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POSITION PAPER by ISDE

Pharmaceuticals and personal care products: contaminants of emerging concern

This text was created by the Association of Doctors for the Environment, ISDE, curated by Vitalia Murgia, Agostino Di Ciaula, Roberto Romizi.

Editorial Supplement. First edition (November 2024)

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Introduction

Contaminants of "emerging interest" are a broad group of chemical compounds that could potentially lead to various environmental problems. These are chemical substances that are not currently regulated (i.e., not subject to routine monitoring and/or emission control measures) but may be under scrutiny for future regulation [1]. The term "emerging" should not be taken to imply newly developed chemicals. In many cases these are substances that have been used for years and sometimes have been found in environmental matrices for quite some time, with a potential environmental impact still needing to be comprehensively investigated. The sets of "pharmaceuticals" and "personal care products" (PPCP) have been recognized in recent decades as contaminants of "emerging concern" due to their persistent presence in aquatic environments. The first "P" in the acronym refers to pharmaceuticals, specifically the active pharmaceutical ingredients (APIs) with pharmacological action, while the "PCP" part refers to personal care products, including among others bactericidal/disinfectant preservatives, insect repellents, fragrances, ultraviolet (UV) sunscreens, emulsifiers, additives, and much more. The United States Environmental Protection Agency (US EPA) defines PPCP as

"any product used by individuals for personal health or hygiene reasons, or for aesthetic purposes, or used by the agricultural industry to enhance the growth or health of livestock" [2]. This definition encompasses thousands of chemical substances, including active pharmaceutical ingredients (APIs) and other compounds widely used in the pharmaceutical or food sectors, such as artificial sweeteners [3,4,5], preservatives [6,7], as well as additives, flavors, and colorants present in drugs, cosmetics, and personal hygiene products. Due to analytical limitations and the need for substantial human and economic resources, the presence of many PPCPs in the environment has not yet been fully documented. Additionally, metabolites of various substances are usually not sought. This may have led to a critical underestimation of the actual number of PPCPs present in different environmental compartments. From a reduced list of 133 studies containing data on PPCPs derived from real samples, 580 unique compounds were identified in various matrices [8]. Many PPCPs are biodegradable and quickly disperse in the environment, but their extensive and universal use results in a pseudo-persistence in aquatic environments, with serious ecological impacts on the organisms living there, thus posing a risk of selective pressure that may contribute to reducing biodiversity. Concerns about the detection of PPCPs in the environment derive from their ubiquitous presence in water bodies, soils, and biota. PPCPs have been identified and confirmed as relevant pollutants even in the Arctic environment, and their presence is reported in various environmental compartments [9]. Even when PPCPs can be partially metabolized or biodegraded, their excreted metabolites can become secondary pollutants and be further altered in receiving water bodies.

A very concerning aspect is that pharmaceuticals or their metabolites can exert significant biological actions even at extremely low concentrations (e.g., endocrine disruptors) and are often inherently toxic (e.g., oncological drugs). In addition, the environmental behavior of pharmaceuticals and their metabolites is largely unknown. There is evidence that the incorporation of pharmacological substances into organisms and ecosystems threatens genetic diversity, species biodiversity, and community biodiversity. PPCPs can become harmful to human and animal health because their residues tend to accumulate in organisms and enter the food chain. The concentrations of PPCPs residues in the environmental matrices and in the food chain are usually low (from ng/L to μg/L, higher in hospital discharges). Despite this, such substances can have serious negative health effects due to their ability to generate multiple biological effects even at low concentrations (especially in vulnerable populations as children) and their tendency to bioaccumulate. Additionally, the long-term effects of human exposure, particularly in cases of complex mixtures of multiple substances (the most common occurrence), have not yet been comprehensively investigated [10]. PPCPs can alter cellular metabolism, development, and physiology in various unicellular and multicellular organisms. Their presence has been identified in microorganisms, plants, invertebrates, and vertebrates in different habitats and regions worldwide. The increasing global contamination of freshwater systems with thousands of industrial and natural chemical compounds is one of the major environmental challenges humanity faces. To safeguard ecosystem health, the release of PPCPs into the environment must be rapidly reduced through a combination of interventions that address the entire life cycle

of PPCPs. These interventions will need to be implemented by institutions, industries, livestock farmers, healthcare professionals (doctors, pharmacists, and veterinarians), and regular people. Doctors, pharmacists, and veterinarians, particularly those caring for companion animals, should play a key role in advising people on the proper use of pharmaceuticals and could each contribute significantly within their area of expertise to limit the spread of PPCPs into the environment. However, for effective actions, healthcare professionals must at least be aware of the fundamental aspects of the issue and should fully understand the virtuous pathways to be implemented to reduce pollution intensity and to mitigate damage to the biota and human health. The goal of this document is, therefore, to provide these professional categories with a summary of the main available knowledge on PPCPs contamination and indications of possible solutions.

Which substances fall under the definition of PPCP?

PPCPs are classified into two main categories based on their uses: a) Pharmaceuticals primarily used to diagnose, prevent, or treat diseases in humans and animals, and pesticides; b) Personal care products (PCP). This category includes various chemical substances that serve to preserve the product, improve its palatability (taste, texture, fragrance, etc.), or its applicability, all aimed at providing longer lasting and more appreciated products to make life more comfortable [11]. Many personal care products are designed to improve individual appearance and hygiene. For this reason, they are used daily in personal care routines and include a wide range of products such as soaps, facial cosmetics, perfumes, toothpaste, sunscreens, lotions, hair dyes, and others. Worldwide, an adult uses on average nine PCPs per day [12].

Sources of PPCP dispersion in the environment

PPCPs are released into the environment from multiple sources. The primary source appears to be their use. The ways these substances spread into the environment may vary depending on whether they are used for human or animal treatment. Once ingested by humans orally, PPCPs can be absorbed by the body, metabolized, and excreted either unchanged or as metabolites, and discharged into the sewage system. Between 30% and 90% of the orally administered dose is typically excreted as an active ingredient in the urine of both animals and humans [13]. Hospital activities have been identified as a significant source of PPCPs through their effluents due to the high use of drugs (including those not typically dispensed in community pharmacies) and other chemicals, the large amounts of water consumed in these facilities, and the activities performed (diagnostic care, laboratory, research) [14]. PPCPs applied to the skin for therapeutic, hygienic, or cosmetic purposes are released when washing and are again directed towards the sewers. PPCPs are also present in wastewater from aquaculture and livestock farming, in residential and industrial wastewater, and in the discharges from beauty centers or hairdressers, etc. They can also reach the environment through leaching

Life cycle of the drug and factors influencing environmental release

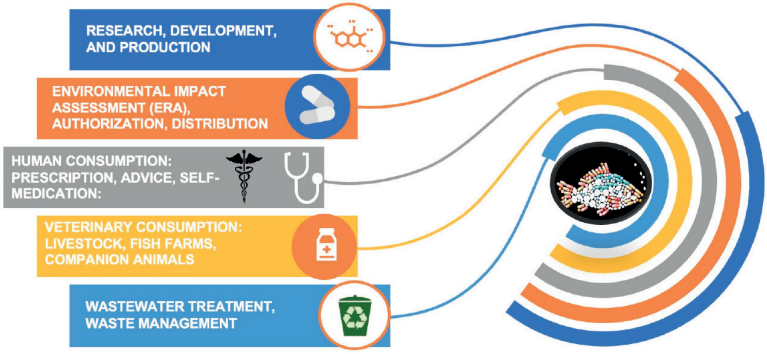

Figure 1. Life cycle of pharmaceuticals and potential routes of release into the environment.

from landfills or through accidental and intentional release of untreated wastewater [15]. Veterinary medicines are released directly into the environment (e.g., use in aquaculture and grazing animals) or indirectly during the application of manure and slurry from livestock farms, mainly for fertilization purposes. Pharmaceuticals may also enter the environment directly through feed surpluses, particularly in aquaculture. Additionally, PPCPs are introduced into the environment from industrial production sites [16]. The concentration of PPCPs in the effluents of wastewater treatment plants from pharmaceutical companies typically ranges from hundreds of μg/L to mg/L, while in municipal effluents treating domestic wastewater, concentrations are usually in the ng/L range [17]. All PPCPs have complex chemical structures, and most of them are found in combinations of various active chemicals

in widely available commercial products. For such combinations of substances, the only traceable source of their release is production plants. Once they leave the manufacturing site and reach the retail market, the pathways towards environmental exposure for the various substances become widespread, making them difficult to trace and analyze [18]. From the perspective of environmental spread and persistence, the key stages in a drug's life cycle are design, synthesis, marketing authorization, production, prescription, sale, and waste management. Figure 1 shows the life cycle of pharmaceuticals and the potential routes of release into the environment.

An analysis of the factors that can influence the spread of PPCPs in the environment clearly highlights the importance of their biodegradability, underscoring the need for more eco-friendly and sustainable approaches to design and synthesis. This is to ensure that pharmacological molecules and other chemicals present in products degrade easily after excretion or washing, do not promote bioaccumulation, and are less toxic to aquatic organisms, thus lacking the characteristics of "persistence" [15]. The high persistence of a substance implies the potential for long-term environmental and human exposure, which is difficult to control and resolve. Cousins et al. [19] argue that chemical persistence is an intrinsic risk factor, regardless of the molecule's toxicity, and emphasize the need for current regulations to be appropriately revised to ensure adequate environmental and human protection from highly persistent environmental chemicals. Before conducting a deeper analysis of the current effects of PPCP contamination, it is important to first evaluate how effective wastewater treatment systems are in handling effluents containing PPCPs.

Efficiency of wastewater treatment

Wastewater treatment can partially eliminate or remove pharmaceutical residues, but varying amounts are still detectable in effluents, receiving surface waters, and groundwater. Despite significant improvements in wastewater management, it is estimated that 80% of wastewater produced globally is discharged directly into the environment without any treatment [8]. Unfortunately, PPCPs are not consistently and completely removed during wastewater treatment processes [20]. A key factor influencing this issue is the "mobility" of the chemical molecule. Mobility refers to a molecule's ability to avoid being retained by natural barriers (such as soil, sediment, and suspended organic matter) or anthropogenic ones, like activated sludge and adsorbents such as Granular Activated Carbon (GAC). Mobility is a critical factor in the spread of molecules from the discharge point to natural water bodies, which are often used as sources of drinking water [21]. Residual concentrations of PPCPs have still been detected in water after several treatment phases, indicating that some compounds are resistant to degradation. In one study [22], which investigated the presence of 156 organic chemical contaminants in wastewater from 90 wastewater treatment plants (WWTP) across Europe, 125 compounds were detected at least once, and around 45 compounds were found with a frequency of 80-100%. A year-long study of an urban drinking water treatment plant involving 30 PPCPs, some of which exhibited endocrine-disrupting activity (24 pharmaceuticals, 1 herbicide, and 5 personal care products), found that the average removal efficiency for all substances was between 76%-18%, varying significantly between different compounds. Erythromycin,

bisphenol-A, trimethoprim, triclosan, and a flame retardant (tris(2-chloroethyl) phosphate TCEP) were among the most difficult to remove, with an average removal efficiency of less than 60% of their original concentrations. The authors noted that the performance of individual processes in removing PPCPs and EDCs could vary significantly over time [23]. The burden of residuals after wastewater treatment depends on the composition of the pharmaceutical, the wastewater treatment process, and the initial concentrations in the influent. For instance, ibuprofen, which is present in significant amount in wastewater, is reduced by 60-96% through treatment, whereas the removal rates for carbamazepine are significantly lower. Carbamazepine, caffeine, diclofenac, and sulfamethoxazole are the compounds most frequently detected in treated wastewater [8]. The removal of organic micropollutants by WWTP can range from 0% to 100%, with an average total removal rate of 60%-70%. As a result, significant concentrations of pharmaceuticals are found in WWTP effluents, which eventually enter surface waters and, consequently, in the sources of drinking water [24]. Landfills that receive pharmaceuticals release leachates containing concentrations similar to or even higher than those found in wastewater entering treatment plants [13]. In short, neither conventional water treatment methods nor the natural resilience of water bodies can completely and consistently remove these complex molecules, which are frequently detected in groundwater, surface waters, and drinking water [18]. From the above, to protect water sources from PPCPs contamination, priority must be given to developing more efficient water supply services [25].

Pharmaceutical consumption: an overview

The consumption of pharmaceuticals is considered the main contributor to the release of medicinal products into the environment, particularly through excretion in urine and feces and the improper disposal of expired/unused medicines. Therefore, particular attention must be given upstream to reducing the consumption of pharmaceuticals, as downstream, monitoring and controlling the release of pharmaceuticals into the environment is difficult, and wastewater treatment techniques are not always efficient [26]. Global pharmaceutical spending, based on list prices, has increased by 35% in the past five years and is expected to grow by 38% by 2028 [27]. Medicines are an important element of medical practice, and their beneficial effects on human and veterinary health cannot be denied. They have undoubtedly contributed to significant medical advances over the last 70 years. However, according to the World Health Organization [28], global estimates suggest that half of all medicines are prescribed, dispensed, or sold inappropriately, and that half of all patients do not take them as directed. One of the most important sources of pharmaceutical pollution in the environment is their use in human health care. The ways pharmaceuticals spread into the environment

may vary depending on whether they are used for human or animal treatment. Recent pharmacovigilance legislation in the EU recognizes that pollution of water and soil with pharmaceutical residues is an emerging environmental issue [29]. The global market size for active pharmaceutical ingredients (APIs) was valued at 2,224 billion dollars in 2022 and is expected to expand at a compound annual growth rate (CAGR) of 5.90% from 2023 to 2030. This growth can be attributed to advances in the design and production of active pharmaceutical ingredients and the increasing prevalence of chronic diseases such as metabolic, cardiovascular diseases, and cancer [30]. The total number of APIs reported in the literature varies significantly depending on the sources and individual countries. Weber et al., in 2014 [31], reported that approximately 4,000 APIs are administered worldwide in prescription medicines, over-the-counter drugs, and veterinary medicines. These include a variety of synthetic chemicals produced by pharmaceutical companies both in the industrialized and developing world, at a rate of 100,000 tons per year. About 600 of these 4,000 APIs are widely distributed in terrestrial and aquatic habitats on a global scale (Reyes et al. 2021) [8]. Burns et al., in 2018 [32], reported that there are approximately 2,000 APIs registered for use in the UK.

