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Pharmaceuticals in the environment

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Pharmaceuticals gather more than 1000 biologically active molecules used in human and veterinary medicine around the world. The increase in drugs consumption and the development of improved analytical environmental techniques have resulted in identifying these emerging pollutants in all aquatic compartments, ranging from surface water and groundwater ressources to the marine environment. Numerous investigations have indicated that a hundred of pharmaceuticals and their metabolites are frequently detected in the aquatic environment, at international level, at concentrations ranging from ng/l to µg/l. The concentrations even surpass the mg/l level in sewage treatment effluents. Once there, they may be responsible for chronic poisoning of aquatic species due to their still effective biological activity. The European authorities have considered this hazard for years, leading to investigations only for new pharmaceuticals entering the market and when the predicted exposure concentration is greater than 100 ng/l.

So, despite the work provided on some of these substances, many of progress remains to be made because our knowledge is still limited on the occurrence, distribution pathways and ecotoxicological potential of most of pharmaceuticals in the environment.

The special issue addresses studies targeting the occurrence, fate and transport of pharmaceuticals and their degradation products in the environment, including chemical analysis and methods development, and the characterization of their effects on aquatic organisms. A particular attention is paid in this special issue of ESPR to marine ecosystems.

Contamination of marine ecosystems by pharmaceuticals begins to be known, despite the number of journal papers devoted to describing this contamination remains relatively small at the moment. If few studies have been conducted in the marine environment, the reasons are mainly due to the very low concentration of pharmaceuticals controlled by dilution and diffusion processes, and to the complex hydrodynamics of the marine environment. Arpin-Pont et al. propose an examination of papers focused on analyzing and describing the contamination of coastal and marine waters, by studying a total of 111 papers concerning 196 pharmaceuticals and 37 personal care products reported from more than 50 marine sites. An interesting selection of the analyzed data was conducted considering their analytical quality, which allowed providing levels of the most frequently found molecules, leading to different pharmaceutical classes: antibiotics, Non-steroidal antiinflammatory drugs (NSAIDs), central nervous system drugs, analgesics, analeptics and illicit drugs, as well as personal care products, in both marine water and sediment. Point source pollution such as sewage treatment plant (STP) outfalls or estuaries impacts the surrounding area, with concentrations most often found to decrease with increasing distance from the pollution source. Salicylic acid, acetaminophen or venlafaxine accumulate in marine bivalves, suggesting that a particular interest may be payed to undesirable effects of these substances in marine organisms.

A study of one of these point source sites is provided by Martinez-Bueno et al., in the vicinity of a STP outfall. A persistent pharmaceutical, the antiepileptic carbamazepine (CBZ), and its main human metabolites have been analyzed during a year using Polar Organic Chemical Integrative Sampling (POCIS) as sampling tool, calibrated for marine waters. POCIS allowed the detection of CBZ in every sampling point, some of its researched metabolites and also different other non-target compounds as β-Blockers and analgesics. Target analysis proves to be very useful in investigating the dynamics of pharmaceuticals in the marine environment where concentrations are most often in the low ng/L

range. Combination with multi-residue analysis provide a wider view of this subtle contamination represented by pharmaceuticals.

Some pharmaceuticals are conceived to activate hormonal receptors in wildlife. This concerns hormones currently used in hormonal therapy (i.e. estrogen /progesterone treatments used to reduce or eliminate symptoms of menopause, or in hormonal contraception). However, other substances of diverse origins present in the aquatic environment are also able to activate hormonal receptors. The diversity of these multiple substances biologically active, combined with the fact that a part of the substances that can activate a receptor are not known, renders extremely difficult to identify relevant substances for monitoring or implement management actions of aquatic ecosystems. Several tools have been developed to selectively separate the active substances in complex environmental matrices using nuclear receptor columns (Creusot et al., 2013; Pillon et al., 2005). A new application of these tools is presented by Jondeau-Cabaton et al. , allowing the identification of the structure of known, as well as unknown, nuclear receptor (NR) ligands present in complex matrices. Bisphenol A and octylphenol, two recognized estrogenic compounds, were then isolated from sediments together with two unexpected ERα ligands, n-butylparaben and hydroxyl-methylbenzofuranone, demonstrating the interest of pursuing the development of such applications for a better characterization of hazardous substances in the aquatic environment.

However, there are still gaps in our knowledge on the effects of this compounds in the environment. The most available ecotoxicological data mainly focused on about 15 molecules, such Paracetamol(analgesic) , Ibuprofen and diclofenac (nonsteroidal anti-inflammatory drugs) or fluoxetine (antidepressant). Many of the other drug classes are still poorly studied.

