POPULARIZED SCIENTIFIC SUMMARY OF THE PROJECT

1. AIM OF THE STUDY

Recently the public concern has been focused on persistent organic pollutants (POPs) and endocrine disrupting chemical (EDC) effects on brain function, concomitantly with the increase in neuropsychiatric disorders, including autism, attention deficit and hyperactivity disorder (ADHD) as well as learning disabilities and aggressiveness. There are dioxins, polychlorinated biphenyls (PCBs), pesticides, fungicides and plasticizers, such as bisphenol A (BPA) and phthalates. Apart from acting as EDCs, altering hormone-dependent processes and disrupting functioning of endocrine glands, they act as *neural disrupting chemicals* due to their ability of altering neural transmission and formation of neural networks. In recent rank of organic pollutants the potentially most dangerous are perfluorinated compounds. Antimicrobial compounds such as triclocarban (3,4,4'- Trichlorocarbanilide) are in the middle of the rank, far before BPA and phtalate esters. Triclocarban is a phenyl ether, which has antimicrobial properties and is often added to personal and health care products, including cloths, plastics, and even products dedicated for newborns. One of the most toxic compound is dichlorodifenyldichloroetylene (DDE) which is metabolite of the pesticide DDT. The limited use of DDT continues, mainly to fight the spread of malaria due to targeting the voltage-gated sodium channels on the insect neurons. Despite worldwide restrictions that have been in place for long periods of time, DDT continues to be a ubiquitous contaminant whose environmental concentrations have not declined in some areas in decades. DDE may easily cross the skin and blood-brain barrier. It accumulates in human organisms, especially in adipose and brain tissues.

There is a growing body of evidence that triclocarban and DDE are present in human tissues, but little is known about the impact of triclocarban and DDE on the nervous system, especially at early developmental stages. Systematic and complex data concerning mechanisms of actions of triclocarban and DDE in neuronal cells are missing. The influence of triclocarban and DDE on apoptosis and autophagy as well as on the estrogen receptors (ERα, ERβ, GPR30), aryl hydrocarbon receptor (AhR), and constitutive androstan receptor (CAR) remains largely unknown. The proposed project takes into consideration developmental toxicity that is based upon loss of homeostasis in developing neural cells and the whole organisms in response to environmental contaminants i.e., triclocarban and DDE. This project shares the concept of studies that focus on identification of anthropogenic risk factors for human health.

2. THE APPLIED RESEARCH METHODS

The study will be carried out *in vitro* on primary cell cultures of mouse embryonic neuronal cells, and *in vivo* on one month-old animals which were prenatally exposed to triclocarban or DDE. Therefore, the neurodevelopmental aspect will be taken into consideration in assessment of patomechanisms of actions of chosen compounds. In addition, the *in vitro* experiments performed on primary cell cultures require far less animals than the *in vivo* experiments.

The basic research hypothesis assumes that triclocarban and DDE are neurotoxic, induce apoptosis, and disturb autophagy. These processes are accompanied by alteration of epigenetic status, AhR and CAR activation, and impairment of ERα, ERβ, and GPR30. The particular value of the proposed project is that it combines *in vitro* and *in vivo* approaches that underlay neurodevelopmental aspects of the study, i.e. mechanisms of actions of triclocarban and DDE in embryonic neuronal cells (*in vitro*) and in postnatal neuronal tissues (*in vivo*). Original idea is complemented by innovative methodology, including molecular and epigenetic analyzes as well as a gene silencing with the use of specific siRNAs.

3. REASONS OF UNDERTAKING THE RESEARCH

The idea of the project is entirely original. It is based on studies of triclocarban- and DDE-induced effects in mouse neuronal cells in respect to apoptosis and autophagy and combines these effects with DNA methylation and interactions with ERs, AhR and CAR. Recognition of these mechanisms is particularly important because triclocarban and DDE through alteration of epigenetic status and dysregulation of apoptosis and autophagy could impair neural development and/or cause neurodegenerations. Furthermore, interactions of triclocarban and DDE with ER, AhR and CAR signaling pathways at early developmental stages could cause abnormalities which might reveal in adolescent or adult nervous system.

Realization of the project gives prospects for understanding the neurodevelopmental pathomechanisms of actions of triclocarban and DDE, both at the cellular and organism levels. It may provide the lacking data on deleterious effects of triclocarban and DDE that could be asset in searching for effective neuroprotective strategies against these EDCs and their controlled use.