Taking pharmaceuticals is a daily occurrence for most people. Unfortunately, the pharmaceutical load in the environment is expected to increase for several reasons. First, the production, consumption, and discharge of APIs into aquatic environments are constantly increasing. As the Western population ages, it is expected that the use of pharmaceuticals will increase in the future. While a 20-24-year-old man consumes an average of 56

defined daily doses, men over the age of 60 require 649 defined daily doses, nearly twelve times as much [33].

Thus, as the number of elderly people increases, there will be an extensive use of pharmaceuticals, and many people will be taking multiple drugs simultaneously. Furthermore, the average age of onset for non-communicable chronic diseases is gradually decreasing, also involving children and adolescents. This implies, among other consequences, a life-time long period of medicalization over the entire course of life, with a growing gap between lifespan and healthspan. Moreover, climate change and air pollution exacerbate existing diseases and increase both non-communicable diseases (e.g., cardiovascular, metabolic, and neuropsychiatric diseases) and a number of infections. Respiratory infections, waterborne diseases, vector-borne diseases, foodborne diseases, and toxic substances become more common as climate change intensifies, leading to an increase in pharmaceutical consumption [34]. Furthermore, with rising living standards and increased access to pharmaceuticals, their use will increase worldwide, especially in rapidly growing economies [35]. The consumption of pharmaceuticals varies greatly among different countries. In 2008, a global average of 15 grams of APIs per capita per year was reported, and the annual global consumption of APIs was estimated to be at least 100,000 tons [36]. The approximate consumption of diclofenac in 2015 was over 2,400 tons per year globally, and 660 tons in Europe. Several hundred tons remain in human waste, and only a small portion—about 7%—is filtered by treatment plants [37]. The veterinary sector, although less impactful than the human sector, also contributes to pharmaceutical consumption, particularly antibiotics. A 2017 report by the European

Medicines Agency (EMA) on the sales of veterinary medicines from 31 European countries indicated that total sales amounted to 6,703 tons of active ingredients. Of these, 686 tons were in tablet form (primarily used for companion animals) and 6,634 tons were in other pharmaceutical forms (mainly used for food-producing animals) [38]. The prescription drug segment held the largest market share in 2022 (79.31%). The over the counter (OTC) segment is expected to grow at the fastest rate during the forecast period due to increasing awareness of self-medication and the ease of purchasing products through online pharmacies [39].

Personal care substances: an overview of consumption

This paragraph will refer, as examples, only to some of the chemical substances frequently included in the formulation of pharmaceuticals, which are also widely present in personal care products and, in some cases, in food and beverages.

Triclosan

Triclosan is a disinfectant, preservative, or antiseptic widely used in healthcare, animal husbandry, and personal care products. It is included in cosmetics as a preservative [40]. According to a market analysis in Asia, total production is about 3,200 tons per year, while production in the EU in 2015 was 850 tons. Most of the triclosan produced in the EU is used for production within the EU itself, with modest importation from countries outside the EU [41].

Parabens

Parabens is the name given to a group of esters of p-hydroxybenzoic acid (PHBA). The group includes, among others, methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben. Due to their antimicrobial properties, which inhibit the growth of germs

and fungi and promote a longer shelf life for the product. Parabens are widely used as preservatives in cosmetic products and also in the pharmaceutical sector to preserve medicines from contamination. The global paraben market size was valued at $911 million in 2021 and is projected to reach $1,648 million by 2031, growing at a compound annual growth rate (CAGR) of 6.2% from 2022 to 2031 [42].

Methylparaben and propylparaben are commonly used in combination in oral pharmaceutical formulations, with typical concentrations ranging from 0.015% to 0.2% for methylparaben and from 0.02% to 0.06% for propylparaben. Other parabens are used to a lesser extent in pharmaceuticals, such as ethylparaben and butylparaben. The latter is primarily used in topical pharmaceutical formulations [43].

They are also used in over 22,000 cosmetic products as preservatives, at concentrations of up to 0.8% (paraben mixtures) or up to 0.4% (single parabens). Industry estimates suggest that daily use of cosmetic products that may contain parabens is approximately 17,76 grams for adults and 378 mg for infants [44]. The use of five other parabens— isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben—is prohibited in cosmetic products (see Commission Regulation (EU) No. 358/2014) due to the lack of necessary data for the reassessment of their safety.

Artificial Sweeteners

The main types of synthetic sweeteners are aspartame, acesulfame K (ACE-K), saccharin (SAC), sucralose (SUC), neotame, aspartame (ASP), and others. The market/consumption of artificial sweeteners is of considerable importance. Global con-

sumption of artificial sweeteners exceeds 159,000 tons. China is currently the leading country, consuming the majority of AS (32%), followed by Asia/Oceania (23%), the United States (23%), Europe (12%), and Africa (7%). The global artificial sweetener market is expected to grow from $46,23 billion in 2021 to $65,95 billion by 2026, at a compound annual growth rate (CAGR) of 7.2% [45].

Global consumption of artificial sweeteners exceeds 159,000 tons. The most commonly used are aspartame (ASP) at 18.5 thousand tons, followed by saccharin (SAC) at 97 thousand tons, acesulfame (ACE-K) at 6.8 thousand tons, and sucralose (SUC) at 33 thousand tons.

Presence of PPCPs in the environment in Italy

For reasons of brevity, a deliberate choice was made to report only a selection of the numerous studies evaluating the presence of PPCPs in Italian water compartments. Overall, they suggest that in Italy, as in many other countries worldwide, water contamination by PPCPs is ubiquitous and affects rivers, lakes, drinking water, and wildlife.

Residues of various types of medicines (hormones, antineoplastics, antidepressants, antibiotics, etc.) have been detected worldwide in various environmental compartments, such as surface and groundwater, drinking water, soil, air, and biota. This widespread environmental distribution of PPCPs raises concerns that the already present concentrations of medicines, although minimal (typically at nanogram or microgram per liter levels in water), could pose a risk to biota or humans [46]. Higher concentrations are found in freshwater near metropolises and densely populated areas, especially (but not exclusively) in developing countries.

Future scenario analyses suggest that technological improvements in water treatment methods alone will not solve the problem. Therefore, consumption reduction strategies should be implemented; it is also increasingly evident that certain

medicines, particularly antiparasitics, antifungals, antibiotics, and (xeno)estrogens, pose environmental risks under specific exposure conditions.

Once in the environment, depending on its physicochemical properties, the drug may be degraded or persist for a long time, accumulating. Drugs like erythromycin, cyclophosphamide, naproxen, sulfamethoxazole, and sulfasalazine have a half-life in the environment of over one year, while others, such as clofibric acid, the main metabolite of clofibrate, have an average environmental persistence of 21 years [47]. One of the first monitoring campaigns on the presence of drugs in the environment was conducted in Italy. Antibiotics, antineoplastics, anti-inflammatories, diuretics, antihypertensives, bezafibrate, ranitidine, and spiramycin were found in Lombard waters, the sediments of the Po, Lambro, and Adda rivers, and the aqueducts of Varese and Lodi, as reported in a research letter in The Lancet [48]. The presence of pharmaceuticals in water has also been confirmed in other regions of Italy and Europe, with variations in the types of substances detected: for instance, sedatives and antidepressants are more prevalent in Northern Europe, while antibiotics are more commonly found in the South [49].

A study analyzed samples taken from the Tiber River, two lakes in Lazio (Bracciano and Vico), and treated effluents discharged into the Tiber River by WWTP to determine the presence of some pharmaceutical compounds: ibuprofen, fenoprofen, ketoprofen, naproxen, diclofenac, and salicylic acid (a deacetylated derivative of acetylsalicylic acid). Drug concentrations in samples from wastewater treatment plants ranged from undetectable values up to 12 and 95 μg/L, respectively,

for salicylic acid and ibuprofen. Most of the analyzed samples ranged between 20 and 200 ng/L [50].

Castiglioni et al. (2006) [51] evaluated the presence, loads, and removal rates (RR) of several therapeutic categories, such as antibiotics, anti-inflammatories, cardiovascular drugs, diuretics, gastrointestinal drugs, and lipid-control medications in six wastewater treatment plants (STP) in 2004. Total loads varied from 1.5 to 4.5 g/day/1000 inhabitants in the influents and from 1.0 to 3.0 g/day/1000 inhabitants in the effluents. Based on these values, the authors estimated that the total amount of such drugs discharged into the environment in Italy is between 60 and 180 kg/day.

To investigate the presence of 11 sulfonamides in surface, municipal, and mineral waters, samples were analyzed from rivers in Abruzzo and Lazio (Liri, Treste, Trigno, Tiber) and five samples from lakes in Abruzzo, Umbria, and Lazio (Scanno, Sinizzo, Campotosto, Trasimeno, Bolsena). Three of the four river samples tested positive for sulfonamides, particularly the "Tiber" sample collected in central Rome and near a hospital. Sulfonamides were also detected in mineral waters from four different brands purchased in Roman supermarkets [52].

In 2010, several antibiotics were measured in wastewater and river waters in Italy, chosen according to their theoretical environmental load. Macrolides, particularly clarithromycin and spiramycin, and quinolones, particularly ciprofloxacin and l-floxacin/ofloxacin, were the most abundant antibiotics found in untreated wastewater. Each year, on average, 115-237 g of the antibiotics studied per 1000 inhabitants are discharged by wastewater treatment plants in the cities of Milan, Como, and Varese. Based on these loads, it is estimated that 7-14 tons

of active ingredients are discharged annually into the aquatic environment in Italy [53].

An environmental risk assessment conducted on hospital effluents, influent, and effluent from treatment plants revealed a high risk for nine drugs in hospital effluents and four of the nine substances in the influent and effluent of the treatment plant. Antibiotics are the most critical compounds in terms of environmental contribution and potential risk for hospitals [54].

Naproxen, a non-steroidal anti-inflammatory drug, and gemfibrozil, a lipid regulator fibrate, have been found in various natural surface waters in the EU and Italy, including the Tiber River (Rome). The presence of gemfibrozil is due to its persistence (DT50 > 70 days). Naproxen is a more degradable drug with a DT50 of 27 days; therefore, it cannot be considered intrinsically persistent. However, like many other PPCPs, being continuously introduced into the aquatic ecosystem, it becomes a pseudo-persistent compound, so much so that in the river samples analyzed, it was found in higher concentrations than gemfibrozil [55].

In the Lambro River basin, one of Italy's most urbanized and industrialized areas, the presence of various classes of emerging contaminants (> 80 molecules selected from pharmaceuticals, personal care products, disinfectants, etc.) was assessed. Almost all emerging contaminants were ubiquitous in untreated wastewater, at concentrations up to the μg/L range, suggesting a high anthropogenic impact in this area. The most resistant substances during various wastewater treatment processes were pharmaceuticals and personal care products. The levels of some drugs were much higher than expected in the Lambro River south of Milan, an area with numerous livestock farms [56].

A study investigated the presence of multiple classes of emerging contaminants, including pharmaceuticals and personal care products, in 21 wells in the Milan drinking water network, in Italy's most populated and industrialized area. Carbamazepine among pharmaceuticals, perfluorinated substances, personal care products, and anthropogenic markers (caffeine, nicotine, and cotinine) were the most commonly detected contaminants, as in other countries. Generally, drinking water concentrations were in the very low ng/L range, so researchers stated that they pose only negligible risks to human health. However, they also specified that in calculating potential human risks, they applied a traditional toxicological approach assuming that effects are proportional to exposure doses or concentrations, and this approach, particularly when investigating the risk of endocrine-disrupting chemicals, may lead to an underestimation of effects at low exposure levels [57].

A study was conducted in the Venice Lagoon to evaluate the exposure of wildlife to certain active pharmaceutical ingredients. Distefano et al. [58] investigated the presence of non-steroidal anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (SNRIs) in wild birds. Non-flying chicks of sandwich terns (*Thalasseus sandvicensis*) and Mediterranean gulls (*Ichthyaetus melanocephalus*) were studied because they depend entirely on their parents for food. Adult specimens of these birds obtain food for their offspring within a few square kilometers around nesting colonies. Consequently, contaminants present in the chicks are entirely attributable to local contamination of the nesting area. Antidepressants and NSAIDs were detected in the feathers, with diclofenac being the most

detected active ingredient at levels between 3.6 and 56.0 ng g-1 in both species. The authors stated that "the active ingredient that raises the main concern for the ecosystem and the welfare of waterbirds is diclofenac due to its high prevalence, detected concentrations in feathers, and its documented toxicity towards certain birds."

