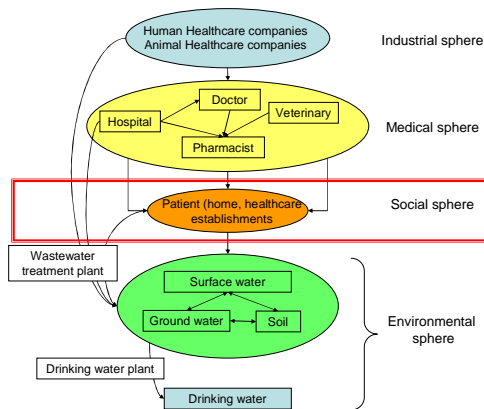


RECOMMENDATIONS

The presence of Pharmaceutical Products in the environment is the responsibility of all actors involved in the PPs life cycle from its manufacture to its exposure to aquatic and terrestrial organisms. In order to find some solutions allowing lowering the occurrence and the impact of PPs, we need to take actions, now. In most cases, the selected measures will not require cross-sector agreements but their efficiency will depend on the cooperative approach. Moreover, work on the basis of shared responsibilities will be promoted in particular to minimize the costs and to open potentials for innovation.



In the frame of above, five spheres of actions, corresponding to the main actors in the PPs life cycle, can be defined and recommendations are proposed according to these spheres of influence.

In the following proposed recommendations, the objective is not to prevent to the appropriate treatment of patients with pharmaceutical products, but to mitigate the environmental impact of this use. Considering the patient as the central actor, we can define these recommendations as:

- **pro-actions:** actions that have to be taken in order to prevent the introduction of PPs in the environment by acting upstream from the use by the patient (preventive approach) :
 - green pharmacy or development of more environmental compatible drugs
 - promotion of take back schemes
 - implementation of an environmental classification showing risk and hazards of PPs
 - communication about environmental concern of drugs
- **post-actions:** actions that have to be taken in order to treat the consequences of the release of PPs in the environment by acting downstream from the use by the patient (curative approach):
 - upgrade of conventional treatments and development of new treatment processes
 - development of analytical methods
- **actions:** actions that have to be taken at the same time as the use of PPs (day to day approach) , :
 - implementation of monitoring programs
 - increase understanding on interaction of PPs with sludges
 - increase knowledge on effect of PPs (alone, mixture) on organisms
 - use of Intelligent Testing Strategies for chronic exposure assessment

EDITORIAL

Pharmaceutical products are considered today as emerging pollutants within the classification of environmental micropollutants. They are not a new generation of molecules introduced in the environment by human or industrial activities, but they are more and more investigated since the high evolution of the performances of analytical techniques. The consequence was an exponential increase of studies published in this area since 2000. More than 400 publications at national of international level, 5 European projects (FP5) and several dozens of national programs have produced huge amount of data and information related to the presence, behaviour, impact and effect of pharmaceutical products (human and/or veterinary) in the environment.

Then, it was important to assess the state of the current knowledge, in order to prioritize future actions and research. Knappe project was launched to establish such a state. The originality of this project was the involvement of all actors involved in the life cycle of the drug, from its manufacture to its release in the environment and its exposure to aquatic and terrestrial organisms.

Data collection has been carried out within several European countries allowing to draw up an inventory of the available information dealing with the manufacture, the prescription/delivering/consumption practices and the environmental characteristics (occurrence & fate, risks, legislation) of these products.

These data were discussed during the project not only on the scientific (environmental) point of view but also with the social and industrial vision, by involving in the Knappe events members of the medical, patient, pharmaceutical industry communities.

This Newsletter presents the main points required for a good understanding of the topic and some recommendations as discussed during the Knappe final conference. The whole recommendations, proposed to the European Commission, are accessible in a specific report available in the Knappe website.

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Properties of Pharmaceutical products

Pharmaceutical Products (PPs) or Active Pharmaceutical Ingredients (APIs) are complex molecules with different functionalities and physicochemical and biological properties. Most of them are polar compounds. They are developed in order to have a range of biological activity. They are mainly small molecules (200 to 1000 Daltons) and are considered as “micro-pollutants” because their concentrations are found in the range of $\mu\text{g/L}$ to ng/L in aquatic environments.

