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PREFACE

On behalf of the Scientific and Organizational Committee, it is my honor and great pleasure to present the Proceedings of the 3rd EUROSA International Conference, held on 14-17 May 2025 in Vrnjačka Banja, Serbia.

The papers contained in this Proceedings represent current scientific and professional informations in the field of *Engineering and Occupational Safety Management, Environmental Engineering and Management; Fire Protection Engineerig and Management, Engineering and Management of Disaster and Emerency Protection, Good use of practice in protection* and represent a mix of scientific research and professional opinion, shared with us by participants from academia and industry professionals.

We sincerely thank all the conference participants for their contribution, ensuring the success of the conference. Special thanks to all the participants of the round tables and panel discussions, keynote speakers, chairmen of the sessions and of course the reviewers for their invaluable contribution.

Last but not least, I would like to express my sincere gratitude to all members of the Scientific and Organizing Committee, whose efforts and work led to the successful realization of the EUROSA 2025 conference.

Vrnjačka Banja, May 2025

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CONTENTS

HEALTH PROFILE OF THE SELECTED PHARMACEUTICAL POLLUTANTS IN THE AQUATIC ENVIRONMENT

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Abstract: This article investigated whether pharmaceuticals such as Carbamazepine and 4-AAA (4-acetyl-amino-antipyrine) as water pollutants can cause health issues and toxicological risks. The OPERA models were used for detail characterization of pharmacokinetic profile and the SILIS-PTOXRA software was used to predict acute based toxicity on multiple linear regression models. The results indicate increased concentrations in the liver and organs of the fetus after consuming contaminated water. In addition, significant effects on aquatic organisms are also expected.

Keywords: *pharmaceutical pollutants; aquatic environment; health effect; ecopharmacovigilance*

INTRODUCTION

In recent years, pharmaceuticals, a significant group of emerging environmental contaminants, have garnered global attention. Their usage and consumption have been steadily increasing due to the development of new drugs, a growing population, and shifts in the age structure of the general population. For example, there are approximately 3,000 different pharmaceutically active compounds in the European Union (EU) that are approved for medical use and have been thoroughly examined for their safety and toxicology. However, the potential environmental impacts associated with their production and use are less understood and have recently attracted research interest (Petrović et al., 2014)

These pharmaceuticals are not managed properly and they can enter aquatic environments through discharging directly into drains. Their main route into the environment is through municipal wastewater, as only a small amount is metabolized after ingestion, while the majority is excreted unchanged or as metabolites that enter the sewage system. Consequently, the presence of pharmaceuticals in the environment raises numerous questions regarding their biological effects on flora, fauna, and humans. Overall, there is very limited knowledge about the long-term effects and behaviours of these pharmaceuticals.

The most frequently pharmaceuticals found in surface water are carbamazepine and metamizole metabolite 4-AAA (Radović et al., 2015). Metamizole is among the most popular analgesic and antipyretic drugs that have been used for more than 70 years and carbamazepine is widely

used as antiepileptic and is antidepressant drug and is known as a very persistent substance (Moldovan, 2006).
The aim of this manuscript was to estimate the pharmacokinetic profile of detected compounds also including vulnerable populations such as pregnant women, after consuming a contaminated water as well as to estimate their aquatic toxicity potential.

MATERIALS AND METHODS

Radovic et al. (2015) developed the method for determination of 25 different organic contaminants and investigated the presence of pharmaceuticals in aquatic environment (ground water, surface water and sediment in Serbia). 4-AAA and Carbamazepine were measured and the maximum concentrations were obtained in rivers Tisa and Morava, the Danube tributaries, at about 1 km before the confluence (Table 1).

Table 1. The detected concentrations of selected pharmaceutical pollutants in surface water (rivers Tisa and Morava) (Radović et al., 2015)

Pharmaceuticals	Surface waters (ng/l)
4-acetyl-amino-antipyrine (AAA)	512
Carbamazepine	94

The OPERA models as a part of the CompTox Chemistry Dashboard project (Żandarek et al., 2024) were used for more detail characterization of pharmacokinetic profile of carbamazepine and 4-AAA. The CompTox Chemistry Dashboard is a web-based application and the data hub was developed by EPA's National Centre for Computational Toxicology. In OPERA simulations for detected compounds, we applied solve_pbtk and solve_fetal_pbtk modeling.
OPERA models were used to estimate the physiologically-based pharmacokinetic profile of detected compounds in aquatic environment. The first simulation for plasma (Css) and tissue (Cmax) concentration was done by using the solve_pbtk modeling. The solve_pbtk is a multiple-compartment PBPK model from EPA's httk R package (v. 2.2.2) that includes gut, artery, vein, lung, liver, kidney, and rest-of-body compartments. For the detected compounds, the following conditions of solve_pbtk modeling were applied: human (70 kg), exposure dose was estimated concentration per liter of water intake, exposure route oral, exposure interval hours (24 h), simulation length days 3. The second simulation for plasma (Css) and tissue (Cmax) concentration was done by using the solve_fetal_pbtk modeling type. The solve_fetal_pbtk is a multiple-compartment human PBPK model from EPA's httk R package (v 2.2.2) that includes maternal compartments, fetal compartments, and a placenta modeled as a joint organ shared by mother and fetus. The model is for simulating maternal and fetal chemical distribution for exposure via the oral or intravenous injection route starting at 91–280 days gestation. The solve_fetal_pbtk model is design only for human. For the cefepime-related compounds, the following conditions of solve_fetal_pbtk modeling were applied: human (70 kg), exposure dose was estimated concentration per liter of water intake, exposure route oral,