A monthly monitoring campaign was conducted from April to December 2020 to detect the presence of drugs used for COVID-19 treatment in three wastewater treatment plants in the Lombardy region, where the first European cluster of SARS-CoV-2 cases was identified. The results show that the temporal trends of some anti-COVID-19 drugs were positively correlated with COVID-19 cases and deaths. The highest loads of hydroxychloroquine, azithromycin, and ciprofloxacin were measured in the plant receiving wastewater from a hospital specializing in COVID-19 patient treatment. The emission loads of the three WWTP highlighted the impressive concentrations of certain drugs known to be used during the first wave (azithromycin and paracetamol) in addition to ciprofloxacin, a fluoroquinolone antibiotic never recommended for COVID-19 [59]. This study underscores the importance of greater appropriateness in drug prescription.

Worldwide presence of PPCPs in the environment

There is a large number of articles documenting the presence of pharmaceuticals and personal care products on a global scale. This chapter presents only data from some recent studies and reviews that provide a concise yet clear picture of the current global and European condition. Once in the environment, the pharmaceutical, depending on its physicochemical characteristics, may degrade or persist for long periods, accumulating over time.

The largest and most recent global study is that of Wilkinson et al. (2022) [60]. It is a global-scale study of API pollution that covered 258 rivers worldwide, representing the environmental influence of 471.4 million people in 137 geographic regions. Samples obtained from 1,052 locations in 104 countries (representing all continents and including 36 countries previously unstudied for API contamination) were analyzed for 61 APIs. The highest cumulative API concentrations were observed in Sub-Saharan Africa, South Asia, and South America. The most contaminated sites were in middle- and low-income countries, associated with areas with poor infrastructure for wastewater and waste management and pharmaceutical production. The APIs most frequently detected were carbamazepine, metformin,

and caffeine (a compound also derived from lifestyle use), found in more than half of the monitored sites. In 25.7% of sampling sites, the concentrations of at least one API were above levels considered safe for aquatic organisms or of concern for antimicrobial resistance selection. The great value of this study lies in its ability to quantify the scale of the problem from a global perspective because a sensitive, internationally validated sampling and analytical method was used, applied in a single research laboratory, allowing for a true comparison of pharmaceutical exposure data on a global scale.

The study confirms that pharmaceutical pollution poses a global threat to environmental and human health, as well as to the achievement of the United Nations Sustainable Development Goals. The lowest API concentrations were found in areas with limited anthropogenic influence, low use of modern medicine, sophisticated wastewater treatment infrastructure, or high river flow rates with significant dilution factors.

A literature review published in the year 2022 [61] identified 271 studies examining the presence of PPCPs in water, sediments, and biota of lakes worldwide. The presence of PPCPs was reported in 260 lakes across 44 different countries. In Europe, PPCPs are present in 95 lakes across 18 different countries, most of these lakes being located in Germany, Sweden, and Switzerland. The most frequently detected drugs in lake waters are sulfamethoxazole, caffeine, carbamazepine, ibuprofen, and naproxen. In lake sediments, caffeine, ciprofloxacin, sulfadiazine, sulfamethoxazole, and 17β-estradiol were found; in biota, ofloxacin, sulfamethoxazole, and 17β-estradiol were detected. Ofloxacin has the highest frequency of simultaneous presence in water, sediments, and biota of the same lake.

Fluoroquinolones are the group of antibiotics with the highest concentrations reported in lake waters.

The frequency of PPCPs in Europe was previously described in a 2010 study that analyzed effluents from 90 European wastewater treatment plants (WWTPs) for 156 polar organic chemical contaminants. Substances with the highest median concentration levels in wastewater included the artificial sweeteners acesulfame and sucralose, benzotriazoles (corrosion inhibitors), various flame retardants and plasticizers, and several pharmaceutical compounds such as carbamazepine, tramadol, telmisartan, venlafaxine, irbesartan, fluconazole, oxazepam, fexofenadine, diclofenac, and citalopram [22].

Antibiotics are continuously discharged into the aquatic environment, where they can be found in the ng/L–μg/L range.

A study investigating the environmental presence of 40 PPCPs found that the categories with the highest percentage of PPCP findings were antibiotics at 27.5%, followed by anti-inflammatories and antifungals at 15%. The compounds with the highest reported concentrations were ibuprofen, caffeine, paracetamol, nicotine, and 4-aminoantipyrine [62].

The fate and transport of PPCPs in soils and groundwater are strongly influenced by the interaction strength between PPCPs and soil components, which are determined by the physicochemical properties of PPCPs (e.g., molecular structure, hydrophobicity, polarity, polarizability, and spatial configuration) and the surrounding environment, such as soil type, soil pH, coexisting ions, and soil organic matter [63].

Soil microbes and plants also affect the fate of PPCPs. The degradation of PPCPs is primarily caused by microbial activity, with aerobic microbes being more effective than anaerobic ones.

The degradation rates of PPCPs are influenced by soil texture, the aerobic condition of the soil, and the properties of PPCPs themselves [64]. Antibiotic residues have a significant impact on the soil microbiome, which can not only affect the activity, composition, and function of the soil microbiome but also promote the emergence and development of microbial community resistance and accelerate the transmission of related antimicrobial resistance genes [65].

The situation is equally concerning when it comes to personal care products. The results of a study [66] that, over the course of two monitoring campaigns, analyzed the presence frequency of 220 emerging contaminants belonging to different classes (artificial sweeteners, personal care products, coffee- and tobacco-related compounds, and industrial chemicals) in wastewater from a Greek hospital showed that 16 of the target compounds were present in 100% of the samples. Specifically, the compounds: acesulfame, cyclamic acid, saccharin, methylparaben, propylparaben, caffeine, theobromine, nicotine, cotinine, hydroxycotinine, benzalkonium, lauryl diethanolamide, N,N-dimethyldodecylamine, N,N-dimethyltetradecylamine, N-methyldodecylamine, and triethyl citrate were detected in all hospital wastewater samples. Among these, artificial sweeteners were the most frequently present emerging contaminants, with detection rates between 39.6% and 55.1%. The study confirms that hospitals are a significant source of environmental emissions not only of pharmaceuticals but also of other groups of emerging pollutants, such as artificial sweeteners, parabens, and stimulants.

Artificial sweeteners

Artificial sweeteners have frequently been detected in aquatic environments worldwide in recent years. This is mainly due to their high consumption, solubility in water, and environmental persistence. For example, sucralose has high stability and persistence with a half-life of several years [67]. These substances have been detected in the influents and effluents of treatment plants in Switzerland, Sweden, the United States, Germany, Greece, Canada, China, Singapore, Vietnam, and the Philippines [68]. In a study detecting artificial sweeteners in Australian waters, cyclamate, aspartame, acesulfame, sucralose, and saccharin were found in over 90% of wastewater samples collected during census week in 2016. Neotame and neohesperidin dihydrochalcone were not detected in any of these samples. The population-weighted daily per capita mass loads for individual artificial sweeteners ranged from 0.12 ± 0.14 mg d−1p−1 (aspartame) to 6.9 ± 2.8 mg d−1p−1 (acesulfame). Using data from treatment plants receiving wastewater from more than half of the Australian population, it was estimated that about 1,004 kg of artificial sweeteners (cyclamate, aspartame, acesulfame, sucralose, and saccharin) are consumed daily in Australia. It is estimated that 142 kg are subsequently discharged into the aquatic environment, representing 14% of what was consumed [68].

Naik et al., 2021 [3], report that acesulfame K, saccharin, sucralose, and cyclamate are the most frequently detected food additives/sweeteners in soils and groundwater. The authors, studying the estimated environmental inputs from agriculture, households, degradation, and leaching into groundwater, noted that a significant concentration of saccharin can end up in

soils through slurry. Saccharin, which is found as an additive in piglet feed, is largely excreted, and thus, can reach soils in significant quantities through manure, up to a concentration of 12 mg/L, remaining stable for two months. It was also observed that saccharin is a soil metabolite of certain sulfonylurea-based herbicides.

Artificial sweeteners can also penetrate soil through irrigation with surface waters polluted by wastewater, fertilization with sewage sludge (1–43 μg/L), or through leaking sewers.

Data obtained through computer simulations to analyze the relative importance of different sweetener entry pathways into soils, as well as degradation and leaching into groundwater, suggest that saccharin detection in groundwater (observed concentrations up to 0.26 μg/L) is most likely due to the application of contaminated manure. However, high concentrations of acesulfame in groundwater (up to 5 μg/L) may primarily result from the infiltration of surface waters polluted by wastewater through riverbeds [69].

The most commonly detected sweeteners in various environmental compartments are ACE-K and SUC, with their concentration levels measured in the following order: wastewater treatment plant (WWTP) influents > WWTP effluents > surface waters > groundwater > drinking water; and atmosphere > soil [4].

A study in Germany demonstrated the persistence of some artificial sweeteners during groundwater treatment and confirmed their environmental relevance. Concentrations in two influents of German wastewater treatment plants were up to 190 μg/L for cyclamate, about 40 μg/L for acesulfame and saccharin, and less than 1 μg/L for sucralose. Removal in wastewa-

ter treatment plants was limited for acesulfame K and sucralose and >94% for saccharin and cyclamate [70].

It has been reported that a considerable amount of these substances remains unchanged and poorly absorbed. Artificial sweeteners discharged from various sources flow toward wastewater treatment plants, and it appears that most of them also escape even the most efficient treatment plants. Treated effluents from these plants are considered the primary point sources of artificial sweeteners, which ultimately make their way into the environment [3].

The effectiveness of wastewater treatment for removing various artificial sweeteners varies and depends on both the physicochemical characteristics of the substances and the different treatment processes employed. The biodegradation of six artificial sweeteners using nitrifying activated sludge resulted in good removal of aspartame and neohesperidin dihydrochalcone, followed by saccharin and cyclamate, while acesulfame and sucralose were poorly removed [68].

Saccharin and cyclamate removal rates are >90%, while sucralose is not significantly removed by the plants (<2.0%), and acesulfame showed a negative removal efficiency. Sucralose was barely removed by treatment plants in Switzerland (-5%), China (17.7%), Germany (20%), and Sweden (<10%) [71]. Saccharin and cyclamate are subject to microbial degradation, whereas sucralose is not due to the presence of chlorine atoms [68]. In addition to the inefficacy of conventional drinking water treatment processes for eliminating sucralose [72], there are negative reports directly linked to its chemical structure. The sucralose molecule differs from sucrose due to three chlorine atoms [73]. Consequently, sucralose has the potential to hy-

drolyze into toxic compounds if exposed to high-temperature conditions, forming chloropropanols and other related chlorinated compounds [74].

In 2011, Buerge and colleagues [69] highlighted the challenges of removing acesulfame and sucralose in wastewater treatment plants (WWTPs) and also noted that, despite being readily biodegradable, cyclamate and saccharin remained detectable in treated wastewater. As a result, all four sweeteners were also found in surface waters receiving WWTP discharges. Additionally, acesulfame was detected in a large number of groundwater samples. High concentrations up to 5 μg/L were observed in areas with known, significant river water infiltration. Some studies have indicated that acesulfame may serve as a suitable chemical marker to indicate the contamination of rivers and water bodies with domestic wastewater. However, more recent studies suggest higher degradability of this substance, casting doubt on its utility as a marker [75].

Sucralose appears to have all the characteristics of an excellent wastewater tracer: it is highly soluble, not produced naturally, slowly degradable, produced and discharged in high concentrations, and detectable at low concentrations [76].

The levels of artificial sweeteners in the environment show significant differences between various regions. Further analyses indicate that the phenomenon is highly correlated with consumption patterns and treatment efficiency of plants in a given country [4]. In soil incubation experiments, cyclamate, saccharin, acesulfame, and sucralose were degraded with half-lives of 0.4-6 days, 3-12 days, 3-49 days, and 8-124 days, respectively [3].

A study examining the photodegradation of different sweeteners found that prolonged exposure to intense solar radiation led to the formation of persistent compounds from acesulfame and sucralose. The photoinduced transformation of acesulfame leads to a collection of more persistent byproducts that are >500 times more toxic than the original compound. The results imply that acesulfame is significantly more phototoxic compared to other organic pollutants reported so far [77, 78].

Parabens

Despite being biodegradable, parabens are widespread in surface waters and sediments, largely due to the extensive use of paraben-based products and their ongoing release into the environment. The predominant compounds are methylparaben and propylparaben, reflecting the composition of paraben mixtures in common consumer products. As compounds containing phenolic hydroxyl groups, parabens can readily react with free chlorine, producing halogenated by-products. Chlorinated parabens have been detected in wastewater, pools, and rivers, but not yet in drinking water. These chlorinated by-products are more stable and persistent than the parent compounds, and further research is needed to study their toxicity.

González-Mariño et al. [79] reported data on the presence in wastewater and biodegradability of seven parabens and three halogenated derivatives of methylparaben. Researchers collected several wastewater samples from three different wastewater treatment plants (WWTPs) in April and May 2010; samples were concentrated using solid-phase extraction (SPE) and analyzed by liquid chromatography-electrospray-time-of-flight mass spectrometry (LC-QTOF-MS). Laboratory degradation tests,

both with activated sludge and raw wastewater, demonstrated that dihalogenated methylparaben derivatives had significantly higher half-lives compared to methylparaben itself.

The widespread presence of parabens in numerous consumer products explains their detection in various environmental matrices at μg/L and ng/L scales. Cosmetics pose urgent ecological concerns due to the spread of parabens in the environment. Cosmetic products are used in large quantities over a lifetime, and since they are intended for external application, parabens do not undergo metabolic transformation by the body, leading to the discharge of the unchanged molecule into the environment in large amounts during washing, showering, and bathing.

The concentration of parabens in European waters in 2014 was up to 400 ng/L for methylparaben. These levels have significantly increased in recent years, as reported in a recent study [7].

