The drug take-back program in spain is effective and has the opportunity to be successful across Europe [26]. Especially if people are warned of the effects of certain drugs on the environment, such as hormone replacement patches- which keep most of the hormone on the patch after use [22]. Therefore releasing the medicine into the environment. Improving water treatment techniques is necessary to stop the increase of antibiotic resistance genes available in water [8]. This is not a priority for reduction of PhACs and instead water testing at regular intervals will be more effective to ascertain the effectiveness of policies put into place to reduce PhACs in the water. In the future, sustainable water treatment techniques should be explored, such as the use of White rot fungi to remove organic materials in water easily in bioreactors [27].

Investment into sustainable drug manufacture via incentivising pharmaceutical companies to produce drugs with low impact. Introducing bans on particular substances such that innovation can occur to stop the use of banned substances will be effective but should not be relied on as a first line of action. As the bans will have to be phased in to reduce the impact on human health.

If action is taken in accordance with the EU's proposed strategic approach: [19] investment into innovation, more stringent control of water treatment and sustainable drug manufacture. There is potential for a good reduction of PhACs in the environment and lower impact on wildlife and human health. It should be noted that the EU's suggestions will only be effective if implemented alongside immediate policy made to reduce entrance of drugs. such as change in prescription choices, sewage usage, and very strict protocols for use of drugs in aquacultural and agricultural circles.

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