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Active Pharmaceutical Ingredients in Aqueous Matrices: an integrated approach for assessing effects

ABSTRACT

The occurrence of active pharmaceutical ingredients (APIs) in the environment, due to their incomplete removal at the sewage treatment plants (STPs), has been welldocumented since the mid-1990s. The possible adverse effects to unintentionally exposed organisms preoccupy, nowadays, the scientific community. Since a broad range of APIs is used and consequently released into the environment and each API is subjected to continuous biotic and abiotic transformation, APIs are present in the environment as multi-component mixtures. This dissertation is among the first research efforts to investigate the effects of multi-component mixtures of APIs to biological systems. In the framework of this study a battery assay was developed for the investigation of acute toxicity, chronic toxicity, genotoxicity, biodegradability and estrogenicity. Ten different bioassays using organisms from the trophic levels of producers, consumers and decomposers were evaluated. Namely, the bioassays were the Pseudokirchneriella subcapitata and Lepidium sativum chronic toxicity tests, the Daphnia magna and Artemia salina acute toxicity tests, the Cytokinesis-block micronucleus cytome genotoxicity test, the Vibrio fischeri acute and chronic toxicity tests, the Pseudomonas putida chronic toxicity test, the Closed Bottle biodegradability test and the yeast estrogen screen. Three underlining objectives were set to fulfill the purpose of this dissertation. The first was to investigate the effects of wastewater to the battery assay. Physicochemical parameters were monitored in parallel. The weak correlations between the physicochemical parameters and the results obtained from the assessment of the effects indicate that the “traditional” parameters are not sufficient to explain the toxicity observed mainly during summer periods. A hazard classification identified freshwater microorganisms to be the most affected. A clustering approach demonstrated that the quality of the wastewater of each STP is different due to significant difference between the values of the physicochemical parameters investigated. The second objective was to assess the effects of APIs. Eight APIs were investigated namely, atenolol, metoprolol, propranolol, diclofenac, ibuprofen, erythromycin, ofloxacin and sulfamethoxazole. These APIs were selected due to their occurrence at higher concentrations in wastewater of Cyprus. The APIs were assessed as single compounds and in various combinations using selected bioassays from the battery assay. A risk characterization approach identified propranolol and ofloxacin as having significant risk for algae and bacteria, respectively. The Chou-Talalay method was applied to quantify the predominantly antagonistic effects of mixtures. No acute effects were found from the exposure to the investigated mixtures of APIs. Wastewater was found to decrease the toxicity of the APIs, suggesting that in a multicomponent mixture, both stimulating and inhibiting substances, co-exist and potentially interact. The third objective was to increase our understanding on the effects of transformation products of APIs. The photolytic and photocatalytic treatment of photolabile APIs, like ofloxacin, may result to a reduction of the concentration of the parent compound and, at the same time, to the formation of oxidation by-products, with different characteristics. These transformation products

were identified through advanced chromatographic analysis. During the treatment applied, the by-products formed led to a decrease of the chronic toxicity and an increase of the genotoxicity. The biodegradation of the by-products formed was very low and improved in the presence of sodium acetate, probably due to a co-metabolic process, which is well worth investigating in future studies. To conclude, it is hoped that this research will provide assistance to governmental departments and other organizations dealing with pharmaceuticals in the environment.