Parabens have been found in urban waterways where treated or untreated effluents from wastewater treatment plants converge. Consequently, these chemical compounds have been identified in rivers and drinking water sources. Parabens have been detected in the soil of agricultural fields, likely due to irrigation or fertilization practices. In a 2003 study conducted on 120 homes in Cape Cod (USA), it was also discovered that household dust contains parabens. Three parabens (butylparaben, ethylparaben, and methylparaben) were detected in indoor air and household dust. Methylparaben was the most frequently detected, with indoor air concentrations exceeding the reporting limit of 1 ng/m^3 in 67% of homes. The median indoor air concentration of methylparaben was 2.9 ng/m^3, with a maximum of 21 ng/m^3 [80].

All parabens were detected in influent samples at municipal

wastewater treatment plants. In the United States, the highest concentration of methylparaben before 2012 was 79,600 ng/L during the dry season in influents at wastewater treatment plants, while during the rainy season, its concentration was 21,700 ng/L [3].

The introduction of these compounds into nature is linked to domestic and industrial wastewater discharges. Although some authors suggest that parabens are satisfactorily removed by conventional wastewater treatment technologies, in reality, the presence of these emerging compounds in ecosystems is increasing, with possible negative impacts on the environment, animals, and even humans. The concentrations of parabens reported in WWTP effluents compared to influents indicate that, although treatment plants have a high removal efficiency for these substances, residual levels remain elevated.

The detection of these compounds can be explained by the increased presence of parabens in products and/or low efficiency of conventional wastewater treatment technologies [81]. Parabens detected in effluents, once released, can contaminate aquatic environments such as rivers, lakes, seas, and even drinking water.

The concentrations of parabens reported in sewage sludge were up to two orders of magnitude higher than in effluents, suggesting that parabens are more stable in sludge than in the aqueous phase. This is due to the moderate hydrophobicity of parabens and their tendency to adsorb to organic matter, which favors their partitioning into the particulate fraction. Through sludge and effluents, parabens can further penetrate the environment and pose a health risk. For example, the levels of methylparaben measured in landfill leachate and ground-

water monitoring wells at a landfill in Poland were 10,110 ng/L and 2,880 ng/L, respectively, which were twice as high as in the influent at the wastewater treatment plant [6]. It is worth noting that levels of para-hydroxybenzoic acid (p-HBA, a paraben metabolite) and other by-products were hundreds of times higher than the parent paraben concentrations in the plants. Although data on the degradation and toxicity of paraben metabolites are limited, p-HBA has been identified as the main degradation product of parabens in wastewater treatment plants. Other chlorinated by-products of parabens have also been detected in wastewater treatment processes. The presence of these concentration levels of degradation products and/or by-products in WWTP effluents and sludge cannot be ignored, even though little is known about the potential risks of these compounds [4].

According to Haman et al. [82], parabens are generally predominantly present in the aqueous phase of the influent (>97%), likely due to their moderate water solubility; the authors also report that methylparaben is predominantly found in aquatic systems compared to other parabens, and chlorinated parabens are more persistent in water than other parabens.

Soils, groundwater, and sludge are also contaminated by parabens, particularly through irrigation using water with high levels of parabens and the indiscriminate release of improperly treated wastewater. In the aforementioned study by Wei et al. [6], the authors concluded that although human exposure levels to parabens are higher in the United States and EU countries than in India and China, this may change with the increasing production of paraben-preserved products in the latter countries.

Bioaccumulation of PPCPs in Biota

Bioaccumulation[1], that is, the absorption of pharmaceuticals and personal care products through water and ingestion of contaminated prey (biomagnification[2]), is species-specific. It is important to distinguish the contribution of these two phenomena because if only bioconcentration is studied for a substance, the importance of different levels of bioaccumulation between species is overlooked. For example, the bioaccumulation factors (BAFs) of oxazepam in perch and crucian carp at the same concentration levels in water vary significantly (9.7 and 1.4, respectively). About 46% of the oxazepam accumulated by perch results from consuming contaminated prey and is thus a biomagnification rather than a bioaccumulation process [83]. In the United States, a national pilot study evaluated the accumulation of pharmaceuticals and personal care products in fish sampled from five rivers receiving direct discharge from wastewater treatment plants in major cities (Chicago, Dallas, Orlando, Phoenix, West Chester). HPLC detected the presence

1 The Bioaccumulation Factor (BAF) can be expressed as the concentration ratio of a substance in an organism to that in the surrounding medium at equilibrium.
2 Biomagnification: the increase of a substance in an organism due to absorption through contaminated food or prey; it leads to the transfer and accumulation of the substance along the food chain.

of norfluoxetine, sertraline, diphenhydramine, diltiazem, and carbamazepine at nanogram-per-gram concentrations in fish fillets, and fluoxetine and gemfibrozil in liver tissue. Sertraline was detected at concentrations up to 19 ng/g in the fillet and 545 ng/g in liver tissue, respectively [84]. It is important to note that this study also revealed the significant influence of the degree and type of wastewater treatment processes on the removal efficiency of pharmaceuticals.

A more recent study [85] found higher detection frequencies in invertebrates than in fish. This was particularly observed for SSRI antidepressants and anti-inflammatory drugs such as diclofenac and celecoxib. Diphenhydramine and carbamazepine were the only drugs found ubiquitously in periphyton[3], invertebrates, and fish. Antihistamines were also found to have a high degree of bioaccumulation in aquatic invertebrates. In wild fish, muscle tissue, which is frequently chosen for its easy accessibility and relevance to human consumption, proved to be a less sensitive matrix for assessing bioaccumulation compared to other tissues like kidneys, liver, skin, and heart. In fact, it was in these latter tissues that the most significant number of the 30 wastewater-contaminating compounds studied was detected. Sertraline, amantadine, and bisoprolol were detected in almost all matrices with high prevalence [86]. The accumulation potential of thirty-three neuroactive drugs was analyzed in 25 surface water samples and biota from various estuaries along the North Atlantic coast of Portugal. In individual water samples, between 10 and 26 different compounds were

3 Periphyton is a complex mixture composed of algae, cyanobacteria, heterotrophic microbes, and detritus, which is present in most aquatic ecosystems attached to submerged surfaces.

detected. Neuroactive compounds from all seven therapeutic groups considered were detected in at least one of the four estuaries: two opioids, three antiepileptics, four antipsychotics, four anxiolytics, eleven antidepressants, one psychostimulant, and three other drugs used in various therapeutic treatments. Thirteen of the 33 neuroactive drugs screened were detected in at least one of the fish tissues (i.e., brain, liver, and muscle tissues). Bioaccumulation of neuroactive compounds was observed in all seven fish species collected in the different estuaries, with neuroactive compounds detected in every fish brain and in 95% of fish liver and muscle tissues [87]. Parabens have also been found in underwater animals due to their interaction with water contaminated by these substances. For instance, in adult fish in Manila Bay, Philippines, a paraben level of 4,700 ng/g was reported, while it was 2,200 ng/g in younger fish [88]. The highest concentration of propylparaben (0.65 ng/g) in fish and seafood was detected in Europe and North Africa. A study by Chiesa et al. [89] aimed to develop and apply an LC-HRMS method for determining parabens and metabolites in various fish and seafood samples collected from the Milan fish market, as well as in fish-containing baby foods purchased in supermarkets in the same city. A total of 54 fish of different species, 10 bivalves, and baby food samples with fish were analyzed. In fish and bivalves, methylparaben levels ranged from 0.8 to 32 ng/g. In all baby food samples, a significant presence of para-hydroxybenzoic acid (pHBA) was found. This data suggests global contamination by parabens and supports the hypothesis that the measured levels of PB degradation products in baby food samples could be dangerous to children's health.

The bioaccumulation of PPCPs in fish, when these contaminated fish are consumed as food, cannot be excluded from potentially having long-term negative effects on human health, as parabens can also bioaccumulate in the human body.

Negative effects of PPCPs on Biota

Environmental exposure to active pharmaceutical ingredients (APIs) can negatively impact the health of ecosystems and humans. Biodiversity and human health are interconnected in various ways. First, biodiversity benefits health. One example of this interaction is the impact of healthcare sector interventions on biodiversity and the influence of biodiversity-related interventions on human health. For instance, the use of pharmaceuticals can lead to the release of active ingredients into the environment, harming species and ecosystems, which, in turn, can have adverse effects on human health [90]. For some PPCPs, especially active pharmaceutical ingredients (but not limited to them), concerns are heightened due to specific characteristics, such as being designed to act at very low doses and to 'last' a long time. Additionally, their significant stability limits biodegradability, leading to prolonged persistence in the environment. The chemical and/or metabolic stability of certain drugs results in the excretion (or elimination) of up to 90% of the active ingredient in its original state. High-risk environmental APIs include hormones, antibiotics, analgesics, antidepressants, and antineoplastic drugs for human use, as well as antiparasitic, antibiotics, and hormones for veterinary

use. Artificial sweeteners, preservatives, and additives are other large classes of PPCPs that alone or in combination endanger both environmental and human health. PPCPs vary widely in type and have distinct properties; thus, their environmental impacts and risks may be very different. However, the potential risks of PPCPs to the environment and ecosystems can never be underestimated, as most of them share similar characteristics. Examples of ecotoxicological effects of certain drugs include altered reproductive capabilities in fish populations exposed to ethinylestradiol; the effects of various antibiotics on environmental bacteria and algae; the impacts of oxazepam on European perch; and the effects of diclofenac on vultures. The following text will briefly analyze some of these cases.

Impact on non-target species: effects on animals

The bioaccumulation, metabolism, and potential effects of PPCPs in fish have been an active area of research over the last 20–30 years. Due to the characteristics listed above, PPCPs can be more potent than many historical environmental contaminants. Even those that are more biodegradable can be considered pseudo-persistent contaminants due to high consumption, long-term use, and low degradation rates. Furthermore, organisms living in soil and especially aquatic organisms in systems receiving wastewater are exposed not only to one or two PPCPs but rather to a cocktail of pharmaceuticals and other chemical contaminants. Currently, there are still several uncertainties about environmental risk assessment for pharmaceuticals because we do not fully understand their fate in waste and the environment, intake levels, metabolism and excretion by wildlife, their affinity for receptors in non-target species, and

the consequent functional effects (pharmacodynamics). Once introduced into the environment, PPCPs can act on aquatic organisms with target organs, tissues, cells, or biomolecules that are identical or similar to those in humans. Due to evolutionary conservation, meaning the preservation of genetic, structural, or functional characteristics across generations and species because of their importance for survival and reproduction, some receptors in aquatic organisms, even those far removed from humans, may resemble human receptors; therefore, pharmaceuticals for human or veterinary use can act on many non-target species [91]. Depending on their physicochemical properties, drugs released into the environment can be degraded, partitioned into water or the solid phase of soil, including biosolids (such as sewage sludge), dispersed in aquatic and terrestrial habitats, and in some cases bioaccumulated in food chains, potentially impacting organisms at higher trophic levels.

Effects of PPCPs on aquatic ecosystem inhabitants

Toxicity studies in fish are one of the most effective methods for understanding the deleterious effects of environmental contaminants in aquatic systems. Environmental risk assessments (ERAs) concerning the susceptibility of fish to pharmaceuticals, however, are based on studies of a few model fish species and rarely extend to quantifying population-level effects [91]. Fish can be found practically everywhere in the aquatic environment and play an important ecological role in aquatic food webs because they function as energy carriers from lower to higher trophic levels, where they generally occupy an intermediate or higher position; they are also one of the main food sources for humans worldwide [92]. Common carp (*Cyprinus carpio*)

is commonly used as a bioindicator species since cyprinids are quantitatively the most important group of teleost fish bred worldwide for commercial purposes and are also highly resilient and easy to breed. Many studies report clear and significant effects from water and environmental contamination by drugs, such as the feminization of fish and frog sterility due to contraceptive pill residues [93]. It has been observed that the introduction of just a few ng of ethinylestradiol into an experimental basin can cause the extinction of a cyprinid [94]. Diclofenac caused the death of many thousands of vultures in Pakistan, and at concentrations found in freshwater, it causes lesions in the kidneys and gills of trout [93]. Excessive use of antibiotics has led to the emergence of resistant pathogenic bacteria, and this phenomenon is not limited to hospitals; for instance, sulfadiazine used in pig farming induces antibiotic resistance in soil bacteria. The results of a study [95] show that high levels of micro-contaminants, comparable to PPCP concentrations detected downstream of wastewater effluents, have caused significant effects on the phenotypic composition of natural phytoplankton communities. Micro-contaminants can alter the individual characteristics of lake phytoplankton communities, thereby affecting their ability to respond to natural environmental principles, potentially influencing aquatic ecosystem development processes. There is well-established evidence of male fish feminization downstream of wastewater treatment plants that discharge 17β-estradiol and 17α-ethinylestradiol resulting from contraceptive treatments or hormone replacement therapies. Harmful effects on the reproductive organ characteristics of male fish have been observed, and it has been shown that increased feminization reduces

individual male reproductive capacity, even though intersex fish may still reproduce. In one study, it was observed that in male *Rutilus rutilus*, a freshwater fish widespread in English rivers, exposure to endocrine disruptors can cause different levels of feminization severity; ovarian cavities similar to those of females were observed in an otherwise normal testis; testes with intersex modifications such as numerous oocytes in isolated areas or numerous primary and secondary oocytes scattered throughout the testis were also noted [96].

