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POLLUTION OF PHARMACEUTICALS IN ENVIRONMENT

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ABSTRACT

The presences of pharmaceuticals in the environment are increasingly a worldwide concern. Patients, in case of drugs for human use, or animals for veterinary drugs are the main sources of contamination. Several pharmaceuticals widely used in human medicine are excreted unchanged or as active metabolites in high percentages and continuously discharged into domestic waste waters. Pharmaceuticals may have long half-lives in the environment, so they can accumulate, reaching detectable and biologically active levels. Recent studies have demonstrated that many pharmaceuticals are incompletely eliminated at sewage treatment plants. The existence of drugs in surface waters, groundwater and even marine systems has been confirmed at concentrations of high to low level. Ecotoxicological effects, Pharmacological effects and Resistance development of micro-organisms are potential risks exposure to concentrations of pharmaceuticals in the environment but there is insufficient ecotoxicity, physicochemical and biodegradability data for most pharmaceuticals for executing a complete risk evaluation as well as influence on ecological processes in ecosystems, is lacking. Therefore, human health risk assessment and ecotoxicological hazard evaluation must be developed.

INTRODUCTION

Pharmaceutical products for humans or animals, as well as their related metabolites (degradation products) end up in the aquatic environment after use. Recent investigations showed that low concentrations of pharmaceuticals are detectable in municipal waste water, surface water, groundwater and even drinking water. Little is known about the effects and with that the risk, of long term exposure to low concentrations of pharmaceuticals for aquatic organisms.

Occurrence of pharmaceuticals in surface, waste, drinking water and sediments are not well known except for two preliminary studies that measured levels of pharmaceuticals in the environment, published in 1977 (Hignite & Azarnoff, 1977) and in 1985 (Richardson & Bowron, 1985), the first work with a systematic approach started to appear in the 1990s, dealing with levels of pharmaceuticals in local rivers in Germany (Ternes 1998; Hirsch *et al*. 1999). The presence of several pharmaceuticals in effluents was soon confirmed in The Netherlands (Belfroid *et al*. 1999),

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Switzerland (Golet *et al*. 2001), United Kingdom (Johnson & Sumpter, 2001); France, Greece, and Sweden (Andreozzi *et al*. 2003); Spain (Carballa *et al*. 2004); USA (Kolpin *et al*. 2002; Huggett *et al*. 2003; Yang & Carlson, 2004); Canada (Metcalfe *et al*. 2003); Brazil (Stumpf *et al*. 1999) and Australia (Braga *et al*. 2004).

In world wide ranges of pharmaceuticals are 12,000 human and 2,500 veterinary pharmaceuticals. Each pharmaceutical consists of an active substance, mixed with a number of auxiliary substances to make it possible to handle and dose the pharmaceutical. From an environmental point of view, especially the active substances are of interest. The relatively recent awareness of pharmaceutical products impact on environment is reflected in literature since the 1990s through the exponentially increasing number of studies concerning this emergent class of water pollutants. Pharmaceutically active compounds are produced and used in very large volumes and their use and diversity is increasing every year.

The majority of studies on pharmaceutical products in aquatic system concerns their analysis, occurrence and fate in wastewater and wastewater treatment plant, with an emphasis on processes efficiency with respect to their removal. As the majority of organic micropollutants, the contamination origin is above all anthropogenic and continuously released in wastewater or directly in the environment.

The researches showed that pharmaceuticals were detectable in untreated and biologically treated municipal waste water, surface water and a very few also in drinking water. These findings triggered a cascade of investigations of the presence of both human and veterinary pharmaceutical products in the environment as well as the possible risks this presence may pose to humans and the environment. Accurate assessment of pharmaceutical products (PPs) impact on the environment is as difficult as there is a multitude of input sources in environment with no evident quantitative data available concerning the relative distribution of PPs from all emission sources (Fig. 1).

Pharmaceutical products are widely used in the human health sector and in the animal husbandry. These substances have been designed to be biologically active and to cause very specific effects. The pharmaceuticals and their metabolites are excreted via faeces and urine and end up in the aquatic environment, either by discharge after passage of a sewage water treatment plant, or by run-off from the surface, leaching via the soil or drainage to the surface water after spreading of manure on the land.

The emission routes of veterinary drugs and feed additives to surface water are more complex than those of human pharmaceuticals. Emission to the surface water can take place either directly, when the animals are kept on pasture, or indirectly by run-off and/or leaching through the soil. The manure of animals in the stable is stored temporarily. The extent of run-off and leaching depends on climatological conditions, chemical and physical properties of the substance, type of animal and agricultural practice. Although humans and animals treated with PPs constitute the main contamination source of potable water resources (surface water and ground water), PPs are qualitatively, quantitatively, spatially and temporally shared out into different routes depending on whether patients are located in private households or in hospitals and other places. Indeed, prescribed drugs in hospitals are rather designated to treat heavier pathologies than in households. Improper disposal of unused or expired drugs, which are directly thrown in toilets or end up in landfill, and pharmaceutical residues from manufacture spill accidents (Reddersen *et al*. 2002) can also be regarded as other significant local points of potential contamination. Therefore, the most significant entry route for pharmaceuticals into the aquatic environment is the release from wastewater treatment works. This is because a large proportion of medication taken by patients passes through their body unmodified and travels via urine and faeces to wastewater.

