

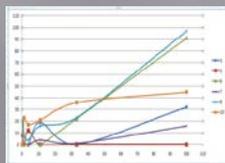
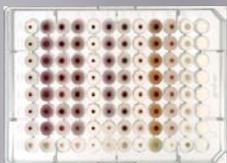
# ARE THE PHARMACEUTICAL INGREDIENTS HARMFUL FOR AQUATIC ECOSYSTEMS?

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## INTRODUCTION

The scientific researches have show that the pharmaceutical ingredients are frequently present in the environment aquatic component (surface water). For some pharmaceutical effects on aquatic organisms have been investigated in acute toxicity assays. The chronic toxicity and potential effects are least known. Whiting this context and according with REACH Regulation, the present work assessed the aquatic acute (LC<sub>50</sub> / EC<sub>50</sub>) and chronic toxicity (the maximum allowable concentrations in water - MATC) for the 4 most abundantly used human pharmaceuticals: diclophenac, ketoprophen, indometacin and carbamazepine. The toxicity biotests were conducted on fresh water fish (*Cyprinus carpio sp.* - a common species from Romanian surface waters) and crustacean (*Daphnia magna sp.*). To comply the OECD/ISO methodology, the testing procedure have followed the biological parameters: mortality, behavior and physiological modifications (for fish); immobilization and reproduction inhibition (for crustacean); inhibition and stimulation (for luminescent bacteria). Analytical control of test solutions concentrations was performed through HPLC-UV method - ECOIND methodology.



## METHODS

**ACUTE LETHAL TOXICITY BIOASSAYS** (Romanian standard SR 13126/1994 or OECD method-C01), determination of the mean lethal concentration which determine the death of half from the test organisms (fish *Cyprinus carpio*) - LC<sub>50</sub>

**DAPHTOXKIT F™** - acute toxicity test with the freshwater crustaceans *Daphnia magna* and *Daphnia pulex*, according to OECD 202 and ISO 6341:1996. Assays are based on immobility or mortality of the test organisms, with calculation of the EC50 or LC50.

**MICROTOX** - acute toxicity test with liquid-dried luminescent bacteria according to DIN EN ISO 11348-2. the measuring unit is the natural light output (luminescence) of the microorganisms *Vibrio fischeri*.

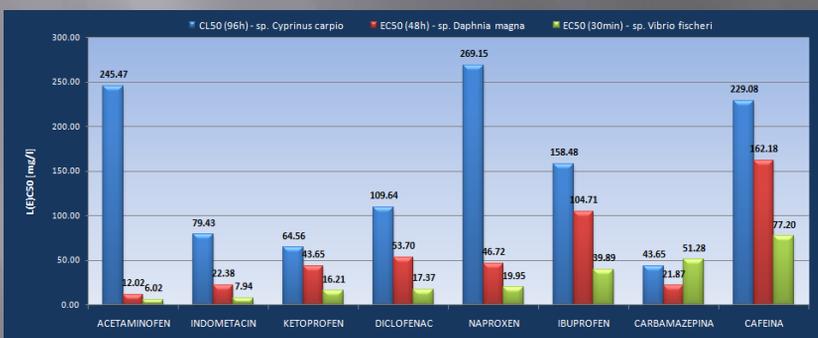
**MICROBIAL ASSAY FOR RISK ASSESSMENT (MARA)** - eukaryote bacteria) at toxic compounds, a multi-species toxicity test based on responses of the 11 microorganisms (prokaryotes and eukaryotes)

**CHRONIC TOXICITY TESTS** on *Cyprinus carpio* and *Daphnia magna* to establish the maximum allowable concentrations in water - MATC and NOEC (no observed effect concentration)

## RESULTS and CONCLUSIONS

According to EPA norms and National regulations for chemicals toxicity classification, the acute toxicity tests on fish have showed:

- The pharmaceutical chemicals acetaminophen, diclophenac, naproxen, ibuprophen and caffeine don't have any harm on aquatic organisms - fish *Cyprinus carpio sp.* The indometacin, ketoprophen and carbamazepine have a LC<sub>50</sub> (96h) <100mg/l - toxic for fish with possibility to induce long-term effect.
- All test farmaceutical chemicals may have a toxic effect on *Daphnia magna sp.*, except the ibuprophen and caffeine wich have a EC<sub>50</sub> (48h) >100mg/l.
- All farmaceutical chemicals test on *Vibrio fischeri sp.* inhibit the bacteria luminiscence and we consider that induce a toxic effect on these bacteria, except the carbamazepine and caffeine wich have a EC<sub>50</sub> (48h) >50mg/l.
- The carbamazepine and caffeine have a slow microbial toxicity show through MARA test (MTC 16h =>50 mg/l)



| Tested substance       | MATC [mg/l] | NOEC [mg/l] |
|------------------------|-------------|-------------|
| <i>Cyprinus carpio</i> |             |             |
| CARBAMAZEPINA          | 0,8         | 0,8         |
| KETOPROFEN             | 0,92        | -           |
| INDOMETACIN            | 0,85        | -           |
| DICLOFENAC             | 1,84        | 1,84        |
| <i>Daphnia magna</i>   |             |             |
| CARBAMAZEPINA          | -           | 0,89        |
| KETOPROFEN             | -           | 0,96        |
| INDOMETACIN            | -           | 0,43        |
| DICLOFENAC             | -           | 0,45        |

Chronic biotests were performed for diclophenac, ketoprophen, indometacin and carbamazepine, in concentration domain of 1 mg/l - 10 mg/l for 90 days in case of fish and 1-5 mg/l for 96h for crustacean. We observed that diclophenac don't have significant effects on juvenil fish and crustacean. The indometacin, ketoprophen and carbamazepine have a low toxicity on test organisms. Also were determined the NOEC (No Observed Effect Concentration) and LOEC (Lowest Observed Effect Concentration) in concentration values of 1-2 mg/l. These data are necessary to estimate their predicted no-effect concentrations (PNEC) which will be presented in a future paper.



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