exposure interval hours (24 h), simulation length days 3, gestational day when exposure start (91).
Toxic Hazard and Risk Assessment, is a freely available software developed for the prediction (Żandarek et al., 2025) of toxicological endpoints. In our analysis, we used the SILIS-PTOXRA software to predict acute based toxicity on multiple linear regression models. The following ecotoxicological endpoints were observed:

• Acute Toxicity towards Zebrafish Embryo. Regression model to predict acute toxicity (pLC50) time toward zebrafish embryo.

• Acute Toxicity towards Freshwater Crustacean *Thamnocephalus platyurus*. Regression model to predict acute toxicity towards Freshwater Crustacean *Thamnocephalus platyurus* (*T. platyurus*).

RESULTS AND DISCUSSION

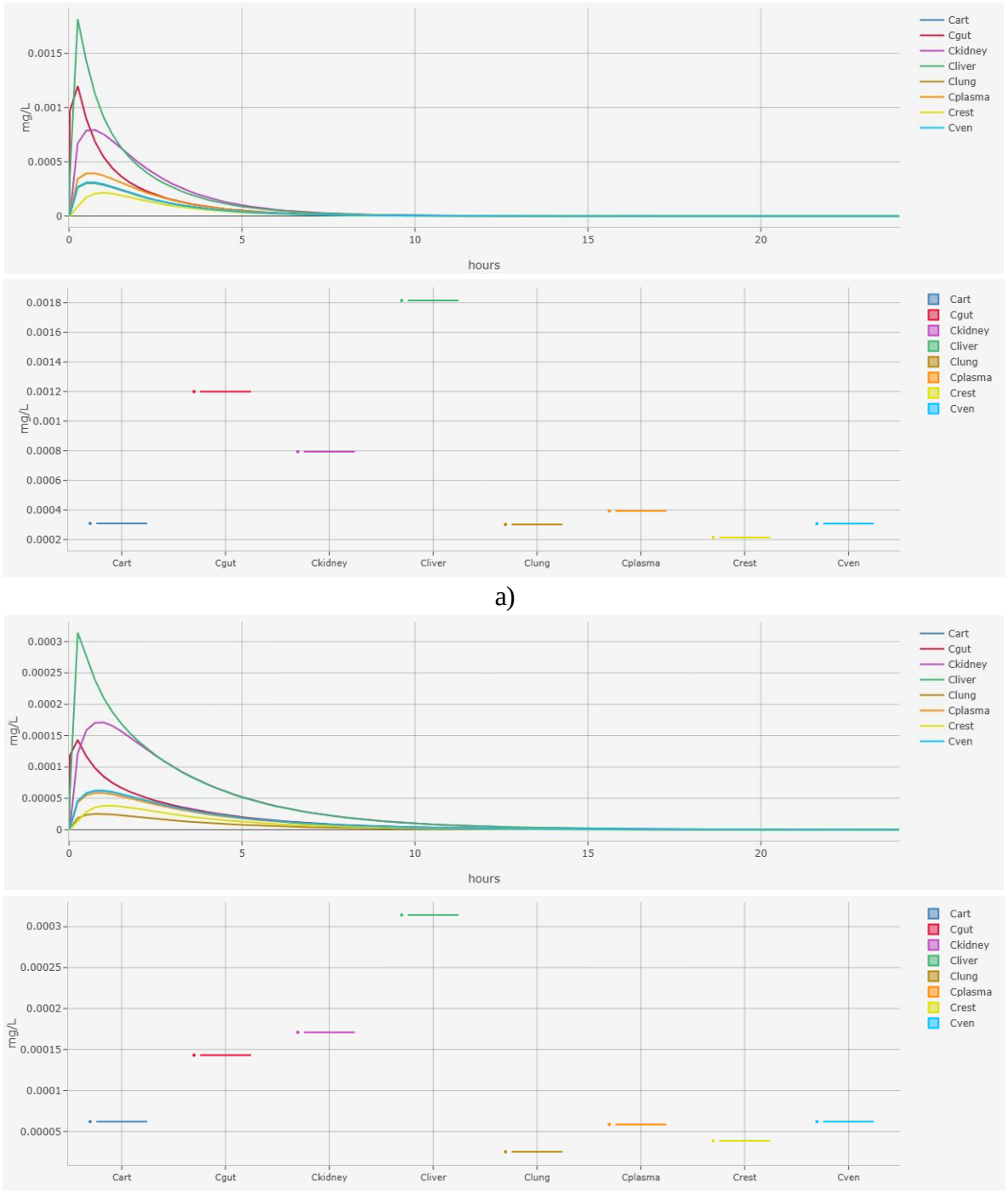
A graphical representation of the obtained results is given in Figures 1-2, showing the concentration profile curves (Css) for the display of the concentration profile graph (time series) for each compound, as well as the box plots of the Cmax values. The points in the box plot correspond to the compartment Cmax for selected compounds, and the boxes show the median Cmax and interquartile range for each compartment.