Differently, direct release of veterinary pharmaceuticals in environment may occur via application in aquaculture (i.e. fish farming), but also indirect release by way of animals topically treated, and mostly via run-off and leaching through fields from manure spreading to agricultural fields and livestock wastes (Boxall, 2008; Khan *et al*. 2007; Kemper, 2008). Pharmaceuticals are potentially ubiquitous pollutants because they could be found in any environment inhabited by man. As yet, there is little evidence that pharmaceuticals are present in the environment in sufficient quantity to cause significant harm, though their use is expected to grow with the completion of the human genome project and the rising age of the population. Pharmaceuticals and their metabolites are more and more likely to be found in the receiving waters of areas adjacent to human activity and therefore further research in this area is warranted.

Water resources and pharmaceutical products

Increasing demands on the world's water sources will

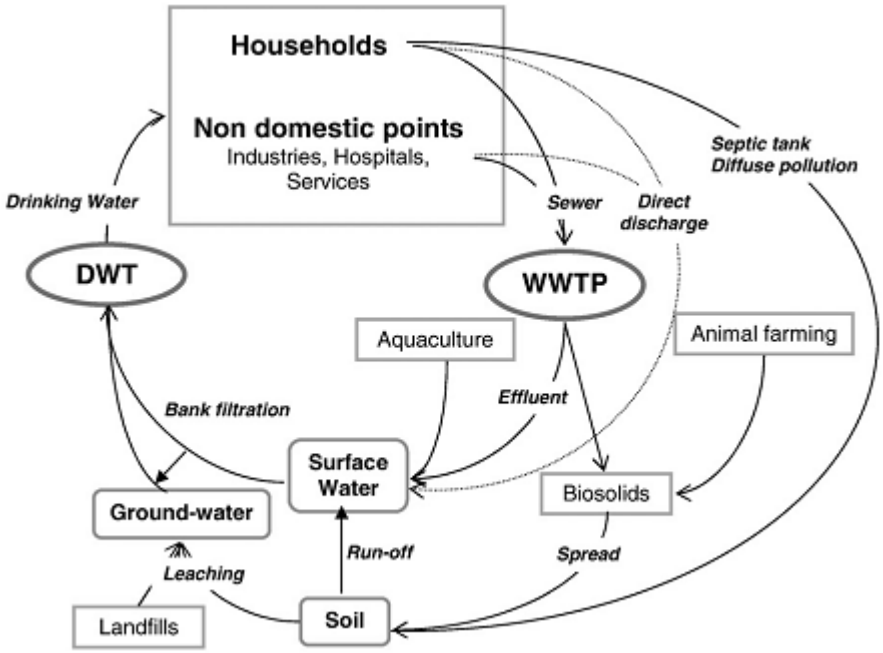

Fig. 1 Origin and routes of pharmaceutical products (after Petrovic *et al*. 2003).

be likely to lead to greater incidences of indirect and direct water reuse situations in the future. Drinking-water is a direct route to the human body, including for any drug compounds or other pollutants that may be present. Municipal wastewater is never treated in this way because of a lack of suitable technology and the high economic investment required. The occurrence of pharmaceuticals in the aquatic environment is an emerging concern. The majority of studies attest of the general presence of PPs in water bodies but of prime importance for human health, in drinking water. Considering the fate of PPs, their concentration obviously decreases from wastewater to the environment. For instance, Ofloxacin, a Fluoroquinolone antibiotic, were detected up to 35.5 µg/L in New Mexico hospital effluents while 410 ng/L, 110 ng/L were found in the Albuquerque waste water treatment plants influents and effluents, respectively, corresponding to 77% of wastewater treatment plants attenuation rate, and finally not been detected in the Rio Grande river (Brown et al., 2006). The low volume drug would be a candidate for the full risk assessment procedure. The difficulties of quantifying mixture effects are not unique to pharmaceutical risk assessment. The lack of data about environmental concentrations and the possible mechanisms of interaction are common to the assessment of all chemicals in the environment. considering, the lack of knowledge about PPs consumption, metabolization, biodegradation, added to the cross variability depending on the consumption and temporal contexts, occurrence studies of PPs must be completed with recognized protocols for field investigations and data processing in order to make relevant comparisons possible.

The presence of PPs from the main sources of contamination, i.e., discharge of wastewater treatment plants effluents, and animal farming, is firstly attenuated by dilution in surface water up to trace level (µg/L to ng/L). The other potential attenuation factor of PPs in receiving waters is the adsorption on suspended solids, colloids and organic matter (Osenbruck *et al*. 2007). PPs may also undergo biotic, chemical and physico-chemical transformations in water, although PPs are designed to resist to microbial degradations and to be chemically stable (Sammartino *et al*. 2008; Khetan and Collins, 2007). However, abiotic PPs and residues elimination is the most likely reaction occurring in surface water with predominantly direct and indirect photodegradation (Khetan and Collins, 2007; Nikolaou *et al*. 2007). From water resource to drinking water network, the removal efficiency of PPs in drinking water treatment plant is rather known. However, even if some processes are efficient such as nanofiltration, ozonation, chlorination or photodegradation, degradation may also be potentially toxic and some PPs cannot be totally re-

moved in drinking water treatment (Ternes *et al*. 2002 and Verliefde *et al.* 2007). The knowledge about the presence and the behaviour of pharmaceuticals and especially of veterinary drugs in the aquatic environment is very limited.

