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EXPERIMENTAL AND PREDICTED TOXICITY OF BINARY COMBINATIONS OF DICLOFENAC SODIUM, CARBAMAZEPINE AND CAFFEINE TO *Aliivibrio fischeri*

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Abstract

In this study, the toxic effects of binary mixtures of Pharmaceutical Active Compounds (PhACs) that are observed in the effluents from a wide range sewage treatment plants and surface water bodies were investigated using the bioluminescent bacterium *Aliivibrio fischeri* (Microtox® test). The selected chemicals were the nonsteroidal anti-inflammatory drug (NSAID) diclofenac sodium [DCF] and the anti-epileptic carbamazepine [CBZ]. In addition, caffeine [CFF], a psychoactive stimulant of the central nervous system, was also included in the study. Binary combinations were prepared at a predefined ratio that corresponded to the individual IC₅₀ values of the investigated compounds (equitoxic ratio). The experimental results were compared with those obtained using the two most frequently used predictive models in aquatic toxicology: the Concentration Addition (CA) and Independent Action (IA) models. The results indicated that both models predict the observed mixture toxicity of the DCF-CBZ and DCF-CFF mixtures quite well. However, in the case of CFF-CBZ, both models slightly overestimated the experimental results, suggesting the presence of a potential antagonistic effect. The application of the Combination Index (CI) method, which allows us to identify and quantify the nature of the interactions between the chemicals present in a mixture (synergistic, additive or antagonistic effects), confirmed the additive behaviour of the DCF-CBZ and DCF-CFF combinations and the slightly antagonistic effect observed for the binary mixture of CFF-CBZ.

Key words: *Aliivibrio fischeri*, combination index, concentration addition, human pharmaceuticals, mixture toxicity

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