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Ecological risk assessment of the presence of pharmaceutical residues in a French national water survey

Camille Bouissou-Schurtz [a], Paul Houeto [a,*], Michel Guerbet [b,c], Morgane Bachelot [e], Claude Casellas [d], Anne-Cécile Mauclaire [a], Pascale Panetier [e], Cécile Delval [a], Dominique Masset [a]

[a] Agence Nationale de Sécurité du Médicament (ANSM), 143/147 Boulevard Anatole France, 93285 Saint-Denis, France
[b] ABTE EA 4651, Université de Rouen, 22 Boulevard Gambetta, 76183 Rouen, France
[c] UFR Médecine Pharmacie, Université de Rouen, 22 Boulevard Gambetta, 76183 Rouen, France
[d] Hydrosciences Montpellier UMR 5569, Faculté de Pharmacie, Université Montpellier 1, Avenue Charles Flahault, 34093 Montpellier Cedex 05, France
[e] Agence Nationale de Sécurité Sanitaire (ANSES), 27/31 Avenue du Général Leclerc, F-94701 Maisons-Alfort Cedex, France

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ABSTRACT

In this study, we focused on the list of 33 chemicals that was established through a French national prioritisation strategy. Assessing the potential risks to the environment was a step-wise procedure: (i) we determined the Predicted Environmental Concentration (PEC) of all molecules measured in the national survey based on the highest recommended dose used, (ii) we used the Measured Environmental Concentration (MEC) and the Predicted No-Effect Concentration (PNEC) to establish the Risk Quotient (RQ) based on either a PEC/PNEC (estimated risk) or MEC/PNEC (real risk) ratio. The risk assessment was performed using a binary ecological classification suggesting that appreciable risk is likely ($RQ \geqslant 1$). Of the 15 molecules quantified in the survey, 12 had a PEC higher than the action limit value of 0.01 µg/L. According to the EU Guideline, environmental risk was estimated as likely for the following five compounds: acetaminophen (RQ = 1.6), ibuprofen (RQ = 600), diclofenac (RQ = 15), oxazepam (RQ = 2.1) and carbamazepine (RQ = 3.2). Only ibuprofen was identified as posing real environmental risk based on its MEC (RQ = 1.9).

1. Introduction

As a result of increasingly frequent medical prescriptions and medication consumption, pharmaceuticals and their metabolites have been detected in all environmental compartments (Halling-Sørensen et al., 1998; Kummerer, 2004). This ubiquitous environmental contamination has been demonstrated worldwide with a wide range of drugs (e.g., antibiotics, antidepressants...) found in WasteWater Treatment Plant (WWTP) effluents and surface water at low concentrations, ranging from µg to ng/L. The improved performance of analytical tools has led to better descriptions of the presence of such compounds in the influents and effluents of WWTPs, in the aquatic environment and in water resources (WRs). These molecules are characterised by considerably diverse chemical structures. More than 3000 human-use and 300 veterinary-use drug substances are currently available on the French market. The concentration levels of these molecules vary depending on their chemical stability, biodegradability, physicochemical characteristics and effectiveness of WWTP treatment and particulate filtration.

Pharmaceutical compounds present in WRs can be biologically degraded in WWTPs, and subsequently appear in surface water or be picked up by sludge. Sludge can be used as fertiliser in agriculture, so substances can penetrate into the soil and reach groundwater sources. The degradation of such compounds in complex matrices, like soil, is poorly studied. Pharmaceutical analyses are relatively recent, and data on the environmental fate, behaviour and ecological effects of pharmaceuticals are urgently needed. This situation has led to increased concern and more studies on issues such as environmental species toxicity, microbial ecology disturbances and antibiotic resistance. Current WWTP processes are designed to reduce levels of dissolved organic carbon, as well as nitrates and phosphates at times, but not pharmaceuticals. WWTPs can only remove 10% of carbamazepine, an anticonvulsant and mood stabilizer, but can remove 85% of triclosan, an antibacterial and antifungal agent through biotic or abiotic processes (Andreozzi et al., 2002). Abiotic environmental factors (e.g., temperature, soil composition, amount, intensity and wavelength of sunlight, salinity and pH) significantly transform substances in

* Corresponding author. Fax: +33 (0)1 55 87 35 82.
E-mail address: paul.houeto@ansm.sante.fr (P. Houeto).

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the environment via photolysis or hydrolysis. Biotic factors (bacteria, fungi) are the living parts of the ecosystem with which pharmaceuticals may interact. Biodegradation is also an important process to be considered in the environment.

We are faced with a problem: the risk associated with these low concentrations of drug residues in surface water is uncertain for ecological species. Performing a full ecological risk assessment of pharmaceuticals is difficult because of the paucity of data on exposure scenarios, target aquatic species and dose–response relationships. Such a widespread occurrence clearly begs the question of whether or not environmentally realistic concentrations of pharmaceuticals pose a risk for environmentally exposed biota. Recent EU pharmacovigilance legislation acknowledges that the pollution of waters and soils with pharmaceutical residues is an emerging environmental issue.