Potential hazards of pharmaceutical in water resources

Potential risks exposure to low concentrations of pharmaceuticals in the following negative effects are ecotoxicological effects (acute and chronic toxicity, genotoxicity and carcinogenicity); pharmacological effects (interference of the hormone and immune system) and resistance development of micro-organisms. A significant problem in assessing ecotoxicolgical impacts of PPs at the ecosystem level occurs because of the orientation of usual toxicological trying; individual chemicals are experienced on a single species. Hormones (particularly estrogen compounds) are some of the earliest medicines reported in sewage, and they have been found in significant concentrations (Shore *et al*. 1993 and Tabak *et al*. 1981). Due to the extensive use of antibiotics in aquaculture, veterinarian medicine, animals, and human medicine, extensive literature exists on their environmental effects, the studies show that up to 95% of antibiotic compounds can be released unaltered into the sewage system. This phenomenon may be a cause of the accelerated resistance of bacterial pathogens to antibiotics. High concentrations of antibiotics can lead to alterations in microbial community structure and affect food chains. Antibiotics such as Sulfamethoxazole, Trimethoprim, Erythromycin and Keflex can get into the water and create antibiotic resistance. Antibiotics are turning up in surface and ground waters, and are of concern due to the fact that antibiotics in the environment selects for drug-resistant strains of bacteria. When bacteria are exposed to low doses of antibiotics, they develop a tolerance for those same drugs. When humans are subsequently infected with these drug-resistant bacteria, certain antibiotics are ineffective at treatment. This is of concern to people because there are 14,000 deaths annually due to antibiotic resistance. (Reckhow & Anastas 2007).

Pharmaceutical pollution prevention

Source reduction of hazardous wastes can be achieved in industry through changes in products, raw materials, process technologies, or procedural and organizational practices. Various source reduction alternatives, including material substitution, process modification, and good operating practices, are provided here. Pharmaceutical manufacture is a diverse and highly competitive industry. Due to the highly specific and often confidential nature of each company's specific operations, only very general discussions of material substitution and process modification can be given. The intent is to stimulate the thinking of manufacturers about their own processes.

The best way to reduce pollution is to prevent PPs in the manufactures. Some companies have creatively implemented pollution prevention techniques that improve efficiency and increase profits while at the same time minimizing environmental impacts. Some smaller facilities are able to actually get below regulatory thresholds just by reducing pollutant releases through aggressive pollution prevention policies. Source reduction is one method by which the industry aims to reduce these wastes. However, source reduction methods such as process modifications and material substitutions may not be as easily implemented in the pharmaceutical industry as in other manufacturing sectors. As a result, many pharmaceutical companies are looking at ways to minimize waste in future production processes at the research and development stage. Incorporating pollution prevention at the start of a new drug development process is much more economical, efficient, and environmentally sounds. Many pharmaceutical companies have already implemented pollution prevention programs in their manufacturing facilities. Although pollution prevention may not always be a substitute for control technologies, it is often viable and is an increasingly popular method for meeting environmental compliance requirements. Some examples of innovative waste reduction programs that incorporate source reduction as well as recycling and reuse are presented in the case studies that appear in this section. One of the most common opportunities for material substitutions in the pharmaceuticals industry is found in the tablet coating process. Until recently, many tablet coating operations involved the use of methylene chloride and other chlorinated solvents. By switching to aqueous-based coating films, many firms have reduced the hazardous waste content in their air and effluent waste streams, as well as the cost of purchasing chemicals. Aqueous-based cleaning solutions are also being used more frequently for equipment cleaning instead of solvent-based solutions.

Movement of pharmaceutical products

It is impossible to predict how far the PPs discharged from wastewater treatment plants will travel. Obvi-

ously, factors that affect the distance these substances travel include soil type, groundwater and surface water flow, geology of the landscape, and pumping characteristics of nearby wells. However, Zimmerman (2005) showed that acetaminophen, carbamazepine, and sulfamethoxazole detected in a wastewater plume one mile away from the source.

CONCLUSION

The most important conclusion from the literature points to the ubiquity of PPs in aquatic environments. Existing sewage treatment systems are not designed to remove them. Therefore, now is the time to prevent further harm to living organisms. However, the concentrations are usually low; this is especially true of those which produce serious chronic effects at low concentrations such as endocrine disrupting compounds. Knowledge is rapidly growing, but nevertheless the problem is not yet fully clear, and information on risk assessment and management is far from adequate. Further investigation into the effects of exposure to mixtures of drugs would also be valuable especially if combined with monitoring programmers. To conclude, data human health risk assessment and ecotoxicological risk assessment related to PPs must also be developed.

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