Box-plots of observed pharmaceuticals representing the predicted concentrations in human compartments are presented in the Figures 1a and 1b.

The solve_fetal_pbtk model predictions show that the maximal accumulation for 4-AAA is expected in liver (0.001815 mg/ml) and gastrointestinal system (0.001199 mg/l) (Figure 1a). This includes potential hepatotoxicity. In the case of carbamazepine (Figure 1b), the highest Cmax can also be expected in the liver (0.0003mg/l) and gastrointestinal system (0.0001mg/l).

Graphical illustration of detected compounds representing the predicted concentrations in human compartments for pregnant woman are presented in the Figures 2a and 2b. For 4-AAA, in a case of pregnant woman and woman in lactation (solve_fetal_pbtk model), higher concentrations can be expected in the kidneys (Cfkidney = 0.0009 mg/l; Ckidney = 0.0008 mg/l) and liver (Cfliver = 0.0009 mg/l).

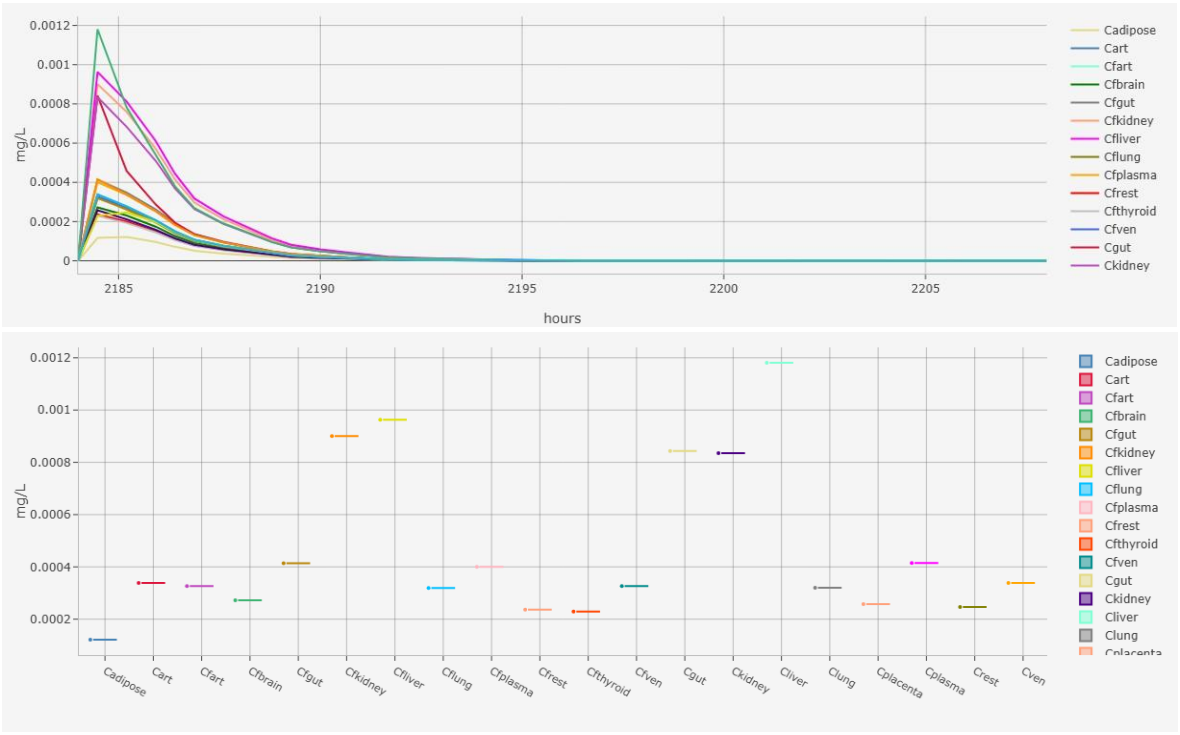
There are especially higher concentrations on the fetus. In the case of administration of contaminated water during pregnancy, the distribution of carbamazepine in the liver (0.00018 mg/ml) and kidneys (0.00018 mg/ml) of the fetus can be expected (Figure 2b).