A study of the effect of large panel of molecules (48 pharmaceutical compounds) belonging to 16 therapeutic classes is provided by Minguez et al. They focused on pharmaceuticals whose predicted environmental concentration exceed 10 ng/l. The danger represented by acute exposure to these molecules was assessed on freshwater species conventionally used in regulations (*Daphnia magna* and *Pseudokirchneriella subcapitata*) and on two marine organisms, i.e., the crustacean *Artemia salina* and the diatom *Skeletonema marinoi*. Some compounds displayed strong toxicities at very low concentration. Comparison between measured environmental concentrations (MEC) in the Normandy (France) and the derivate predicted no effect concentration allowed to calculate a risk quotient (MEC/PNEC). Results showed that antibiotics, antidepressants and antifungals could present high or median ecotoxicological risks on marine and freshwater organism. They also highlight the highest sensibility of marine organisms.

A recognized difficulty in the field of ecotoxicology is to evaluate the impact of pollutants as a result of chronic exposure. This could explain the much reduced number of studies in this domain.

In this special issue, two papers dealt with the effects of an antidepressant: the fluoxetin, on two marine organisms with commercial significance: oysters and cuttlefishes. Fluoxetin acts by blockade of the presynaptic membrane serotonin transporter, thereby increasing serotonin levels. As a neurotransmitter and neurohormone, serotonin is involved in a wide variety of behaviors and physiological functions. One of the highlights of these two publications is the evidence of the bioconcentration capacity of fluoxetine, whereas only few effects were observed.

Bidel et al. process on the impact of prenatal cuttlefish exposure to fluoxetine on neurochemical, neurodevelopmental, behavioral and immunological levels. At the behavioral level, few effects have

been highlighted. However, at the molecular or cell levels, the effects on dopaminergic transmission were observed as well as cell proliferation in the structures involved in cognition and visual process. In the long term, these alterations observed during a critical period of development may impair complex behaviors of the juvenile cuttlefish and thus lead to decrease in their survival. A battery of biomarkers from cellular level to organism at whole was studied on oyster larvae after a long term exposition to environmental or top concentrations (1, 100, 10.000 ng/l) (Di poi et al). At these concentrations, no or only few effect was observed on the battery of biomarkers used. Authors points the difference of their results with those of litterature and highlight the difficulty to predict accurate effect on aquatic organism for highly metabolisable substances.

As noted above, pharmaceuticals occurs in the environment mixed together and with other multiple contaminants. The effects of mixtures is one of the critical points where it remains extremely difficult to provide evidence at environmental concentrations and for which results are expected. The study of Cachot et al deals with the effects of several psychotropics drugs, both alone or in mixture, on fish early life stages. Most of these drugs impacted the behaviour of Japanese medaka larvae at concentrations ranging from 10 to 10.000 µg/l. In mixture, the locomotor activity of Japanese medaka larvae was altered at concentrations a hundred times above environmental concentrations in rivers. A most realistic mixture of pharmaceuticals, a hospital wastewater has been studied by Bebianno et al. The approach used by Bebiano et al. to assess the effects of this mixture in aquatic organisms is proteomics, a holistic approach including most of the pathways that can inflicted and that could be useful to identify relevant new biomarkers. The selected organism, the invader clam Corbicula fluminea, is of great interest due to its large distribution in rivers, lakes, estuaries, and in fresh and marine waters. The exposure to the mixture present in the psychiatric hospital resulted in large variety of down regulations and upregulations that varied with the time of exposure. Multiple changes of structural and cellular proteins function was observed, emphasizing the importance of studies that combine broad spectrum techniques in the study of the effects and exposure conditions approaching environmental conditions.

Keeping in mind the bioconcentration phenomena, the few knowledge on mixtures toxicity, the biotic or abiotic tranformation processes, among other multiple questions, the research effort on pharmaceuticals in the environment should be pursued.

MP Halm received a PhD degree in neuroethologi from University of Caen (France). After a postdoctorate in the field of ecotoxicology, she obtained a assistant professor position at the University of Pharmacy of Caen in 2007. Part of her research has focused on the health of the bee. Currently, she develops a thematic in the field of the ecotoxicological impact of emerging pollutants with respect to aquatic species, with a regulatory aspect. In particular, she has been responsible of a project to assess the impact of drug residues on marine and freshwater species. She just joined the French Research Institute for Exploitation of the Sea (IFREMER).

E Gomez studies organic contaminants in the aquatic environment. She received a PhD degree in environmental sciences from the University of Montpellier (France) where she is currently full professor and head of the research group 'Emerging contaminants' at the 'Hydrosciences' laboratory. Her research theme "Risk assessment of chemical contaminants in aquatic environments: characterization of exposure" focused on study of the distribution of organic contaminants (endocrine disrupters, pharmaceuticals and personal care products residues and their transformation products) and on bioavailability and bioaccumulation of those substances. Se combined *in situ* studies and experimentation in laboratory.

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