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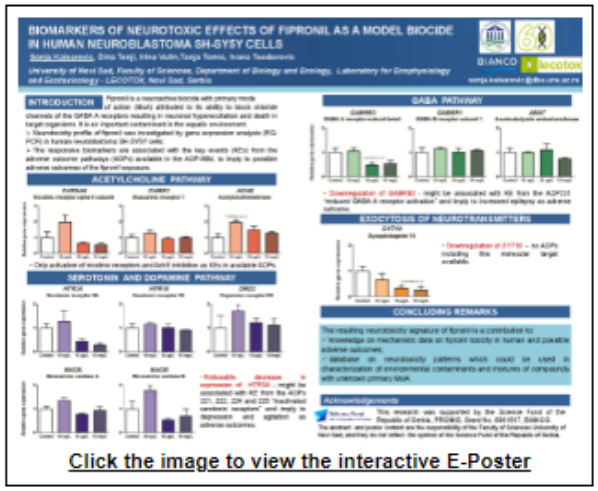
1.03.10 - Biomarkers of Neurotoxic Effects of Fipronil As a Model Biocide in Human Neuroblastoma SH-SY5Y Cells

Abstract

Fipronil is a highly effective neuroactive phenylpyrazole insecticide with primary mode of action attributed to its ability to block chloride channels of the $GABA_A$ receptors, resulting in neuronal hyperexcitation and death in target organisms. It is widely used in control of many agricultural and domestic pests, leading to environmental contamination and exposure of nontarget organisms, including humans. In recent environmental studies, fipronil has been recognized as important contaminant in the aquatic environment. In this study, it was used as a model biocide, to contribute to database on neurotoxicity patterns which could be used in characterization of environmental contaminants. We investigated neurotoxicity profile of fipronil on human neuroblastoma SH-SY5Y cells. Selected concentrations (including environmentally relevant) were used for gene expression analysis (RQ-PCR) of biomarkers of neurotoxicity. The analysis was conducted for genes encoding some of the key elements in neurotransmitter pathways such as neurotransmitter receptors (nicotinic, muscarinic, dopamine, GABA receptors), acetylcholineesterase (AChE) and monoamine oxidase (MAO_A and MAO_B), as well as protein involved in exocytosis of neurotransmitters (synaptotagmin 10). The resulting neurotoxicity signature of fipronil is a contribution to the knowledge on mechanistic data on fipronil toxicity in human. The responsive biomarkers will be associated with the molecular initiating events (MIEs) or key events (KEs) from the adverse outcome pathways (AOP_S) available in the AOP-Wiki, to imply to possible outcomes of the fipronil exposure. Moreover, the disturbances in the expression of responsive genes will be discussed as possible biomarkers of neurotoxic effects of other environmental contaminants and mixtures of compounds with unknown mode of action. *Acknowledgements:* This research was supported by the Science Fund of the Republic of Serbia, PROMIS, Grant No. 6061817, BIANCO. The abstract content is the responsibility of the Faculty of Sciences University of Novi Sad, and it does not reflect the opinion of the Science Fund of the Republic of Serbia.



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BIOMARKERS OF NEUROTOXIC EFFECTS OF FIPRONIL AS A MODEL BIOCIDE IN HUMAN NEUROBLASTOMA SH-SY5Y CELLS

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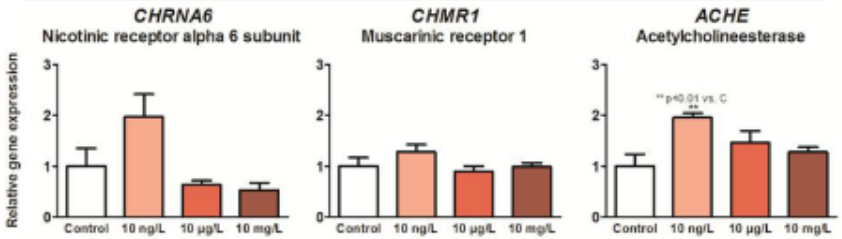
INTRODUCTION

Fipronil is a neuroactive biocide with primary mode of action (MoA) attributed to its ability to block chloride channels of the GABA A receptors resulting in neuronal hyperexcitation and death in target organisms. It is an important contaminant in the aquatic environment.