The aim of this study was to evaluate the potential environmental impact of pharmaceuticals according to the current European Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use (EMA, 2006). In addition to this research, a preventive environmental approach should be examined. Ecological risk is determined by the ratio between the Predicted Environmental Concentration (PEC) or Measured Environmental Concentration (MEC) and the Predicted No-Effect Concentration (PNEC) of the compounds determined during the national survey. Hence, a tailored risk assessment strategy should be followed by an evaluation of the PNEC based on relevant ecological testing in order to define the PEC/PNEC or MEC/PNEC ratio and identify ecotoxicity. We focused on the list of chemicals established through a national prioritisation survey of pharmaceuticals in drinking water. In addition, this study discusses the benefits and limitations of this risk assessment approach as applied to the individual compounds.

2. French national survey

The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) performed a national survey on drug residues in WRs to evaluate their presence in water. Thirty-three (33) molecules in several chemical and therapeutic classes chosen according to discriminant criteria such as tonnage, solubility and activity were tested using a multi-residue method (LC–MSMS). The national survey was conducted from October 2009 to June 2010. In collaboration with regional agencies, 238 sites were selected and 280 samples taken from all over France were analysed (ANSES, 2011).

3. Ecological risk assessment method

3.1. Risk assessment strategy according to the European Guideline on the Environmental

Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) according to the EMA Guideline for the evaluation of environmental for medicinal products for human use (EMA, 2006), the potential risks to the environment is evaluated in a step-wise procedure involving two phases. The first phase (Phase I) estimates the exposure of the environment to the drug substance. In phase I, an assessment of the ability of drugs to move beyond the aquatic environment and bioaccumulate is requested. The *n*-octanol/water partition coefficient indicates the transfer of a drug substance from the aquatic environment into organisms and its potential to bioaccumulate ($\mathrm{Log}\,K_{OW} > 4.5$). Then, a specific risk assessment should be conducted in a step-wise fashion for Persistence, Bioaccumulation and Toxicity (PBT index).

The PEC, which reflects the exposure of the environment to a drug, is calculated in surface water according the formula $PEC_{surfacewater} = (DOSEai \times Fpen)/(WASTEWinhab \times DILUTION)$ where WASTEWinhab is the amount of wastewater per inhabitant per day, Fpen is the percentage of market penetration and DOSEai is the maximum daily dose consumed per inhabitant (or per patient). If the PEC value is below 0.01 μg/L and no other environmental concerns are apparent, it is assumed that the medicinal product is unlikely to represent a risk for the environment if used as prescribed in patients. So, based on an action limit, the assessment may be terminated at this level. In contrast, if the PEC is equal to or greater than 0.01 μg/L, a phase II environmental fate and effect analysis should be performed. Certain substances, such as highly lipophilic compounds and potential endocrine disruptors, may need to be addressed during phase II irrespective of the quantity released into the environment.

In the second phase (phase II), information about the fate and effects of a medicinal product in the environment is obtained and assessed. The recommended phase II assessment is conducted through an evaluation of the PNEC, which is calculated by applying an assessment factor (AF) to the NOEC values from relevant studies. Thus, a tailored risk assessment should be followed by a determination of the PEC/PNEC or MEC/PNEC. Also, in this phase, all relevant data such as physicochemical properties, toxicology, metabolism and excretion, degradability and persistence are taken into account. If the *n*-octanol/water partition coefficient indicates the transfer of the drug substance from the aquatic environment into organisms and a potential to bioaccumulate ($\mathrm{Log}\,K_{OW} > 3$ in phase II), then the PBT index should be considered. The absorption behaviour of substances in sewage sludge is described through the adsorption coefficient (K_{OC}), which is defined as the ratio between the concentration of the substance in sewage sludge's organic carbon and the concentration of the substance in the aqueous phase at adsorption equilibrium. It is assumed that a substance with a high K_{OC} value is retained in the WWTP and may reach the terrestrial compartment through the spreading of sewage sludge over land. If the K_{OC} is higher than 10,000 L/kg, an environmental assessment of the drug substance in the terrestrial compartment should be conducted, unless the substance is readily biodegradable. The terrestrial risk assessment complements the aquatic risk assessment, but does not replace it.

3.2. Ecotoxicity concern evaluation

Firstly, we decided to determine the PEC of molecules quantified in the national survey (excluding caffeine and two metabolites; epoxycarbamazepine and hydroxyibuprofen) according to the European Guideline (EMA, 2006). The calculation of the PEC was based upon the highest recommended dose used for a product. Secondly, we used the MEC found in the context of the national survey in order to compare it to the calculated PEC values. Finally, concerning the ecotoxicity, we opted to search the available PNEC values from the literature to establish the Risk Quotient (RQ) based on either a PEC/PNEC (estimated risk) or MEC/PNEC (real risk) ratio. When the PNEC value was not available in the literature at all, we used the NOEC from chronological studies standardised using an assessment factor (AF). This AF is an expression of the degree of uncertainty in the extrapolation of the test data to a limited number of species in the actual environment. This analysis helps predict the concentration of a substance for which adverse effects are not expected to occur. There is potential risk to the environment when the RQ is >1. It is important to note that PEC/PNEC represents a theoretical or estimated RQ based on calculated exposure, in contrast with the MEC/PNEC ratio, which is considered a real risk based on exposure measured during this national survey. According to the European Guideline (EMA, 2006), the risk