PPs often have basic or acidic functionalities, sometimes even within the same molecule. Under environmental conditions (e.g. pH), PPs can be neutral, cationic, anionic, or zwitterionic. As a consequence, their environmental behaviour (adsorption, absorption, solubilisation, ...) can become more complex to understand and to model.

From an environmental point of view, PPs are generally classified according (i) their purpose and biological activity (e.g. antibiotics, analgesics, anti-neoplastics, anti-inflammatory substances, antibiotics, antihistamines, X-ray contrast media, etc.), (ii) their chemical structure (e.g. within the group of antibiotics such as β -lactams, cephalosporins, penicillins or quinolones), (iii) their mode of action (MOA) e.g. anti-metabolites or alkylating agents within the group of cytotoxics/anti-neoplastics.

On the other hand, it is crucial to consider that a pharmaceutical product can undergo structural transformation at several stages of its life, and can be the precursor of a number of by products that should be called metabolites when issued from human body metabolization and transformation products when resulting of environmental biotic and abiotic processes.

Consumption and use

There is a lot of variation in the practices and mode of consumption of pharmaceuticals from country to country. For example, data from France reflect the total amount consumed including those quantities sold without prescription - freely over the counter (OTC-drugs), while the consumption data from Germany, Poland, Spain and the UK (England and Wales) do not include OTC-drugs. Consequently, it is very difficult to obtain representative data about the worldwide use of pharmaceuticals.

The source of emission of human PPs in the environment varies, but the consensus view is that emission from the pharmaceutical industry is considered to be negligible especially in Europe and the North America (in Asian countries concentrations discharged for single compounds can be up to several mg L^{-1}). On the contrary, excretion by patient in private household has been found to be the most important source of discharge in the environment either by excretion or bad management of unused and expired medicines.

Occurrence and Fate in the Environment

Studies describe the occurrence of pharmaceutical products in all aquatic environments (Waste, Surface, Ground, Drinking Waters) although wastewater and surface water have received most investigation.

All pharmaceutical classes have been studied. More than 45000 records have been identified dealing about 200 molecules (notice that more than 4000 active pharmaceutical ingredients sold all around Europe). It is notable that one third of these records concerned only 10 molecules (diclofenac, carbamazepine, clofibrac acid, ibuprofen, bezafibrate, sulfamethoxazole, trimethoprim, phenazon, ketoprofen, roxithromycin).

The concentrations in surface waters and STPs effluents are in the ng/L to $\mu\text{g/L}$ range. Less information is available for the concentration in drinking water and marine water (only 2% of the investigations).

On the other hand, little information is available concerning occurrence, fate or activity of metabolites and transformation products.

The behaviour of PPs in wastewater treatment plants is very dependent on the properties of the compound, and the applied treatment process: the removal efficiency of conventional biological processes can vary from 0 to 100%. Advanced treatment processes (adsorption, ultrafiltration, ozonation ...) are proposed to improve the elimination rate of some PPs.

If resistant to STP treatment, PPs enter surface waters, they will be able to undergo photodegradation, sorption, or biodegradation. Little is known about the distribution of PPs between the liquid and solid (sludge) phase in the STP and in the environment (sediments).

Effects/impact

Literature is not very abundant on the effect and/or impact of PPs on aquatic or terrestrial organisms. The majority of the data show that acute effects on adults' aquatic organisms are not expected occur especially at the current environmental concentrations. Indeed, for most of the investigated PPs, the chronic LOEC is higher than the maximal concentrations found in STP effluents (environmental concentrations are more than 10000 times lower than the therapeutic doses).

On the other hand, most of the ecotoxicity studies have been used to assess acute toxicity and then most of the data on chronic exposure is still missing. This is an important data gap in order to understand the behaviour of PPs in the environment (bioaccumulation, bioconcentration, ...) both for parent molecules and metabolites or transformation products.

Finally, most impact investigations have been based on single compounds whereas mixtures (of all micropollutants, not only PPs) have been shown to cause different effects than single compounds alone.

Regulation

Micropollutants are often managed by the regulation, especially in term of surveillance and control in different water bodies. Pharmaceutical products are currently not specifically controlled in these regulations at the European scale. The Water Framework Directive (key directive for surface water), Drinking Water & Groundwater Directives do not include PPs as priority substances to control. Also, in the Urban Wastewater Treatment Directive (end-of-pipe), PP removal is not required and the Sewage Sludge Directive does not define limits set for PPs in urban sludge.