a)

b)

Figure 1. Box-plots of detected compounds representing the predicted concentrations in human compartments: a) 4-AAA, b) Carbamazepine



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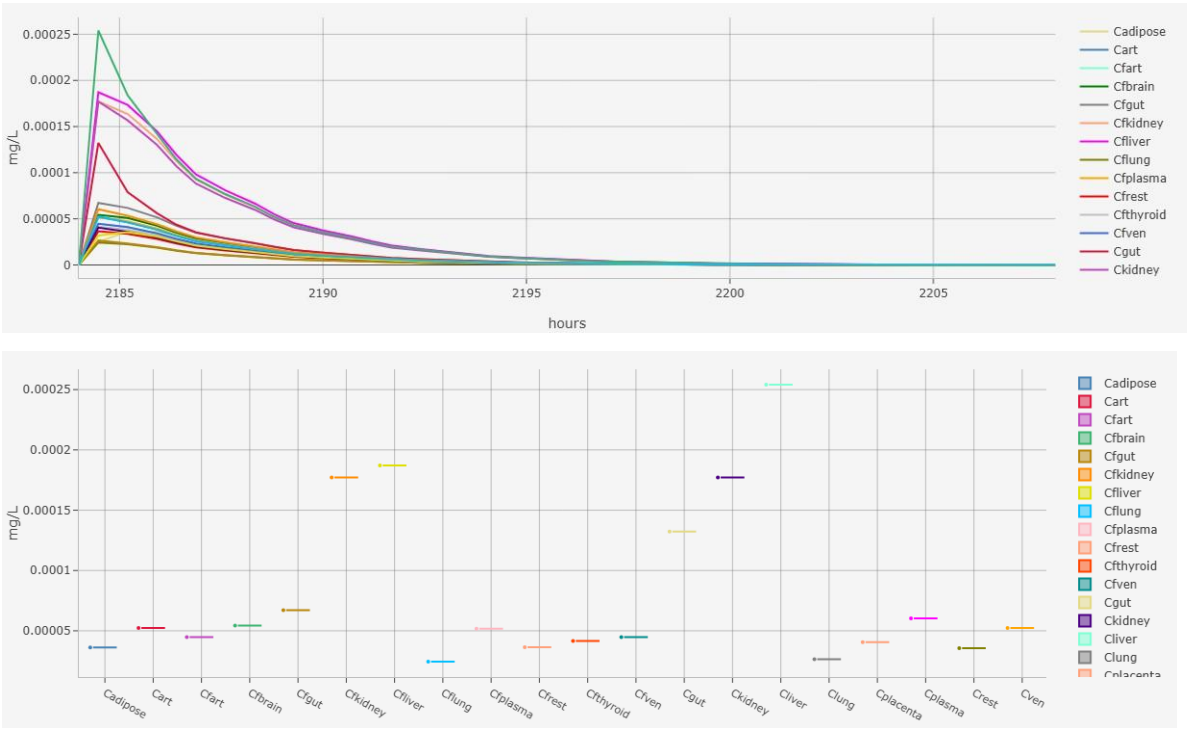

b)

Figure 2. Box-plots of detected compounds representing the predicted concentrations in human compartments for pregnant woman: a) 4-AAA, b) Carbamazepine

The predicted toxicology values (pLC_{50}) against *T. platyurus* and zebrafish are given in Table 2. A lower value of pLC_{50} corresponds to lower toxicity and vice versa. For the zebrafish model, the largest pLC_{50} is expected after 120 hours of exposure. In general, it can be seen that the predicted pLC_{50} values for *T. platyurus* are higher compared to zebrafish model.

Table 2. The predicted aquatic toxicity for *T. platyurus* and zebrafish models.

Molecules	pLC_{50}-*T.platyurus* (MLR)	pLC_{50}-048h-zebrafish_ (MLR)	pLC_{50}-096h-zebrafish_ (MLR)	pLC_{50}-120h-zebrafish_ (MLR)	pLC_{50}-132h-zebrafish_ (MLR)
4-AAA	1.754	0.707	-0.269	2.549	1.174
Carbamazepine	1.377	0.424	-0.534	2.115	1.548

CONCLUSIONS

The modern society is faced with the large use of drugs, their inadequate monitoring and increased presence in the environment. Pharmaceuticals as water pollutants can cause health issues and toxicological risks. The tested compounds (Carbamazepine, 4-AAA) may have increased concentrations in the liver and organs of the fetus after consuming contaminated water. In addition, significant effects on aquatic organisms are also expected. This study is the basis for further investigation of the expected health profile after administration of contaminated water with carbamazepine and 4-AAA substances.

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