The benthic native small fish *Mugilogobius chulae* was used to evaluate the toxic effects of acetaminophen exposure on non-target organisms. The drug altered the DNA methylation pattern of *M. chulae*, showing significant epigenetic effects and impacting its stress responses. Lower exposure concentrations of acetaminophen (0.5 μg/L) showed greater fluctuations in DNA methylation compared to a higher concentration (500 μg/L), primarily in terms of overall DNA methylation changes and regions with differing degrees of methylation. In the groups exposed to the drug, some hepatocytes of irregular size and shape with unclear intermembrane boundaries were observed [97]. Antidepressants, psychiatric drugs (benzodiazepines), and antihistamines can induce behavioral changes in fish at concentrations close to those found in natural systems (from ng/L to mg/L). Several pharmaceuticals can induce similar behavioral alterations in different species, but drug-specific and species-specific effects have also been observed. For example, both activity and feeding rate were influenced by antidepressants, psychiatric drugs, and antihistamines, though not in all species. Table 1, taken from Brodin et al. [98], shows ecologically important behavioral aspects (such as activity,

Tabella 1.
Ecologically important behavioral traits

Behavioral traits	Direct ecological effects	Indirect ecological effects
activity	cooperation [b,e]	community structure
aggressiveness	dispersal/migration [a,c,d,e]	effects across ecological boundaries
boldness	feeding rate [a,b,c,d]	ecosystem function
exploration	reproductive success [b,e]	feedback
sociality	parental care [b,e]	population dynamics
	predator avoidance [c,e]	trophic cascades [4]

Legend: [a]Activity; [b]Aggressiveness; [c]Boldness; [d]Exploration; [e]Sociality. Adapted from Brodin et al. (2014) [98].

aggression, boldness, exploration, socialization) that are central to assessing the side effects of pharmaceutical exposure and potential subsequent ecological effects (direct or indirect). Any indirect effect could potentially arise from changes in any of the direct effects. Perch displayed behavioral changes that did not appear in crucian carp [85].

A study evaluated the effect of long-term exposure to amitriptyline, nortriptyline, clomipramine, and their mixture on the early life stages of common carp (*Cyprinus carpio*). Long-term exposure at environmentally relevant concentrations resulted in a significant increase in mortality, developmental delays, morphological anomalies, and pathological alterations

4. Trophic cascades refer to an ecological process in which changes in the population of one trophic level (such as predators) influence lower trophic levels, often causing a chain reaction throughout the entire food web.

in the brain, heart, and anterior and posterior kidneys [99]. Numerous studies indicate that analgesics and NSAIDs (e.g., acetaminophen, diclofenac, naproxen, and ibuprofen) have effects on fish at environmentally relevant concentrations, including interference with CYP enzymes involved in steroid biosynthesis. Moreover, the complex mixture of PPCPs present in aquatic environments includes compounds that can adversely affect mitochondrial function (e.g., antibiotics, triclosan) [100]. To investigate the health conditions of the Mediterranean Sea, numerous species, mostly invertebrates, are used, such as the mollusk *Mytilus galloprovincialis*, which, as a benthic filter organism, is an excellent bioindicator for detecting toxic substances in the marine environment. Invertebrates have become valuable experimental organisms for toxicological screening due to their rapid reproduction rates, low maintenance costs, and some physiological responses that closely resemble those of vertebrates. These characteristics make them an accessible and cost-effective choice for monitoring environmental health and detecting toxic substances [101].

In samples of *M. galloprovincialis* exposed to ASA concentrations (10 and 100 μg/L)—much lower than those estimated in aquatic environments—for 10 and 20 days, both physiological changes and histological inflammation, particularly in the digestive gland, were observed [102].

From the perspective of acute and chronic toxicity, parabens are generally considered potentially harmful to the aquatic environment, with toxicity increasing for aquatic species at three trophic levels (fish, crustaceans, algae) as the alkyl chain length increases. To assess their toxicity relative to alkyl chain length, four parabens were studied: methylparaben, ethylpar-

aben, propylparaben, and dibutylparaben. For acute toxicity, all four parabens proved toxic to at least one of the three aquatic organisms, particularly *Daphnia magna*. For example, methylparaben was toxic to *Daphnia m*. and harmful to fish and green algae. These results align well with the experimental observation that *D. magna* growth was more sensitive to paraben exposure than *Pimephales promelas* minnows. For chronic toxicity, methylparaben and butylparaben were respectively harmful and toxic to all three aquatic organisms; ethylparaben and propylparaben were harmful to green algae and toxic to daphnia and fish. Additionally, paraben ecotoxicity and their degradation products increased with alkyl chain length. While all degradation products were less toxic to *D. magna* and fishes than the parent parabens, they could still be harmful to these aquatic organisms [103].

In practice, the aquatic toxicity of parabens on fishes, daphnia, and algae is lower for those with shorter alkyl chains compared to those with longer chains. Moreover, both acute and chronic toxicity show a linear relationship with log Kow[5], indicating that aquatic toxicity increases with hydrophobicity. This may be explained by the fact that large hydrophobic pollutants are more potent in penetrating cell membranes, leading to increased aquatic toxicity. The study by Terasaki et al. [104] demonstrated that parabens, including their chlorinated derivatives, exhibit chronic toxicity toward *Ceriodaphnia dubia*. The authors investigated the chronic toxicity of 12 paraben

5 Log Kow: refers to the octanol/water partition coefficient. It indicates the degree of hydrophilicity or hydrophobicity of a chemical substance, an important factor in determining the compartments within an organism where the substance is most likely to distribute. This coefficient measures the tendency of an active substance to accumulate in living organisms and is typically expressed as a logarithmic value (pKow).

compounds and their chlorinated by-products using the 7-day static renewal *C. dubia* test to gather information on how to sanitize preservative by-products released into aquatic systems. Mortality and reproductive inhibition in *C. dubia* tended to increase with rising hydrophobicity and decreased with the degree of paraben chlorination. Results indicated that non-chlorinated parabens with a bulky substituent exert chronic effects on aquatic organisms. According to the authors, preliminary risk assessment results based on the PEC/PNEC calculation indicate negligible risk for downstream rivers. However, considering that parabens have antimicrobial activity and are continuously discharged into aquatic environments in low concentrations via domestic wastewater, it is essential to examine their long-term impact. Chronic data, focusing on more specific endpoints like bioaccumulation potential, metabolite contribution, long-term exposure, and multigenerational tests, should be studied as part of the ecological risk assessment.

Artificial sweeteners, depending on their presence, persistence, and bioaccumulation potential, have various toxic effects on ecosystems, plant growth, and aquatic organisms. Numerous studies, as well as scientific rationale, support the potential ecotoxic effects of artificial sweeteners.

Potential controversies on this topic stem from the fact that authors who do not report toxic effects mostly base their conclusions on standard acute or chronic toxicity tests, overlooking the complex changes in living conditions and physiology of aquatic organisms caused by contaminants.

Literature strongly indicates that artificial sweeteners, even those without intrinsic toxicity, may pose a threat. To fully understand this premise, attention must be paid to the importance

of chemical signals in aquatic systems, as they are the primary means of communication, governing feeding, habitat, and mating choices. They also stabilize dominance hierarchies and influence whether animals forage for food or remain hidden to avoid predation [105]. Taste is the dominant regulatory signal and driving force of feeding behavior, and the fundamental principles of the taste system are the same across distantly related organisms like mammals and insects [106]. Evidence from recent studies confirms the presence of sweet taste receptors in crustaceans. Studies on chemoreceptors in crustaceans have shown that "meat-eating" species detect amino acids, while herbivorous and omnivorous species are also sensitive to carbohydrates. The movement behavior in lobsters is influenced by the taste of sugar. Specific sucrose taste sensilla[6] in crabs, which are important in food searching, have also been described. This implies that sucralose or other artificial sweeteners could potentially attract and mask the scent of "real food," leading to the foraging of all particle sizes, whether nutritious or not. Chemical signals influence not only individual behavior and population-level processes but also community organization and the function of the entire ecosystem. For instance, sugar receptors have been found in *Daphnia pulex* [107]. The persistence of sucralose, combined with its high-water solubility, structural similarity to sucrose, and sweet taste, make it an interesting potential marker for environmental risk assessment in aquatic settings. Consequently, Eriksson-Wiklund et al. [108] studied its acute toxicity and accumulation in aquatic species, using

6 The sensillum is a simple sensory organ of an arthropod or another invertebrate, composed of one or more sensory cells, supporting chitin-producing cells, and a covering cuticle. It can take the form of a hair or bristle. There are also scale-shaped, basiconic, and ampullaceous sensilla.

Daphnia magna, *Nitocra spinipes*, and two gammarid species: *Gammarus oceanicus* and *Gammarus zaddachi*. Behavioral and physiological changes were observed in these species. Sucralose affected the locomotion of both D. magna and *G. zaddachi*. The two most impacted factors were swimming speed and height. Gammarids exposed to sucralose took longer to reach food and seek shelter in *F. vesiculosus* algae compared to a control group. In practice, control group gammarids and those exposed to the lowest sucralose concentrations swam directly towards the *F. vesiculosus* branch placed in a corner of the tank and attached to it, while those exposed to higher concentrations tended to move randomly before attaching. The authors argue that regardless of whether these behavioral responses were triggered by traditional toxic mechanisms or stimulatory effects, they should be considered a warning since they cause animals to deviate from normal behavior, potentially leading to significant ecological consequences. Overall, these results show that when tests and endpoints focused on behavior are applied, new response patterns can be observed that would not be identifiable with tests under current regulatory systems. In a subsequent study, Eriksson-Wiklund et al. [109] also found a significant positive correlation between SUC concentration (0.0001–5 mg/L) and neurological and oxidative alterations in *Daphnia magna*, which could induce sublethal effects.

Sucralose altered the normal levels of antioxidant enzymes and induced oxidative damage in lipids and proteins of *Cyprinus carpio*, with the organs showing the most damage being the gills, muscles, brain, and liver, in descending order, and blood was the only tissue with negligible effects. The results indicated that lipid peroxidation, hydroperoxide, and protein carbonyl

group content, as well as antioxidant enzyme activity, were significantly increased in the tested organisms, particularly in the gills, brain, and muscles [110]. More recently, similar effects of acesulfame potassium (ACE) were observed on *Cyprinus carpio*. ACE was shown to induce oxidative stress in common carp at two environmentally relevant concentrations (0.05 and 149 μg L−1). ACE was detected and quantified in several organs of *Cyprinus carpio*, producing a significant increase in damage biomarkers in all organs, especially in the gills, brain, and muscles, as well as significant changes in antioxidant enzyme activity in these organs [111]. Lee and Wang [112] used medaka embryos (*Oryzias latipes*), a small freshwater and brackish fish, to investigate the developmental toxicity and ecological impact of aspartame (ASP) and saccharin (SAC), along with natural sweetener sucrose and caffeine (CAF). To assess developmental impact, various endpoints were selected, such as heart rate, eye density, hatching time, and anxiety-like behavior. Sucrose, ASP, SAC, CAF, and CAF mixed with sweeteners influenced embryo development and/or behavior. All substances and their mixtures affected embryonic heart rate. Additionally, CAF mixtures with sweeteners promoted eye development, shortened body length, and/or altered behavior. Developmental toxicity of the substances was ranked as follows: SAC > CAF > ASP > SUC, with a cumulative effect observed when CAF was combined with sweeteners. In Liu et al. [113], the influence of sweetener coexistence on heavy metal mobility and toxicity associated with sediments was studied. Sediments act as a reservoir or internal source for heavy metals, with over 99% of heavy metals associating with sediments, significantly reducing mobility and heavy metal risk for aquatic organisms.

Therefore, it is important to understand the impact artificial sweeteners may have on heavy metal deposits in lake sediments. Researchers used acesulfame, sucralose, and commercial humic acid (a widely distributed natural chelating agent). The presence of 1.00–100 mg/L of acesulfame, sucralose, and HA significantly increased the release rates (Rrelease) of Cd, Cu, and Pb from "virgin" lake sediment by up to 46.7%, 86.0%, and 79.9%, respectively. Microcosm experiments revealed that the presence of 1.00–10.0 mg/L of acesulfame, sucralose, and humic acid in the aqueous phase induced the release and toxicity of heavy metals associated with Cd- and Cu-amended sediments on the green freshwater algae *Scenedesmus obliquus*. Cell growth rate inhibition of algae significantly increased with elevated levels of acesulfame and humic acid ($p < 0.05$). Algal photosynthesis was also affected by the coexistence of sweeteners, humic acid, and heavy metals released from sediments, as indicated by fluorescence parameter changes. The data from this study provide valuable information on the likelihood of combined effects of artificial sweeteners and heavy metals on aquatic organisms.

Another study demonstrated that the bioconcentration of Cd2+ in microalgae could be increased by acesulfame and could biomagnify through the food chain, posing a potential risk for organisms living in the same ecosystem [114]. Increased toxicity of ACE and SUC intermediates for living organisms after photolysis or electrolysis has also been reported. The increased ecotoxicity of ACE after UV irradiation was induced by OH• accumulation, causing an evident oxidative state in fish liver even at a concentration of 0.1 mg/L [3].

These findings suggest that more attention should be given to the transformation stages of artificial sweeteners in envi-

ronmental risk assessment. Additionally, the toxic effects of artificial sweetener mixtures with other environmental chemicals should also be considered, as various pollutants can coexist in the environment. Lee and Wang [118] demonstrated that artificial sweeteners can affect heart rate, eye density, and body length in juveniles, with a cumulative effect observed when combined with caffeine. Moreover, some acute toxicity studies might suggest that artificial sweeteners, at current environmental levels, have relatively low acute toxicity for organisms. However, information on the chronic ecotoxicity of artificial sweeteners is scarce, especially considering their persistence, increasing use, and high concentrations [4].

