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An international conference on “Pharmaceutical products in the environment: Is there a problem?” in the framework of the EU PHARMAS Project

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Is there really a problem with the presence of Pharmaceutical Products (PPs) in the environment? This is one of the main questions the scientific community has been trying to answer in recent years.

In spite of the exponentially – increasing number of scientific papers, national and international reports, workshops and conferences, there remains a need for discussions and debates aimed at identifying the key issues to be addressed in order to better understand and manage the risks of PPs in the environment for both humans and wildlife.

In terms of risk to human health, there is a tendency to consider it to be negligible (WHO, 2012), given that drinking water is the main source of exposure and that PP concentration in water is between a million-fold and a billion-fold below the level of therapeutic doses. But what about other sources of exposure (food, fish, soil, etc.)? On the contrary to risk for humans, environmental risk is admitted to, with some effects bring described in the literature – such as fish feminization (Kidd et al., 2007, Pérez et al., 2012, Yan et al., 2012), bird decline (Oaks et al., 2004), genotoxic effects on wildlife (Rocco et al., 2010, Rocco et al., 2012) and fish behavior modification (Brodin et al., 2013, Olsén et al., 2014) – even though a recent study investigating more than 50 active ingredients showed that for 95% of them, environmental risk is not significant (Roos et al., 2012).

Uncertainty is thus a reality, in terms of both human and ecological risk assessment, due in particular to the limited number of studies (especially for human health) on the one hand, and to the lack of certain data required for robust risk calculation on the other. A workshop organized as part of the PHARMAS EU project recently attempted to identify, prioritize and quantify the main sources of these uncertainties by distinguishing between model uncertainties, fundamental uncertainties or non-quantifiable uncertainties. Expert discussions have established a list of 100 questions, classifying the 20 most important ones into several categories such as prioritization of substances, pathways of exposure, bioavailability and uptake, effects characterization, risk and relative risk, and risk management (Boxall et al., 2012).

Within this context, an international conference entitled “Pharmaceuticals in the Environment: is there a problem?” was held in the framework of the PHARMAS Cluster (www.pharmas-

eu.org). This conference, organized in Nimes, France by the LERES Biodiagnostic Unit of the French School of Public Health (EHESP) on June 3–4th 2013, aimed to bring answers to influence areas of risk assessment, water management and pharmaceutical production as well as regulatory affairs and public perception – not just in terms of human and wildlife health, but also from a regulatory and social perspective.

More than a hundred participants, from research institutes, sanitary agencies, water companies, academic research groups, the pharmaceutical industry, and other organisations attended the three oral sessions completed by a poster exhibition. In the course of the 2-day conference, 50 communications were presented, offering new information and data on European-level actions, environmental and human risk assessment of pharmaceuticals, perspectives on problem assessment and future actions.

This Special Issue of Chemosphere brings together selected papers presented at this event (the whole proceedings are available upon request to the corresponding author) and deals with risk assessment and management, including toxicity and hazard characterization, fate and behavior of parent molecule and transformation products. Papers in this special issue also serve to increase our knowledge and understanding regarding the difficult identification and quantification of the potential risk PPs represent for humans and the environment.

Nowadays, more than 3000 active ingredients are used all around the word in the civil pharmacopeia. However only around 15% of these have been researched and ultimately described as contaminating our environment. 5% of these seem to potentially put human health or wildlife at risk. Since it is not possible, to date, to characterize all substances, prioritization works have been undertaken in order to identify the main compounds of interest. Several approaches have been published (Besse and Garric, 2008, De Voogt et al., 2009, Diamond et al., 2011, Roos et al., 2012), based on different criteria (consumption, usage, PNEC, excretion, etc.) leading to diverse lists of substances. Caldwell et al. propose a critical view of several of these approaches, highlighting their limitations and incorporating various elements aimed at reducing the uncertainties linked to the current approaches.

The main source of these pharmaceuticals in the environment has long since been attributed to patient consumption followed by excretion to the urban sewage network and finally release to environment compartments via wastewater treatment plants (Roig, 2010). Occurrence in the environment has often been estimated by modeling such a pathway. The corresponding Predicted Environmental Concentration (PEC) has been shown in various studies as non equal to the real amount present in the environment (Castiglioni et al., 2004, Bound and Voulvoulis, 2006, Coetsier et al., 2009). Data required for PEC calculation, poor consideration of other sources of contamination and of how PPs travel are probably some of the missing parameters explaining the difference between PEC and MEC (Measured Environmental Concentrations). In their paper, Lenczewski et al. focus on the behavior of PPs on a column experiment modeling sandy aquifer. The resulting small elimination of the targeted substances under these specific conditions illustrates water quality vulnerability due to the nature of the aquifer. Other sources of PPs have also been addressed in the articles by Sanchez et al. and Orias et al., in which they studied the influence of industrial manufacture and hospital effluents on the general wastewater network, concluding that there is a need for further consideration of such potentially important sources with regard to toxicity and ecotoxicity.

Risk assessment is generally based on exposure and hazard levels of active ingredients (mother molecules). Human metabolites and Transformation Products (TPs) resulting from

natural degradation or water treatments have been little studied in terms of either occurrence or impact. These by-products are increasingly of interest, given that additional treatments are implemented to eliminate PP traces. Indeed, the tendency is to add tertiary processes – such as advanced oxidation – at wastewater treatment plants in order to obtain total elimination and mineralization. In many cases, the results are not those expected and, what is worse, lead to the production of oxidized and chlorinated by-products, potentially more stable and more toxic than their parent products (Fatta-Kassinos et al., 2011). But, although a great deal of improvement has been recorded in the detection of parent molecules over the past decade, few transformation products have been chemically and biologically characterized. In this special issue, Kummerer et al. give an example of such work by describing the production of stable ciprofloxacine's TPs obtained after photodegradation, which maintain biological antimicrobial activity.

Hazard of active ingredients is also under discussion because it appears that methods currently employed for toxicity evaluation are more or less adapted to the mode of action and sensitivity of tested biological targets (Ankley et al., 2007, Brooks et al., 2009). Works on new toxicity end points, new in vivo models or computer modeling have been proposed recently (Ortiz de García et al., 2013, Parolini et al., 2013, Scholz et al., 2013). In this special issue, examples of recent works on the genotoxicity and cytotoxicity of anti-cancer drugs and antibiotics are described. Knasmuller et al. study the genotoxicity and acute toxicity of one of the most cytostatic used in developed countries (imatinib) using different plant species, and demonstrate a non-acute effect at environmental concentrations. Isidori et al. investigate the acute and chronic toxicity of a list of anti-cancer drugs showing an acute effect at high concentrations but a potentially chronic impact at the lowest levels (environmental concentrations). In another work, Dallabona et al. consider antibiotics in discussing the sensitivity of *daphnia magna* (a model used in classically environmental risk assessment in comparison with those of another microcrustacean, *daphnia curvirostris* and conclude on the influence of the model sensitivity in hazard determination. They also take a look at the effects of mixtures, concluding that concentration addition is usually the worst case of estimation of a whole biological effect.

All these papers illustrate some of the limitations of current methodology in ecological and human risk assessment linked to the presence of pharmaceutical products in the environment. They highlight the need for other works to improve the quality of risk assessment data. Yet pharmaceutical products are not the only contaminants in our environment, and in the final paper of this special issue, Taylor et al. discuss the relevance to study pharmaceutical products as a particular group of micropollutants.

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