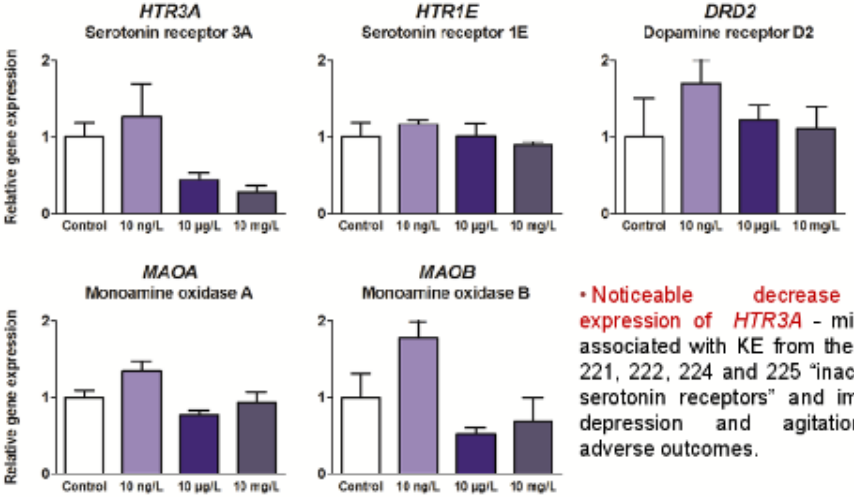
- Neurotoxicity profile of fipronil was investigated by gene expression analysis (RQ-PCR) in human neuroblastoma SH-SY5Y cells;
- The responsive biomarkers are associated with the key events (KEs) from the adverse outcome pathways (AOPs) available in the AOP-Wiki, to imply to possible adverse outcomes of the fipronil exposure.

ACETYLCHOLINE PATHWAY



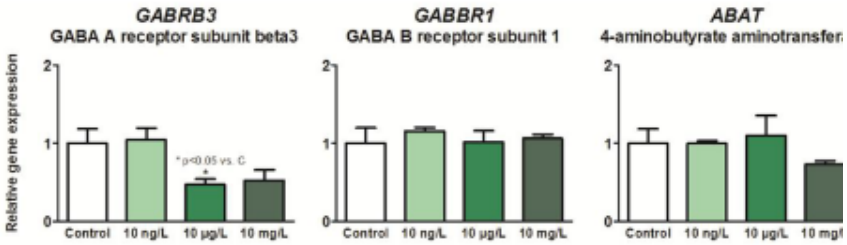
- Only activation of nicotinic receptors and AchE inhibition as KEs in available AOPs.

SEROTONIN AND DOPAMINE PATHWAY



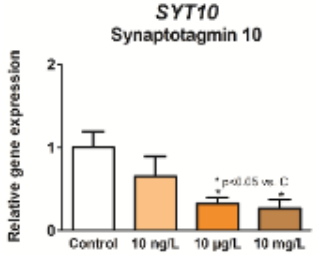
- Noticeable decrease in expression of *HTR3A* - might be associated with KE from the AOPs 221, 222, 224 and 225 "inactivated serotonin receptors" and imply to depression and agitation as adverse outcomes.

GABA PATHWAY



- Downregulation of *GABRB3* - might be associated with KE from the AOP231 "reduced GABA A receptor activation" and imply to increased epilepsy as adverse outcome.

EXOCYTOSIS OF NEUROTRANSMITTERS



- Downregulation of *SYT10* - no AOPs including this molecular target available.

CONCLUDING REMARKS

The resulting neurotoxicity signature of fipronil is a contribution to:

- ✓ knowledge on mechanistic data on fipronil toxicity in human and possible adverse outcomes;
- ✓ database on neurotoxicity patterns which could be used in characterization of environmental contaminants and mixtures of compounds with unknown primary MoA.

Acknowledgements

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