A study conducted a subchronic exposure assessment of methylparaben at environmentally realistic concentrations using adult zebrafish. Subchronic exposure to methylparaben induced hepatocellular vacuolation in zebrafish, inhibited synthesis, and conjugation of primary bile acid in female liver. The study highlighted that methylparaben causes hepatotoxicity [115].

Some authors argue that fish exposure to PPCPs at environmentally relevant concentrations often results in sublethal effects and does not cause excessive toxicity or mortality. The cellular metabolic mechanism in fish also seems to demonstrate a certain degree of plasticity and physiological adaptation [100].

Effects on birds

The most well-known example of effects on birds is the extreme negative impact of diclofenac on vulture populations in Southeast Asia (Gyps bengalensis, Gyps indicus, and Gyps tenuirostris). In Pakistan, diclofenac poisoning was found to be

by far the most frequent cause of death [116, 117, 118]. Research established that veterinary use of diclofenac was the main cause of the vulture population collapse, with numbers dropping by over 97% between the early 1990s and 2007. Deaths continued for many years even after 2006, when India, Pakistan, and Nepal banned the veterinary use of diclofenac [119]. Diclofenac was used in veterinary practice to treat sick animals in Asia and Europe (e.g., Spain). The carcasses of dead animals were often left exposed and became prey for vultures, which ingested the diclofenac. Vultures are extremely sensitive to this drug, and even minimal doses can cause acute kidney failure and death within a few days. Diclofenac-induced kidney disease was experimentally reproduced in oriental white-backed vultures through direct oral exposure to the drug and/or by feeding vultures carcasses of livestock treated with diclofenac [120]. In Europe, the drug has not yet been fully banned in veterinary practice. Besides the threat of diclofenac, other NSAIDs used in veterinary medicine are toxic to Gyps vultures,CA are legally approved for use in India, and can also cause mortality. These include ketoprofen, for which there is experimental evidence of toxicity to vultures below the maximum exposure level for the white-backed vulture. Additionally, residues of nimesulide associated with visceral gout have been found in vultures found dead in the wild in India [121].

Loss of microbial biodiversity

Microbial biodiversity is functionally important in maintaining biological processes in water and soil. When disinfectants and antibiotics accumulate in the environment, they can disrupt the structure and function of microbial communities in various

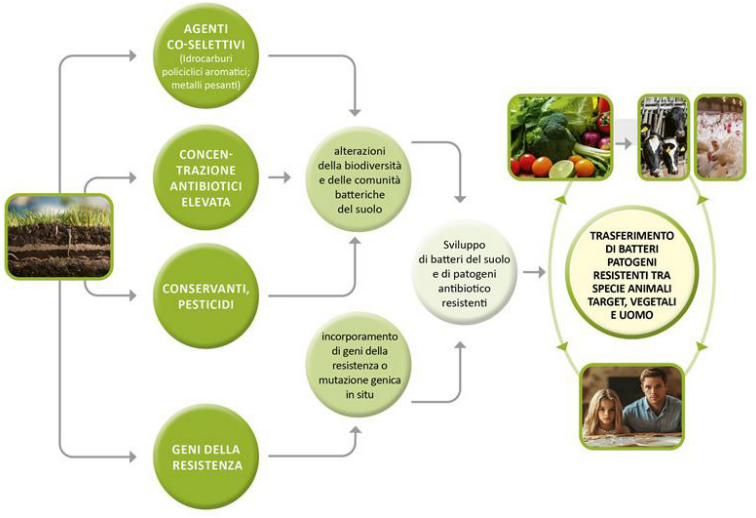

Figura 2. Trasferimento di resistenza agli antibiotici tra le comunità microbiche presenti nel suolo e rischio di infezione umana e animale. Modificata da [55, 122, 123].

ways, having both direct (short-term) and indirect (long-term) effects on these communities. Short-term effects include bactericidal and bacteriostatic actions that lead to the disappearance of certain microbial populations and their ecological functions. Indirect impacts include the development of antibiotic-resistant bacteria. In the presence of environmental antibiotic pressure, antimicrobial resistance genes can rise above usual background levels [55, 122]. Figure 2 shows how the pressure created by antibiotics, disinfectants, and other contaminants, together with resistance determinants present in the soil—known as the soil resistome—promotes the spread of genes that confer antibiotic resistance to both pathogenic and non-pathogenic species present in the environment. One major concern is the potential for the transfer of antibiotic resistance between

microbial populations in the soil and bacteria that can cause infections in animals and humans [123].

In 2018, Fahimipour et al. [124] studied the relationship between the use of antimicrobial chemicals (triclosan, triclocarban, and parabens) in buildings and their impact on indoor microbial communities. The results showed that the bacteria present were cross-resistant to three antibiotics: clarithromycin, ampicillin, and tetracycline.

The relative toxicity of artificial sweeteners was studied using genetically modified bioluminescent *E. coli* bacteria. These bioluminescent bacteria light up when they detect toxic substances. The bacteria were exposed to various concentrations of artificial sweeteners to study their toxic effects. Two patterns of toxicity response were reported in the test, namely the induction and inhibition of the bioluminescent signal. An inhibition of bioluminescence was observed in all strains tested with sucrose. The results of this study may help understand the relative toxicity of artificial sweeteners on *E. coli*, a representative detection model for gut bacteria. Furthermore, the bioluminescent bacterial panel tested may potentially be used to detect artificial sweeteners in the environment, using a specific action mode model [125].

Effects of PPCPs on plants

Saccharin and cyclamate have cytotoxic and mutagenic effects on plants, as observed in a study aimed at evaluating the cytotoxic and mutagenic potential of the sweeteners sodium saccharin and/or sodium cyclamate in plants (*Allium cepa*) and animals (*Mus musculus*) at concentrations permitted by Brazilian law. In *A. cepa*, both the individual sweeteners and

their combinations with exposure time and concentration (ET: 48, 72, and 168 hours) had cytotoxic and mutagenic effects in a dose-dependent manner. An increase in the formation of micronuclei in peripheral blood cells in mice exposed to the sweeteners was also observed. More significant toxic effects were observed with combined doses at 168 ET, suggesting a synergistic effect and DNA damage with increasing concentration and ET. In conclusion, concentrations deemed safe by Brazilian law exhibited significant cytotoxic and mutagenic activity in eukaryotic cells [126].

In a study [127], the effect of the five most frequently used sweeteners— aspartame, saccharin, sucralose, acesulfame K, and stevioside—was tested on the growth and biochemical parameters of duckweed in a laboratory ecotoxicity test. The results indicate that the examined artificial sweeteners showed various effects in the sub-chronic test with *Lemna minor*. Some sweeteners (sucralose and aspartame) can affect the growth rate of this species at milligrams per liter or less. Sweeteners had different effects on Lemna plants. Saccharin, acesulfame K, and stevioside did not cause significant adverse effects on any of the measured parameters. Conversely, stevioside and saccharin slowly produced stimulating effects. Aspartame and sucralose inhibited growth parameters (number and area of fronds), but chlorophyll content was unaffected.

According to an experimental study, sucralose is a competitive inhibitor of ShSUT1 (a plant sucrose transporter) with an inhibition coefficient (Ki) of 16.5 mM. Sucralose is capable of blocking the action of the gene responsible for sucrose absorption in sugarcane, thus inhibiting sucrose uptake and transport within the plant. SUT proteins are involved in loading sucrose

into the phloem[7] and in penetrating tissues, such as seeds, roots, and flowers. Sucralose can bind to the substrate binding site with approximately half the apparent affinity of sucrose [128].

7 The phloem is a complex of living tissues with three main functions: transport or conduction, storage, and support. Soluble organic compounds produced during photosynthesis, particularly sucrose, are transported through it.

Impacts on Humans

Potential human health effects

Human exposure to PPCPs in drinking water can occur through direct consumption of contaminated water or through the intake of food from aquatic environments contaminated with these substances, such as fish and seafood, as well as plants grown in soils contaminated by these substances. The potential health risks associated with chronic exposure to these compounds include reproductive system disorders, metabolic alterations, immune system disorders, neurotoxic effects, and tumor development. Available evidence demonstrates clear health effects in humans resulting from unintentional exposure to antimicrobials/antibiotics (antimicrobial resistance), personal care products (mainly endocrine disruption, metabolic and liver alterations, sperm changes, pregnancy and neurodevelopmental changes), plasticizers (oncological risk), UV filters/blockers (alterations in pregnancy, sexual development, and fertility, and immunological changes) [129].

Currently, the potential impacts of PPCPs present in the environment, water, and food chain on human health in the short and long term are less clear than they are for biota and the environment. However, there are concerns, especially for certain

molecules. This lack of evidence is primarily due to the complexity of assessing the risk associated with the presence of PPCPs in water due to the variety of compounds involved, their diverse modes of action, and the difficulty in predicting the long-term effects of chronic low-dose exposure. Furthermore, current regulations for drinking water quality do not set specific limits for most PPCPs, partly due to a lack of sufficient scientific data on their effects on human health. Little has been done to clarify the combined effects of different compounds. Some studies minimize potential risks because PPCP concentrations are very low, but it cannot be excluded that simultaneous exposure to a mixture of PPCPs may have synergistic or additive effects, increasing health risks. For instance, antibiotics may interact with other endocrine disruptors, affecting the gut microbiome and altering the absorption and metabolism of nutrients and other drugs.

Antimicrobial resistance

Increasing concerns arise particularly from the evident links between PPCPs (including non-antibiotic drugs) and the spread of antimicrobial resistance (AMR), as also noted in a recent UNEP report [130]. Even at low concentrations, PPCPs are capable of generating bacterial populations resistant to antimicrobials and antibiotics, promoting horizontal gene transfer of AMR genes and increasing the risk of exposure and potential transmission of environmental AMR to humans. This issue is critically relevant as AMR represents a growing health challenge, with rising healthcare costs and a progressive increase in AMR-related mortality. Antiparasitics, antifungals, and anticancer drugs are pharmaceutical groups specifically designed to kill their target organism or cells and could be among the

most significant in terms of harming human health through environmental exposure.

Endocrine disruption

There is extensive literature, especially on parabens and sweeteners, which, despite some controversies, indicates a considerable risk to humans when these compounds are introduced through food or pharmaceutical products. Dagher et al. [131] examined the metabolism of three parabens (methylparaben, benzylparaben, and butylparaben) on the MCF-7 cell line, an immortalized human breast adenocarcinoma cell line that predominantly expresses ERα, along with some ERβ. This line was used for screening estrogenic disruptors in human breast cancer. The studied parabens did not undergo metabolism in MCF-7 cells, resulting in greater stability and contributing to their accumulation. The toxicity of parabens in MCF-7 cells is correlated with their lipophilicity. The most common paraben metabolite, p-hydroxybenzoic acid, was studied for its estrogenic action, and it was found that this compound can exhibit estrogenic activity in human cells, more specifically in human breast cancer cells; its estrogenic behavior had already been observed in animal models. This is significant for the safety assessment of these compounds, given the estrogenic response of certain breast cancer cells, the presence of parabens in human breast tissue [132], and the involvement of estrogens in breast cancer development. The intrinsic estrogenic activity of p-hydroxybenzoic acid, observed by Pugazhendhi et al. [133], was found to be similar to that of methylparaben in terms of relative binding to estrogen receptors, although its estrogenic activity in terms of gene expression and cell proliferation was lower than that of methylparaben.

Ecotoxicity of Drugs and REACH Regulation

The first Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use from the EMA [134] was approved in June 2006; therefore, most drugs registered before 2006 (legacy drugs) lack an ERA. In 2018, Burns et al. reported that the difference between the number of drugs currently authorized for market use and those with environmental toxicity data is substantial; in the UK, only about 11% of marketed drugs have an ERA assessment.

The old 2006 guidelines will be replaced on September 1, 2024, by a new version released on February 15, 2024 [135].

Environmental risk assessment is a systematic procedure for predicting potential risks to human health or the environment. Environmental exposure concentrations of a chemical are predicted and compared with predicted no-effect concentrations for different environmental compartments. In the case of medicinal products composed of natural substances (e.g., vitamins, electrolytes, amino acids, peptides, proteins, nucleotides, carbohydrates, and lipids) as active substances, the environmental risk assessment (ERA) may consist of a justification for not presenting ERA studies. As defined in Directive 2004/24/EC, the same criteria apply to herbal medicines. The

ERA is conducted using a stepwise approach, beginning with an initial screening phase, Phase I, which follows a decision tree to identify products requiring a Phase II assessment. The Phase I decision tree concludes with the calculation of a predicted environmental concentration in surface waters (PECSW), based on the intended use of the product. When this PECSW is greater than or equal to the action limit of 0.01 $\mu g\ L^{-1}$, a Phase II assessment must be conducted. It should be noted that the ERA exclusively addresses the impact of the use of a medicinal product. It does not consider emissions from manufacturing sites or waste from medicinal packaging [136].

Chemical risk assessment is based on several parameters: Persistence (P), Bioaccumulation (B), and Toxicity (T). Since PBT/vPvB assessment is a risk evaluation, each active substance must be assessed for its PBT/vPvB properties regardless of its PEC. Substances are evaluated and consequently classified according to their degree of Persistence, Bioaccumulation, and Toxicity (PBT). An active substance that does not degrade well in the environment (persistent), accumulates in organisms (bioaccumulative), and is toxic is identified in the PBT/vPvB (very persistent and very bioaccumulative) assessment.

Moreover, in April 2023, the European Commission published a proposal to revise general pharmaceutical legislation and promote innovation, particularly for unmet medical needs, while reducing regulatory burdens and the environmental impact of medicines [137].

The scope of ERAs needs to be broadened to address environmental risks during the production and formulation process, as considered in the European Medicines Agency's network strategy through 2025 [138], including the risks of development

and maintenance of antimicrobial resistance in the environment, from the production, use, and disposal of antimicrobials, as well as the environmental risks of degradation products, metabolites, and combination effects of molecules, in light of increasing evidence that mixtures of drugs may have greater toxicity [139].

The proposal for a prescription requirement for drugs containing PBT, vPvB, PMT, and vPvM as a risk minimization measure for the environment does not enhance environmental protection. Most doctors are not aware of what these classifications mean or the dangers that substances with these characteristics pose to the environment.

In the European Union, the REACH regulation (Registration, Evaluation, Authorisation, and Restriction of Chemicals) came into force in 2006 [140]. To manage the technical, scientific, and administrative aspects of the regulation and ensure consistency at the EU level, the European Chemicals Agency (ECHA) was established [141]. Through REACH, the European Union evaluates chemicals to identify potential risks to human health and the environment. Additionally, according to Directive 2013/39/EU, a monitoring list, the so-called Watch List, was established, which includes some drugs for human and veterinary use, with the aim of identifying "emerging contaminants" in surface waters to be monitored and build an EU-wide dataset on potential contaminants to determine risk and possibly establish regulatory limits (Environmental Quality Standards - EQS). The first Watch List was defined in 2016 and is reviewed periodically every two years, with substances removed once sufficient data has been gathered to complete the risk assessment. The EU's 2020–2022 Watch List for drug mon-

Table 2.
European Union monitoring data 2020 – 2022 for pharmaceuticals on the "watch list" [142]

	EU Member States	Samples	Median Concentration	95th Percentile
Sulfamethoxazole	14	11684	0.025 µg/L	1.17 µg/L
Trimethoprim	4	4613	0.0125 µg/L	0.0674 µg/L
Clotrimazole	2	45	0.0008 µg/L	0.016 µg/L
Fluconazole	1	436	0.01 µg/L	0.06 µg/L
Gemfibrozil	3	2476	N/A	0.0125 µg/L
Norethisterone	1	20	0.003 µg/L	0.0034 µg/L
Venlafaxine and O-desmethilvenlafaxine	1	1395	0.03 µg/L	0.19 µg/L
Clindamycin	1	436	N/A	0.11 µg/L
Metformin	2	2090	N/A	4.8 µg/L
Gabapentin	1	1478	N/A	3.8 µg/L
Ibuprofen	4	4069	N/A	0.02 µg/L
Ofloxacin	3	277	0.01 µg/L	0.18 µg/L

itoring includes 13 APIs (Active Pharmaceutical Ingredients) from various categories: antibiotics, antifungals, anti-inflammatory drugs, and hormones [142]. In Italy, the first monitoring campaign based on the Watch List was coordinated in 2016 by ISPRA (the Higher Institute for Environmental Protection and Research) and carried out by regional environmental protection agencies (ARPA). The monitoring involved 23 stations, with sampling campaigns generally conducted twice in almost all regions. The highest number of detections involved three compounds: 17-beta-estradiol (E2), estrone (E1), and diclofenac, present at most stations. Far fewer detections were made for macrolide antibiotics (mainly clarithromycin and azithromycin). Hormones were found at stations characterized by both urban and diffuse anthropogenic pressures due to the presence of animal farming. Exceedances of the predicted no-effect levels (PNEC) were observed for 17-alpha-ethinylestradiol (EE2), 17-beta-estradiol (E2), diclofenac, azithromycin, clarithromycin, and estrone (E1). Table 2 lists the substances sought, the number of EU Member States from which data is derived, the median concentration, and the 95th percentile. An excess of Predicted No Effect Concentration (PNEC) -the concentration of the substance below which no harmful effects are expected for the environmental compartment at risk - were observed for many of the substances sought [142].

Unsolved issues

Certain unsolved issues remain. Currently, Environmental Risk Assessment (ERA) is mandatory for human-use medicines, yet only a minority of products have been investigated. ERA and risk reduction measures are not binding for the marketing

authorization of human-use medicines. Monitoring programs for pharmaceuticals in water are insufficient to guarantee water safety; specific emission limits are lacking for production plants and pharmaceutical residue concentrations in drinking water and, finally, no specific regulations exist for managing most pharmaceutical waste. Another critical issue is defining which tests are most appropriate for a realistic assessment of environmental risk.

Risk assessment due to pharmaceuticals in the environment

In chemical risk assessments, toxicity studies are generally conducted with single chemicals in animal models based on regulatory testing guidelines, such as those from the Organization for Economic Co-operation and Development [143]. The key objective of these tests is to evaluate the dose-response relationship of a chemical, generally testing various doses to determine the No Observed Adverse Effect Level (NOAEL) and/or the Lowest Observed Adverse Effect Level (LOAEL). NOAEL is considered a conservative threshold below which a chemical is not expected to induce adverse effects regardless of dose. This level, combined with uncertainty factors (accounting for data gaps), is then used to establish safety criteria [144]. This approach relies on the assumption that all substances have a linear dose-response and a threshold level below which toxic effects do not occur.

However, this type of assessment, based on the "dose makes the poison" principle, is unsuitable for evaluating the effects of substances like endocrine disruptors (EDs) or the carcinogenic effects of chemical mixtures at low doses [144]. The modes of action of EDs challenge traditional toxicology concepts, as these substances can exert adverse effects at low doses that are

not predictable from those observed at higher doses. Many studies document that EDs can act within the nanomolar to micromolar range, and some show activity at picomolar levels [145]. A central concept in ED toxicological studies is the non-monotonic dose-response curve (NMDRC), which challenges fundamental toxicology and risk assessment concepts. NMDRC describes a dose-response relationship characterized by a curve that changes direction within the tested dose range. NMDRC can arise from numerous molecular mechanisms such as antagonistic effects induced by the stimulation of multiple receptors with differing affinities, receptor desensitization, negative feedback with increasing dose, or dose-dependent metabolism modulation [146]. NMDRC is essential for toxicological evaluation in environmental health sciences because, with NMDRC, low-dose effects cannot be predicted from effects observed at higher doses. This is supported by findings showing that chemicals have harmful effects on animals and humans at environmental exposure levels, clearly indicating that low doses cannot be ignored.

Unfortunately, environmental testing models used to predict fate, transport, exposure, and bioaccumulation were designed for traditional contaminants and are often inappropriate for assessing pharmaceutical environmental risks. Unlike many historical organic contaminants, the distribution coefficients of most pharmaceuticals are also influenced by hydrogen bonding, cation exchange, cation bridging, and surface complexation. The absorption and elimination of ionizable pharmaceuticals (over 70% of drugs are ionizable) by fish and invertebrates are modified by the pH of surface waters [85]. A recent European Commission document highlights that some studies have shown

direct effects on wildlife by certain pharmaceuticals, even at concentrations lower than those found in water and soil [147].

Pharmaceuticals can cause mild effects on aquatic and terrestrial organisms not detected in standard studies. Since human and veterinary drugs are continuously released into the environment, wild organisms are exposed for much longer periods than those used in standard tests. Chronic toxicity tests expose organisms to different concentrations of test substances over an extended period, covering a substantial part of their life cycle. In contrast to acute tests, which often use mortality as the sole effect measure, chronic tests may include multiple endpoints, such as reproduction, growth, and behavior.

Fish appear to be the most sensitive species to pharmaceutical contamination in water in long-term tests (56% of tested pharmaceuticals). These results highlight the need to use long-term ecotoxicity tests in ERA for pharmaceuticals. In assessing chronic toxicity, it should also be considered that pharmaceuticals are not present in the environment alone but together with many other drugs and contaminants. Thus, the widespread approach of assessing single-substance risk could lead to underestimating actual environmental risks. The conclusion of a recent study, which did not find consistent risks to human health from exposure to estrogen compounds, rightly noted that "*risk assessment did not consider interactions between compounds, which occur in drinking water and may increase risks and adverse health effects*." [148].

Aquatic and terrestrial organisms are exposed to a mixture of medicines and other chemicals, including pesticides, biocides, and industrial products. Interactive effects and synergistic actions between substances with similar modes of action can

lead to additive effects. Little has been done to determine the absorption of pharmaceuticals by organisms and across the food chain. The ecotoxicity of a drug mixture is often higher than the sum of the effects of its individual components. A mixture can have significant ecotoxicity, even if all components are present at concentrations that individually have negligible ecotoxicological effects [26]. The study by Thrupp et al. [149] observed a significant combined effect when adult *Pimephales promelas* fish were exposed to steroid mixtures, even though each steroid in the mixture was present at a concentration that alone would not produce any statistically significant effect (something that arises from what seems like "nothing"). In practice, small effects can add up to reach a statistically and biologically significant response when simultaneous exposure to multiple chemicals occurs in fish. Due to their sensitivity to EDs, fish are often used as research models to study the potential impacts of these chemicals on humans. A team of researchers proposed zebrafish as a model for predicting ED effects on toxicogenomic tests in humans, such as microarrays or whole genome sequencing. This approach is feasible because zebrafish genes, which show significantly altered expression after ED exposure, are very similar to those found in humans. Furthermore, many glandular systems in zebrafish resemble human systems, making this fish model suitable for studying endocrine system alterations [150]. For several decades, concerted efforts have been made to identify individual chemicals and other carcinogenic agents. However, little has been done to determine whether lifelong chronic exposure to mixtures of non-carcinogenic chemicals present in the environment (at low dose levels) may have carcinogenic potential.

To explore the hypothesis that low-dose exposure to mixtures of environmental chemicals may contribute to environmental carcinogenesis, researchers examined 11 hallmark phenotypes of cancer, multiple priority target sites for alteration in each area, and prototype disruptors for all targets. This included characterizations of dose-effect responses, evidence of low-dose effects, and cross-effects between different phenotypes for all targets and chemicals. A total of 85 chemical examples were examined for their actions on key pathways/mechanisms related to carcinogenesis. Only 15% (13/85) showed evidence of a dose-response threshold, while 59% (50/85) showed low-dose effects. The authors suggest that these findings reinforce the concept that chemicals can have harmful effects on critical cancer-related mechanisms at exposure levels commonly found in the environment [151]. A recent literature review analyzed novel health risks and emerging concepts related to emerging contaminants in water, such as pharmaceuticals, and identified future research areas, including latent long-term and intergenerational effects; interactive health effects of emerging contaminant mixtures; challenges posed by multifinality[8] and equifinality[9] of effects; and the evolutionary health-disease hypothesis [129]. Finally, research should be expanded to determine the absorption of pharmaceuticals by organisms and across the food chain.

8 The term multifinality indicates that a single cause or factor can lead to different outcomes. In other words, a single factor can produce a range of diverse results depending on the context or circumstances. For example, exposure to a chemical or contaminant could cause different effects in different people, such as various health issues, depending on genetic predisposition, environmental conditions, or other factors.

9 The term equifinality means that similar or identical outcomes can be achieved through different paths or causes. In other words, various factors or processes can lead to the same final result. For example, in the ecological field, different sources of contamination could cause the same type of environmental impact, even though the processes leading to that result are different.

How to reduce the environmental footprint of pharmaceutical treatments

To minimize the risk of environmental contamination from pharmaceuticals, all stages of pharmaceutical activities (research, production, prescription, distribution, and disposal of medicines) should be controlled. Companies are responsible for pursuing the goal of producing more eco-sustainable medicines, while doctors and pharmacists (for self-care pathways) should work to reduce or minimize the number of inappropriately prescribed or recommended medicines and those left unused. Patients are responsible for following instructions and proper disposal.

Respect for the environment involves not only attention to the characteristics of active ingredients, preservatives, colorants, and other components in the product but also the use of eco-friendly packaging. Companies can adopt more sustainable packaging materials, such as bioplastics or recycled paper. Using biodegradable packaging and reducing the use of non-recyclable plastics can significantly decrease the environmental impact of medicines.

The areas of study, research, and production, when applied together in various fields, should significantly contribute to reducing the ecological footprint of drugs or their metabolites in the environment. These areas include Green Pharmacy, closely linked

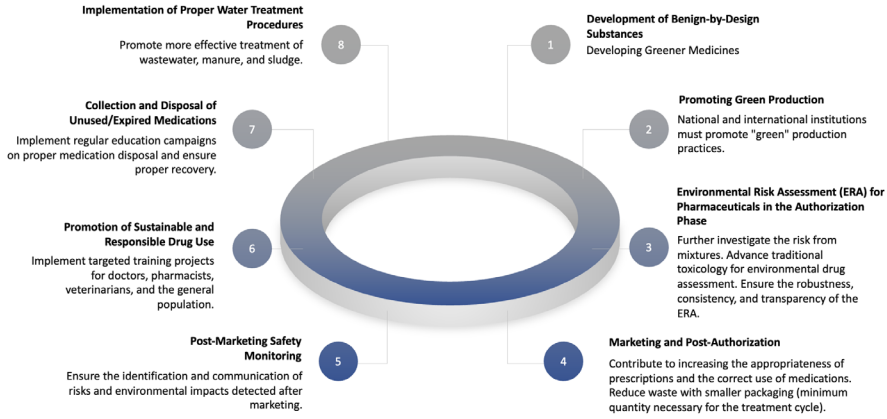

Figure 3. Summarizes the actions needed to reduce the environmental footprint of pharmaceutical treatments.

to green chemistry, eco-pharmacovigilance, pharmaco-eco-kinetics [152], and eco-friendly pharmaceuticals. The areas of focus for these disciplines are often overlapping and intersecting.

Green pharmacy

Green Pharmacy encompasses all measures to design and produce medicinal products with active pharmaceutical ingredients (APIs) that have the lowest possible environmental impact. From a chemical perspective, APIs include a wide range of small molecules with different physicochemical and biological properties, which may be chemical, plant-based, or animal in origin; approximately 3,000 are authorized in the EU market. Minor modifications to the chemical structure of an API can significantly change its environmental fate. Green Pharmacy measures should be applied throughout all pharmaceutical activities, from the design of new molecules to production, distribution, and dis-

posal. The pharmaceutical industry can adopt more sustainable production processes by reducing the use of toxic solvents and optimizing resource use. For example, using "continuous flow" synthesis processes can improve efficiency and reduce waste. An example of "green pharmacy" is modifying the ifosfamide molecule (used in chemotherapy). This drug is non-biodegradable, but the simple addition of a glycidic molecule increases its intestinal absorption, retains its therapeutic properties, reduces side effects, and reduces environmental dispersion by increasing biodegradability [26].

Green chemistry

The concepts of Green Pharmacy and Green Chemistry are closely linked. "Green Chemistry" is essentially the study and design of processes and products that are environmentally sustainable and low in toxicity to humans and the environment. Green chemistry should adhere to twelve well-defined principles [153]. A green chemical process is "benign by design," meaning it is created from scratch to have minimal environmental impact; in other words, environmental respect is an essential feature of the production process. Practicing green chemistry not only benefits the environment but also makes production projects more profitable.

Eco-pharmacovigilance

Eco-pharmacovigilance is the discipline that deals with the environmental fate of drugs and their effects on humans [93]. As mentioned, drugs, although present in the environment at very low concentrations, could interfere with certain bodily functions and contribute to bacterial resistance. Eco-phar-

macovigilance involves the processes of detection, evaluation, understanding, and prevention of adverse reactions or other problems related to the presence of drugs in the environment, affecting both humans and other animal species. For a better understanding of a drug's lifecycle, it is essential to study where APIs (or their metabolites) go and what they do after acting within the human body.

Pharmaco-eco-kinetics of APIs

Pharmaco-eco-kinetics (PEK) complements eco-pharmacovigilance by studying the fate of APIs in the environment [154]. It is a discipline analogous to pharmacokinetics (PK) applied to humans, which considers the fate of active pharmaceutical ingredients in the environment (starting from the point at which an active pharmaceutical ingredient or metabolite is eliminated). The main difference between PK and PEK is that PK focuses on plasma drug levels, while PEK focuses on environmental drug levels, particularly in wastewater, drinking water, biosolids, and biota. All excretion pathways for APIs are essential for preventing pollution. For a long time, it was thought that elimination occurred only through urine and feces. However, there are alternative routes, such as the release of unchanged APIs from the skin during bathing and washing (including clothing washing). These routes are characteristic of topically or transdermally applied drugs and those expelled through sweat. For example, skin excretion can be limited by designing more efficient and targeted transdermal API delivery or educating patients on the proper application of topical products and reducing the overuse of these drugs.

System-level responsibility

The Environmental Risk Assessment (ERA) of the EMA, mandatory since December 2006 (EMA 2006) [134] for human medicines marketed, covers only a minority of products. Furthermore, ERA and risk reduction measures are not binding for human medicine authorization. To date, monitoring levels are insufficient; there are no specific emission limits for production plants; there are no limits for pharmaceutical residue concentrations in drinking water, surface water, or wastewater; and no specific regulations exist for managing most pharmaceutical waste. Therefore, there are significant regulatory gaps that still need to be addressed.

The pharmaceutical system also bears responsibility for the phenomenon of drug accumulation and "inappropriate" prescriptions. This is due to excessive direct-to-consumer advertising; pressure from pharmaceutical companies on doctors (biased medical information, sponsored meetings); and sampling. The lack of disposal systems or shared or inappropriate disposal methods (at the international, national, or regional level) and the absence of regular public awareness campaigns contribute to exacerbating the problem.

Institutional responsibilities also include promoting the adoption of more effective wastewater and sludge treatment methods. Updating or enhancing wastewater filtration processes can effectively control PPCP concentration levels. Some authors suggest that to improve and extend filtration processes' capacity to remove dissolved organic matter, including PPCPs, biological processes could be adopted, as biofiltration combines both biosorption and biodegradation functions, offering numerous advantages for water treatment [155]. Additional-

ly, advanced water treatment technologies, such as oxidation processes, could break down complex pollutants into simpler, less harmful substances [156].

In terms of primary prevention, measures should be adopted to minimize environmental drug emissions used in livestock farming and fish farming.

The literature highlights the need for continuous monitoring and sustainable practices to mitigate the long-term consequences of antibiotics and antibiotic resistance in aquatic environments. Singh et al. [157] emphasize that there should be a strict government policy to control the discharge of antibiotic residues from various sources to reduce the environmental risk of antibiotic contamination.

Prevention: eco-friendly use of medicines

The more eco-friendly use of medicines is encouraged by various factors, of which we will mention and comment on only a few key ones, such as: the correct use of medicines, achieved through the active involvement of healthcare professionals (doctors, pharmacists) and citizens; better education for patients, caregivers, and citizens on the proper disposal of medicines; and the adoption of more technologically advanced wastewater treatment systems, especially at the hospital level, where drug use is particularly high.

Limiting the environmental footprint related to medical prescription and pharmacy advice

While a patient should not be deprived of the most appropriate medication for their illness, unnecessary medications can certainly be limited in prescriptions or recommendations.

Prescription appropriateness plays a central role in managing environmental pollution from pharmaceuticals. Doctors and pharmacists must be aware that when they prescribe or recommend a medication to a patient, they are, in a way, indirectly prescribing it to the entire surrounding environment. This includes prescribing for humanity in general, for animals, and for the entire ecosystem. If more than one medication or therapeutic intervention exists for a health issue, the doctor or pharmacist (in self-care situations) should always choose the option with the least environmental impact. A significant example is antibiotics. These drugs are widely prescribed even for non-bacterial conditions, which contributes to worsening bacterial resistance. Practically, even though the patient's health problem always takes priority in choosing an intervention, much can be done to limit the environmental footprint associated with medical prescriptions and pharmacy advice. In this area, continuing medical education interventions focused on responsible and eco-sustainable prescribing/advice are crucial for doctors and pharmacists.

Tools for choosing medications with lower environmental risks

A useful guide to understanding the environmental impact of prescribed/recommended medications is the Pharmaceuticals and Environment database, created under the Stockholm County Council Environmental Program. In this database, drugs are classified according to their ecotoxicological impact. For each drug, the database provides information on environmental hazard and risk classification according to the levels of Persistence, Bioaccumulability, and Toxicity (PBT). Risk classification is

generally based on theoretical risk calculations. The continuously updated electronic database is accessible at: https://janusinfo.se/inenglish.4.7e3d365215ec82458644daab.html

Patient Responsibility

Patients also play a role in environmental contamination with active pharmaceutical ingredients. Factors contributing to this phenomenon include:

- Prescription pressure on the doctor: Patients often believe that a "good consultation should always end with a prescription."
- Self-medication purchases: Driven by information acquired online or from individuals not trained in the issue.
- Excessive home medicine stockpiling: Due to various reasons, such as non-adherence to the treatment plan, adverse events leading to stopping and accumulating the first drug and the prescription of one or more alternative drugs, "unnecessary" requests to the doctor, such as "backup" medications before a trip, and improper disposal procedures.
- Failure to follow proper disposal guidelines.

Patient Education

Educating patients on the rational use of medicines, adherence to therapeutic guidelines, and proper disposal of unused or expired medicines should be part of doctors' daily clinical practice and pharmacists' work. Additionally, regular institutional awareness campaigns and widespread national dissemination of appropriate medicine collection and disposal procedures are needed. This would not only positively impact therapeutic outcomes but could also have important implications for environmental health.

Several brochures on the correct use and disposal of medicines have been prepared at the regional level, which probably deserved wider distribution nationwide. We mention one only as an example, as there are likely many similarly commendable local initiatives: the "Guide to the Conscious Use of Medicines," a booklet produced by the association "APMAR" [158] in partnership with AIFA - Italian Medicines Agency, and many other institutions and associations. The booklet contains relevant and easily accessible information for the public.

The recommendations listed in Table 3, partially drawn from the APMAR booklet mentioned above, can be helpful in raising awareness of this issue. These can be printed and displayed in waiting rooms, distributed to patients, or sent to them electronically.

Table 3.
Recommendations to give patients for raising awareness

Be Cautious with Medication Use!
Only have medications prescribed or purchase over-the-counter drugs for health issues where the use of medication is essential.
Carefully follow the doctor's and/or pharmacist's instructions regarding dosage, timing, or any other necessary precautions.

If there is leftover medication at the end of the treatment, do not dispose of it down the sink or toilet.
Use a container to collect leftover/expired medications that need to be disposed of, so they are ready the next time you go to the pharmacy.
Dispose of expired medications in the designated bins available at pharmacies, including: syrups; tablets and pills; bottles with medication residues; ointments; injection vials; disinfectants.
Separate different materials at home: blister packs should be disposed of according to the guidelines of local recycling systems; liquid medication bottles should be returned as-is to the pharmacy; paper and cardboard packaging should be recycled with paper waste.

These procedures apply to both prescription and over-the-counter medications. If you have any questions about proper medication disposal, ask your doctor or pharmacist.

Activities of ISDE Italy dedicated to limiting pollution from PPCPs

ISDE Italy has an in-depth knowledge of this topic, having studied it for over 10 years. The association has engaged on many fronts to raise awareness among doctors, pharmacists, and veterinarians about the need to limit this type of pollution and the role these professionals can play. The first expression of interest dates back over ten years with participation in a national workshop organized by the International School for the Environment, Health, and Sustainable Development, titled: Pharmaceuticals, Health, and the Environment. In 2018, during the 11th Environmental Doctors Day at the 13th Healthcare Risk Management Forum (Florence), ISDE contributed to the session with a presentation titled: Pharmaceutical Substances in the Environment. An ISDE working group designed and implemented an e-learning course accredited by the Italian National Continuing Medical Education (ECM) System, titled "Water Contamination by Pharmaceuticals," aimed at doctors, pharmacists, and healthcare workers. The course was accredited in the ECM system in 2019, 2020, and 2022 and has been completed by over 2000 doctors and pharmacists. A fully revised and updated edition of the e-learning course was accredited in November 2023 by the National Continuing

Medical Education System and will be reaccredited for 2025.

This awareness-raising and training initiative has been complemented by significant research efforts. ISDE Italy collaborated with the Water Research Institute (IRSA) of the National Research Council (CNR) on a pilot project to assess the potential environmental risk of a group of pharmaceutical substances reported in the scientific literature to be present in Italian waters. The project's results were presented in a poster at the 33rd annual conference of the Society of Environmental Toxicology and Chemistry (SETAC) in 2023 [159].

A much broader study is currently underway, with ISDE Italy serving as the scientific reference for environmental, informational, and training aspects. The study is being developed by several research centers, particularly the Water Research Institute (IRSA), as part of the National Biodiversity Future Center (NBFC) project, funded by the European Union's Next Generation EU program under PNRR, Mission 4, Component 2, Investment 1.4 - National Biodiversity Future Center (NBFC) - CUP No. B63D21015220004. In this study, 300 compounds used in pharmaceutical products (such as APIs, preservatives, artificial sweeteners, colorants) will be analyzed in approximately one hundred Italian water samples. Literature data on their persistence, toxicity, and bioaccumulation will be collected. For certain substances deemed particularly relevant, and for which ecotoxicity data is unavailable, specific experimental studies will be conducted. All data will be organized into technical sheets reporting the presumed level of "potential environmental risk" calculated using an original scoring system. These sheets will be made available to healthcare professionals on a dedicated website. The goal is to promote a

new culture among doctors, pharmacists, and patients for more conscious and environmentally sustainable medication use, in alignment with the new European "One Health" strategy. The availability of ecotoxicity data on PPCPs will guide doctors and pharmacists in choosing more environmentally sustainable medications without depriving the patient of necessary and appropriate treatment.

Conclusions

Environmental pollution from human and veterinary pharmaceuticals poses a clear threat to wildlife and biota, as evidenced by the damage caused to certain animal species such as fish, birds, and frogs, among others. Current research methods are inadequate for an accurate risk assessment: subtle pollution effects and chronic impacts are seldom studied, and risk assessments are conducted on individual compounds rather than mixtures, as would be appropriate.

Better environmental monitoring of pharmaceuticals and their transformation products in biota, water, and sediments is mandatory. The risk of transferring antimicrobial resistance between soil microbial populations and pathogenic bacteria for animals and humans should be carefully assessed. Evidence indicates that if no mitigation action is taken, the environmental threat from diclofenac alone is expected to rise to 65% by 2050. Technological improvements alone will not be sufficient to reduce current concentration levels, and without a considerable reduction in consumption, a large portion of global river ecosystems will not be adequately protected.

As for human risk, rather than waiting for conclusive evidence of harm, we must take preventive actions in line with

the respect of the precautionary principle. This is particularly crucial as there is growing evidence that precautionary measures do not hinder innovation but can, in fact, encourage it, especially when supported by smart regulation or well-designed tax adjustments. As asserted by the European Environmental Agency, history teaches us that if the precautionary principle had been applied based on early warnings, where "reasonable grounds for concern" existed, many lives would have been saved, and much ecosystem damage could have been prevented.

We can conclude with the exhortation of some researchers who have dedicated significant efforts to this issue, saying: "perhaps it is time to stop, or rather not to limit ourselves to measuring drug pollution levels in water, but to start doing something to combat the phenomenon!"

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